

Overzichtstabel van RCT's naar medicamenteuze behandelingen van COVID-19.

Deze tabel laat een overzicht zien van de gevonden RCTs over de medicamenteuze behandeling van COVID-19.

De literatuur wordt tweewekelijks bekeken en zo nodig wordt de tabel aangevuld. De selectiecriteria voor de geïnccludeerde studies worden weergegeven onder de tabellen. De studies staan gerangschikt op middel en datum van publicatie.

Medication/treatment	Published	1st author	Title	Journal	Status
Updated: May 17, 2022 (date last search: May 12, 2022)					
1. Remdesivir					
	May 02, 2022	Pan	Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses	The Lancet	Published
	September 10, 2021a	Abd-Elsalam	Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial	The American Society of Tropical Medicine and Hygiene	Published online
	September 14, 2021	Ader	Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial	The Lancet Infectious Diseases	Published Online
	July 13, 2021	Barratt-Due	Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19	Annals of Internal Medicine	Published (No direct access)
	March 20, 2021	Mahajan	Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study	Indian Journal of Anaesthesia	Published
	December 02, 2020	Pan (WHO Solidarity Trial Consortium)	Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results <i>(also reported under 'Hydroxychloroquine', 'lopinavir' and 'Interferon β-1a')</i>	New England Journal of Medicine	Published
	October 8, 2020	Beigel	Remdesivir for the Treatment of Covid-19 — Final Report	The New England Journal of Medicine	Published
	August 21, 2020	Spinner	Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19 A Randomized Clinical Trial	JAMA	Published
	April 29, 2020a	Wang	Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial	The Lancet	Published

Medication/treatment	Published	1st author	Title	Journal	Status
2. Corticosteroids					
2.1. Dexamethasone					
	Feb 16, 2021	Jamaati	No clinical benefit of high dose corticosteroid administration in patients with COVID-19: A preliminary report of a randomized clinical trial	European Journal of Pharmacology	Published
	September 02, 2020	Tomazini	Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19. The CoDEX Randomized Clinical Trial	Journal of the American Medical Association	Published
	July 17, 2020a	Horby	Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report	The New England Journal of Medicine	Published
2.2. Hydrocortisone					
	June 27, 2021	Munch	Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: the COVID STEROID randomised, placebo-controlled trial	Acta Anaesthesiologica Scandinavica	Epub ahead of print
	September 02, 2020	Angus	Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial.	Journal of the American Medical Association	Published
	September 02, 2020	Dequin	Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19 - A Randomized Clinical Trial	JAMA	Published
2.3. Inhaled corticosteroids (budesonide, ciclesonide)					
	February, 2022	Agustí	Add-on inhaled budesonide in the treatment of hospitalised patients with COVID-19: a randomised clinical trial	JAMA Internal Medicine	Early view
	January 1, 2022	Clemency	Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial	JAMA Internal Medicine	Published
	August 12, 2021	Song	Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial	Journal of Clinical Medicine	Published online
	August 10, 2021	Yu	Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial	The Lancet	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	April 09, 2021	Ramakrishnan	Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial	The Lancet Respiratory Medicine	Published
2.4. Methylprednisolone					
	June 14, 2021	Solanich	Methylprednisolone Pulses Plus Tacrolimus in Addition to Standard of Care vs. Standard of Care Alone in Patients With Severe COVID-19. A Randomized Controlled Trial. <i>(also reported under 'tractolimus')</i>	Frontiers in Medicine	Published
	January 22, 2021	Tang	Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial	Respiration	Published
	February 03, 2021	Corral-Gudino	Methylprednisolone in adults hospitalized with COVID-19 pneumonia	Wiener klinische Wochenschrift	Published
	December 24, 2020	Edalatifard	Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial	European Respiratory Journal	Published
	August 12, 2020	Jeronimo	Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial	Clinical Infectious Diseases	Published
3. Hydroxychloroquine & Chloroquine					
	July 13, 2021	Barratt-Due	Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19	Annals of Internal Medicine	Published (No direct access)
	July 12, 2021	Arabi	Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial <i>(also reported under 'Lopinavir and ritonavir')</i>	Intensive Care Med	Published online
	June 18, 2021	Schwartz	Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial	CMAJ Open	Published
	May 9, 2021	Ader	An open-label randomized, controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with	Clinical Microbiology and Infection	Published-Pre-proof version

Medication/treatment	Published	1st author	Title	Journal	Status
			COVID-19 <i>(also reported under 'Lopinavir and ritonavir' and 'Interferon β-1α')</i>		
	April 27, 2021	Réa-Neto	An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients <i>(also reported under 'hydroxychloroquine')</i>	Scientific Reports	Published
	April 22, 2021	Reis	Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19 The TOGETHER Randomized Clinical Trial <i>(also reported under 'Lopinavir and ritonavir')</i>	JAMA Network open	Published online
	February 13, 2021a	Gupta	Open-label randomized control trial of hydroxychloroquine in patients with moderate to severe coronavirus disease 2019 infection	Medical Journal Armed Forces India	Published online
	March 31, 2021	Dubée	Hydroxychloroquine in mild-to-moderate COVID-19: a placebo-controlled double blind trial	Clinical Microbiology and Infection	Published
	February 9, 2021	Purwati	A Randomized, Double-Blind, Multicenter Clinical Study Comparing the Efficacy and Safety of a Drug Combination of Lopinavir/Ritonavir-Azithromycin, Lopinavir/Ritonavir-Doxycycline, and Azithromycin-Hydroxychloroquine for Patients Diagnosed with Mild to Moderate COVID-19 Infections <i>(also reported under 'Lopinavir and ritonavir')</i>	Biochemistry Research International	Published
	January 20, 2021	Thakar	Chloroquine nasal drops in asymptomatic & mild COVID-19: An exploratory randomized clinical trial. DOI: 10.4103/ijmr.IJMR_3665_20	Indian J Med Res	Epub ahead of print
	December 02, 2020a	Chen	A Multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19)	Plos One	Published
	December 02, 2020	Pan (WHO Solidarity Trial Consortium)	Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results <i>(also reported under 'remdesivir', 'lopinavir and ritonavir' and 'Interferon β-1α')</i>	New England Journal of Medicine	Published
	November 20, 2020	Omrani	Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19.	The Lancet	Published
	November 09, 2020	Self	Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19 A Randomized Clinical Trial	JAMA	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	October 20, 2020	Lyngbakken	A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics	Nature Communications	Published
	October 8, 2020b	Horby	Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19	The New England Journal of Medicine	Published
	September 23, 2020	Ulrich	Treating COVID-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind Randomized Controlled Trial in Hospitalized Patients	Open Forum Infectious Diseases	Published
	August 14, 2020a	Abd-Elsalam	Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study	The American journal of tropical medicine and hygiene	Published
	August 06, 2020	Brown	Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with COVID-19 (HAHPS): Results of a Randomized, Active Comparator Trial.	American Thoracic Society Journals	Published
	July 23, 2020	Cavalcanti	Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19 <i>(also reported under 'azithromycin')</i>	New England Journal of Medicine	Published
	July 16, 2020	Mitjà	Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial	Clinical Infectious Disease	Accepted Manuscript
	July 16, 2020	Skipper	Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 - A Randomized Trial	Annals of Internal Medicine	Published
	May 14, 2020	Tang	Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial	BMJ	Published
	April 24, 2020	Borba	Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial	JAMA Network Open	Published
4. Immunoglobulin					
4.1. Hyperimmunoglobulin					
	January 27, 2022	Polizzotto	Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial	The Lancet	Published online
	June 4, 2021	Ali	Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial	E Clinical Medicine	Published
4.2. Intravenous immunoglobulin					

Medication/treatment	Published	1st author	Title	Journal	Status
	November 11, 2021	Mazeraud	Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebo-controlled, phase 3 trial	The Lancet Respiratory Medicine	Epub ahead of print
	Februari 15, 2021	Raman	A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in COVID-19 patients with Regular Intravenous Immunoglobulin Therapy	Journal of Infectious Diseases	Published online
	Oktober 21, 2020	Gharebaghi	The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial	BMC Infectious Diseases	Published
	November 13, 2020	Tabarsi	Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial	International Immunopharmacology	Published
4.3. Normal immunoglobulin					
	NA	NA	NA	NA	NA
5. Convalescent plasma					
	March, 2022	Sullivan	Early Outpatient Treatment for Covid-19 with Convalescent Plasma	The New England Journal of Medicine	Published
	March 15, 2022	Song	Treatment of severe COVID-19 patients with either low- or high-volume of convalescent plasma versus standard of care: A multicenter Bayesian randomized open-label clinical trial (COOP-COVID-19-MCTI)	The Lancet Regional Health - Americas	Published
	February 07, 2022	De Santis	High-Dose Convalescent Plasma for Treatment of Severe COVID-19	Emerging Infectious Disease	Early release article
	February, 2022	Alemanly	High-titre methylene blue-treated convalescent plasma as an early treatment for outpatients with COVID-19: a randomised, placebo-controlled trial	The Lancet Respiratory Medicine	Online ahead of print
	January 19, 2022	Ray	A phase 2 single center open label randomised control trial for convalescent plasma therapy in patients with severe COVID-19	Nature communications	Published
	January 12, 2022	Bajpai	Efficacy of convalescent plasma therapy in the patient with COVID-19: a randomised control trial (COPLAI trial)	BMJ Open	Published
	January 09, 2022	Baldéon	Effect of convalescent plasma as complementary treatment in patients with moderate COVID-19 infection	Transfusion Medicine	Published
	December 15, 2021	Bar	A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia	The Journal of Clinical Investigation	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	December 13, 2021	Ortigoza	Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients A Randomized Clinical Trial	JAMA Intern Med.	Published online
	December 04, 2021	Holm	Convalescence plasma treatment of COVID-19: results from a prematurely terminated randomized controlled open-label study in Southern Sweden	BMC Research Notes	Published
	November 29, 2021	Menichetti	Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia A Randomized Clinical Trial	Jama Network Open	Published
	October 4, 2021	Estcourt	Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19 A Randomized Clinical Trial	Journal of American Medical Association	Published online
	September 9, 2021	Bégin	Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial	Nature Medicine	Epub ahead of print
	September 2, 2021	Avendaño-Solá	A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia	Journal of Clinical Investigation	Epub ahead of print
	August 31, 2021	Körper	Results of the CAPSID randomized trial for high-dose convalescent plasma in severe COVID-19 patients	The Journal of Clinical Investigation	Published online
	August 26, 2021	Devos	Early high antibody-titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma	European respiratory journal	Published online
	August 18, 2021	Korley	Early Convalescent Plasma for High-Risk Outpatients with Covid-19	The new England journal of medicine	Published
	Augustus 9, 2021	Kirenga	Efficacy of convalescent plasma for treatment of COVID-19 in Uganda	BMJ Open Respiratory Research	Published online
	July 15, 2021	Bainbridge	Characteristics of High-Titer Convalescent Plasma and Antibody Dynamics After Administration in Patients With Severe Coronavirus Disease 2019	Open Forum Infectious Diseases	Published online
	July 8, 2021	Sekine	Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial	European Respiratory Journal	Epub
	July 1, 2021	O'Donnell	A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19	The Journal of Clinical Investigation	Published online
	May 11, 2021	AlQahtani	Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease	Scientific Reports	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	April 16, 2021	Bennett-Guerrero	Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease 2019 Infected Hospitalized Patients in New York, A Double-Blind Randomized Trial	Critical Care Medicine	Published
	April 10, 2021	Pouladzadeh	A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm	Internal and Emergency Medicine	Online ahead of print
	January 06, 2021	Libster	Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults	New England Journal of Medicine	Published
	November 24, 2020	Simonovich	A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia	The New England Journal of Medicine	Published
	November 03, 2020	Salman	Efficacy and safety of transfusing plasma from COVID-19 survivors to COVID-19 victims with severe illness. A double-blinded controlled preliminary study	Egyptian Journal of Anaesthesia	Published
	October 22, 2020	Agarwal	Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial).	British Medical Journal (BMJ)	Published
	June 03, 2020b	Li	Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial	JAMA	Published
6. Monoclonal antibodies					
6.1. Adalimumab					
	July 7, 2021	Fakharian	Evaluation of adalimumab effects in managing severe cases of COVID-19: A randomized controlled trial.	International Immunopharmacology	Published
6.2. Antibody JS016					
	22 February 2022	Dong	Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody JS016 in Hospitalized Chinese Patients with COVID-19: A Phase 2/3, Multicenter, Randomized, Open-label, Controlled Trial	Antimicrobial Agents and Chemotherapy	Published online
6.3. Anti-granulocyte-macrophage colony-stimulating-factor (anti-GM-CSF)					
	March 15, 2022	Criner	Anti-GM-CSF Monoclonal Antibody Gimsilumab for COVID-19 Pneumonia: A Randomized, Double-Blind, Placebo-Controlled Trial	American Journal of Respiratory and Critical Care Medicine	Published

Medication/treatment	Published	1st author	Title	Journal	Status
6.4. Bamlanivimab (INN, codenamed LY-CoV555, neutralizing monoclonal antibody)					
	December 21, 2021	Lundgren (ACTIV-3TICO Bamlanivimab Study Group)	Responses to a Neutralizing Monoclonal Antibody for Hospitalized Patients With COVID-19 According to Baseline Antibody and Antigen Levels	Annals of Internal Medicine	Published
	January 21, 2021	Chen	SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19	The New England Journal of Medicine	Published
	December 22, 2020	Lundgren	A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19	New England Journal of Medicine	Published
6.5. Bamlanivimab and Etesevimab (LY-CoV016; recombinant fully human monoclonal neutralizing antibody; together is combination of two monoclonal antibodies)					
	April, 2022	Chen	Bamlanivimab and Etesevimab Improve Symptoms and Associated Outcomes in Ambulatory Patients at Increased Risk for Severe Coronavirus Disease 2019: Results From the Placebo-Controlled Double-Blind Phase 3 BLAZE-1 Trial	Open Forum Infectious Diseases	Published
	October 28, 2021a	Dougan	A randomized, placebo-controlled clinical trial of bamlanivimab and etesevimab together in high-risk ambulatory patients with COVID-19 and validation of the prognostic value of persistently high viral load	Clinical Infectious Diseases	Accepted
	July 14, 2021b	Dougan	Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19	The New England Journal of Medicine	Published
	Jan 21, 2021	Gottlieb	Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19 - A Randomized Clinical Trial	JAMA	Published
6.6. Casirivimab and imdevimab (REGN-COV2; combination of two noncompeting, neutralizing human IgG1 antibodies)					
	February, 2022	RECOVERY Collaborative Group	Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial	The Lancet	Published
	Jan 21, 2021	Weinreich	REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19.	The New England journal of medicine	Published
6.7. CERC-002					
	December 6, 2021	Perlin	Randomized, double-blind, controlled trial of human anti-LIGHT monoclonal antibody in COVID-19 acute respiratory distress syndrome	Journal of Clinical Investigation	Epub ahead of print
6.8. Etanercept					
6.9. Gimsilumab					
6.10. Golimumab					

Medication/treatment	Published	1st author	Title	Journal	Status
6.11. Infliximab					
	December 15, 2021	Fisher	Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial (also reported under 'namilumab')	The Lancet Respiratory Medicine	Epub ahead of print
6.12. Itolizumab (humanized monoclonal antibody (IgG1 kappa anti-CD6))					
	April 9, 2021	Kumar	A two-arm, randomized, controlled, multi-centric, open-label phase-2 study to evaluate the efficacy and safety of Itolizumab in moderate to severe ARDS patients due to COVID-19	Expert Opinion on Biological Therapy	Published
6.13. Lenzilumab					
	01, December, 2021	Temesgen	Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebocontrolled trial	Lancet Respir Med	Published online
6.14. Mavrilimumab (human monoclonal antibody; anti-GM-CSF-Rα; human isoform IgG4)					
	March 17, 2021	Cremer	Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial	The Lancet Rheumatology	Published
6.15. Namilumab					
	December 15, 2021	Fisher	Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial (also reported under 'infliximab')	The Lancet Respiratory Medicine	Epub ahead of print
6.16. Regdanvimab					
	February 02, 2022	Streinu-Cercel	Efficacy and Safety of Regdanvimab (CT-P59): A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial in Outpatients With Mild-to-Moderate Coronavirus Disease 2019	Open Forum Infectious Diseases	Published
6.17. Sotrovimab					
	March 14, 2022	Gupta	Effect of Sotrovimab on Hospitalization or Death among High-risk Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial	JAMA	Published
	December 23, 2021	Self	Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial	The Lancet Infectious Diseases	Published online

Medication/treatment	Published	1st author	Title	Journal	Status
	October 27, 2021b	Gupta	Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab	The New England Journal of Medicine	Published
6.18. Tixagevimab and cilgavimab (AZD7442)					
NA	NA	NA	NA	NA	NA
6.19. Vilobelimab (Anti-C5a antibody IFX-1; monoclonal anti-human complement factor C5a antibody)					
	September 28, 2020	Vlaar	Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial	Lancet Rheumatol	Published
6.20. Secukinumab					
	April 29, 2022	Resende	Blockade of interleukin seventeen (IL-17A) with secukinumab in hospitalized COVID-19 patients – the BISHOP study	Infectious Diseases	Published online
7. Polyclonal antibodies					
	April 11, 2021	Lopardo	RBD-specific polyclonal F(ab)2 fragments of equine antibodies in patients with moderate to severe COVID-19 disease: A randomized, multicenter, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial	EclinicalMedicine	Published online
8. Supplements					
8.1. Vitamin C					
	15 December, 2021	Majidi	The Effect of Vitamin C on Pathological Parameters and Survival Duration of Critically Ill Coronavirus Disease 2019 Patients: A Randomized Clinical Trial	Frontiers in Immunology	Published online
	Jan 09,2021	Zhang	Pilot trial of high-dose vitamin C in critically ill COVID-19 patients	Annals of Intensive Care	Published
	February 12, 2021	Thomas	Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection The COVID A to Z Randomized Clinical Trial. (Also reported under 'zinc')	Journal of American medical association (JAMA)	Published
	February 11, 2021	JamaliMoghadamSiahkali	Safety and efectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial.	European Journal of Medical Research	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	December15, 2020	Darban	Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial (Also reported under 'zinc')	Journal of Cellular & Molecular Anesthesia	Published
8.2. Vitamin D					
	February 18, 2022	Cannata-Andia	A single-oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve outcomes in the COVID-19 disease: the COVID-VIT-D-a randomised multicentre international clinical trial	BMC Medicine	Published
	September 8, 2021	Elamir	A randomized pilot study using calcitriol in hospitalized COVID-19 patients	Bone	Online ahead of print
	May 20, 2021	Lakkireddy	Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease	Nature	Published
	February 17, 2021	Murai	Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19	JAMA	Published
	November 12, 2020	Rastogi	Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study).	The British Medical Journal (BMJ)	Published
	August 29, 2020	Castillo	Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study”	Journal of Steroid Biochemistry and Molecular Biology	Published
8.3. Zinc					
	Feb 25, 2021	Patel	A pilot double-blind safety and feasibility randomized controlled trial of high-dose intravenous zinc in hospitalized COVID-19 patients	Journal of Medical Virology	Published
	February 12, 2021	Thomas	Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection The COVID A to Z Randomized Clinical Trial. (Also reported under Vitamin C / Ascorbic acid)	Journal of American medical association (JAMA)	Published
	December, 15 2020	Darban	Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial (Also reported under 'Vitamin C')	Journal of Cellular & Molecular Anesthesia	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	November 27, 2020b	Abd-Elsalam	Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial	Biological Trace Element Research	Published
9. Antiviral treatment					
9.1. Darunavir (antiretroviral treatment; also in combination with cobicistat)					
	June 21, 2020b	Chen	Antiviral Activity and Safety of Darunavir/Cobicistat for the Treatment of COVID-19	Open Forum Infectious Diseases (OFID)	Published
9.2. Favipiravir (be eventually used in combination with Baloxavir and/or marboxil or inhaled interferon β-1b)					
	August 9, 2021	Ivashchenko	AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial	Clinical Infectious Diseases	Published
	April 21, 2021	Zhao	Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial	International Immunopharmacology	Published
	November 16, 2020	Udwadia	Efficacy and Safety of Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial	International Journal of Infectious Diseases	Published
	November 09, 2020	Khamis	Randomized Controlled Open Label Trial on the Use of Favipiravir Combined with Inhaled Interferon beta-1b in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia <i>(also reported under 'Inhaled interferon β-1b')</i>	International Journal of Infectious Diseases	Published
	October 25, 2020	Lou	Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial	MedRxiv	Published
9.3. Lopinavir and ritonavir (brand name = Kaletra; fixed dose combination of antiretroviral treatment)					
	July 12, 2021	Arabi	Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial	Intensive Care Med	Published online
	May 9, 2021	Ader	An open-label randomized, controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19 <i>(also reported under 'Hydroxychloroquine' and 'Interferon β-1a')</i>	Clinical Microbiology and Infection	Published-Pre-proof version

Medication/treatment	Published	1st author	Title	Journal	Status
	April 22, 2021	Reis	Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19 The TOGETHER Randomized Clinical Trial (also reported under 'Hydroxychloroquine')	JAMA Network open	Published online
	Feb 9, 2021	Purwati	A Randomized, Double-Blind, Multicenter Clinical Study Comparing the Efficacy and Safety of a Drug Combination of Lopinavir/Ritonavir-Azithromycin, Lopinavir/Ritonavir-Doxycycline, and Azithromycin-Hydroxychloroquine for Patients Diagnosed with Mild to Moderate COVID-19 Infections (also reported under 'Hydroxychloroquine')	Biochemistry Research International	Published
	December 02, 2020	Pan (WHO Solidarity Trial Consortium)	Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results (also reported under 'Remdesivir', 'Hydroxychloroquine' and 'Interferon β-1a')	New England Journal of Medicine	Published
	October 05, 2020c	Horby	Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.	The Lancet	Published
	July 14, 2020	Huang	No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon- Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon- Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective (also reported under 'ribavarine' and 'Interferon β-1a')	Frontiers in Pharmacology	Published
	May 19, 2020a	Li	Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial	Elsevier Public Health Emergency Collection	Published
	March 18, 2020a	Cao	A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19	The New England Journal of Medicine	Published
9.4. Molnupiravir					
	February 10, 2022	Jayk Bernal	Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients	The New England Journal of Medicine	Published
	December 23, 2021	Fischer	A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus	Science Translational Medicine	Published

Medication/treatment	Published	1st author	Title	Journal	Status
9.5. Nitazoxanide (brand name = Alinia; antiparasitic & broad-spectrum antiviral medication)					
	January 14, 2021	Rocco	Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial	European Respiratory Journal	Published
9.6. Novaferon (broad-spectrum antiviral drug)					
	August 03, 2020	Zheng	SARS-CoV-2 Clearance in COVID-19 Patients with Novaferon Treatment: A Randomized, Open-label, Parallel Group Trial	International Journal of Infectious Diseases	Published
9.7. Oseltamivir (brand name = Tamiflu)					
NA	NA	NA	NA	NA	NA
9.8. Paxlovid					
NA	NA	NA	NA	NA	NA
9.9. Ribavirine (also known as tribavirin)					
	July 14, 2020	Huang	No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon- Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon- Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective (also reported under 'Lopinavir and ritonavir' and 'interferon β-1α')	Frontiers in Pharmacology	Published
	May 08, 2020	Hung	Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomized, phase 2 trial (also reported under 'interferon β-1b')	The Lancet	Published
9.10. Sofosbuvir (brand name = Sovaldi; has role as a prodrug, an antiviral drug and a hepatitis C protease inhibitor; only recommended with some combination of ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir)					
9.10.1. Sofosbuvir i.c.m. Daclatasvir (brand name = Daklinza; used in combination with sofosbuvir, ribavirin, and interferon)					
	December 18, 2020	Roozbeh	Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial	Journal of Antimicrobial Chemotherapy	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	August 19, 2020	Sadeghi	Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial	Journal of Antimicrobial Chemotherapy	Published
9.10.2. Sofosbuvir i.c.m. Ledipasvir (brand name = Harvoni; antiviral for hepatitis C-virus)					
	November 10, 2020	Nourian	Efficacy and safety of sofosbuvir/ ledipasvir in treatment of patients with COVID-19; A randomized clinical trial	Acta Biomedica	Published
9.10.3. Sofosbuvir i.c.m. Velpatasvir (NS5A inhibitor (by Gilead); fixed-dose combination medication with sofosbuvir for the treatment of hepatitis C)					
	April 13, 2021	Sayad	Efficacy and safety of sofosbuvir/velpatasvir versus the standard of care in adults hospitalized with COVID-19: a single-centre, randomized controlled trial	Journal of Antimicrobial Chemotherapy	Published online
9.11. Umifenovir (brand name = Arbidol)					
	July 10, 2021	Darazam	Umifenovir in hospitalized moderate to severe COVID-19 patients: A randomized clinical trial	International Immunopharmacology	Published (online)
	May 19, 2020a	Li	Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial	Elsevier Public Health Emergency Collection	Published
10. Antibiotic treatment					
10.1. Azithromycin					
	July 16, 2021	Oldenburg	Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection A Randomized Clinical Trial	Journal of the American Medical Association	Published online
	July 9, 2021	Hinks	Azithromycin versus standard care in patients with mild-to- moderate COVID-19 (ATOMIC2): an open-label, randomised trial	The Lancet Respiratory Medicine	Published online
	March 4, 2021	Butler	Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial	The Lancet	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	February 02, 2021	Horby (RECOVERY Collaborative Group)	Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial	The Lancet	Published
	September 05, 2020	Furtado	Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial	The Lancet	Published
	August 25, 2020	Sekhavati	Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial	International Journal of Antimicrobial Agents	Published
	August 06, 2020	Brown	Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with COVID-19 (HAHPS): Results of a Randomized, Active Comparator Trial. (also reported under 'hydroxychloroquine')	American Thoracic Society Journals	Published
	July 23, 2020	Cavalcanti	Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19 (also reported under 'hydroxychloroquine')	New England Journal of Medicine	Published
10.2. Doxycycline					
	May 13, 2021	Mahmud	Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial (also reported under 'ivermectine')	Journal of International Medical Research	Published
10.3. Lincomycine					
NA	NA	NA	NA	NA	NA
11. Antifungal treatment					
11.1. Intraconazole					
	March 19, 2021	Liesenborghs	Itraconazole for COVID-19: preclinical studies and a proof-of-concept randomized clinical trial	EBioMedicine	Published
12. Antiparasitic treatment					
12.1. Ivermectin (broad spectrum anti-parasitic agent)					

Medication/treatment	Published	1st author	Title	Journal	Status
	April, 2022	Abbas	The Effect of Ivermectin on Reducing Viral Symptoms in Patients with Mild COVID-19	Indian Journal of Pharmaceutical Sciences	Published
	March 30, 2022	Reis	Effect of Early Treatment with Ivermectin among Patients with Covid-19	The New England Journal of Medicine	Published
	March 03, 2022	Gonzalez	Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial	Infectious Disease Reports	Published
	February 18, 2022	Lim	Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial	JAMA Internal Medicine	Published online
	January 6, 2022	Buonfrate	High dose ivermectin for the early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof of concept clinical trial	Journal of Antimicrobial Agents	In press, pre-proof
	August 25, 2021	Mohan	Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): a single-centre randomized, placebo-controlled trial	Journal of Infection and Chemotherapy	Epub ahead of print
	July 15th, 2021	Ravikirti	Evaluation of Ivermectin as a Potential Treatment for Mild to Moderate COVID-19: A Double-Blind Randomized Placebo Controlled Trial in Eastern India	Journal of Pharmacy & Pharmaceutical Sciences	Published, peer-reviewed
	July 02, 2021	Vallejos	Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebocontrolled trial	BMC infectious Diseases	Published online
	June 02, 2021b	Abd-Elsalam	Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: A randomized controlled study DOI: 10.1002/jmv.27122	Journal of Medical Virology	Published online
	May 26th, 2021	Samaha	Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon	Viruses	Published
	May 25, 2021	Krolewiecki	Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial	EClinicalMedicine	Published
	May 13, 2021	Mahmud	Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial (also reported under 'doxycycline')	Journal of International Medical Research	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	6 May 2021	Shahbaznejad	Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-Blind, Randomized, Controlled Clinical Trial	Clinical Therapeutics	In press, corrected proof
	May 4, 2021	Okumuş	Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients	BMC Infectious Diseases	Published
	March 4, 2021	López-Medina	Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial.	JAMA	Published
	February 18, 2021	Babalola	Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos.	Published by Oxford University Press on behalf of the Association of Physicians	Published
	January 19, 2021	Chaccour	The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial	E Clinical Medicine	Published
	December 02, 2020	Ahmed	A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness	International journal of infectious diseases	Published
13. Interferon					
13.1. Inhaled IFN-k plus TFF2 (= Interferon kappa + Trefoil factor 2)					
	September 20, 2020	Fu	An open-label, randomized trial of the combination of IFN-k plus TFF2 with standard care in the treatment of patients with moderate COVID-19	EClinicalMedicine	Published
13.2. Inhaled Interferon β-1b					
	November 09, 2020	Khamis	Randomized Controlled Open Label Trial on the Use of Favipiravir Combined with Inhaled Interferon beta-1b in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia (also reported under 'Favipiravir')	International Journal of Infectious Diseases	Published
13.3. Interferon α-2b					

Medication/treatment	Published	1st author	Title	Journal	Status
	March 5, 2021	Pandit	Efficacy and Safety of Pegylated Interferon alfa-2b in Moderate COVID-19: A phase II, randomized, controlled, open-label study	International Journal of Infectious Diseases	Journal pre-proof
13.4. Interferon β-1a					
	October 18, 2021	Kalil	Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-blind, randomised, placebo-controlled, phase 3 trial	The Lancet	Published online
	May 9, 2021	Ader	An open-label randomized, controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19 <i>(also reported under 'Lopinavir and ritonavir' and 'Interferon β-1a')</i>	Clinical Microbiology and Infection	Published-Pre-proof version
	April 13, 2021	Alavi Darazam	Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial	Nature	Published
	December 02, 2020	Pan (WHO Solidarity Trial Consortium)	Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results <i>(also reported under 'remdesivir', 'hydroxychloroquine' and 'lopinavir and ritonavir')</i>	New England Journal of Medicine	Published
	November 12, 2020	Monk	Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial	The Lancet	Published
	August 20, 2020	Davoudi-Monfared	A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19	Antimicrobial Agents and Chemotherapy	Published
	July 14, 2020	Huang	No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon- Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon- Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective <i>(also reported under 'ribavirine' and 'lopinavir and ritonavir')</i>	Frontiers in Pharmacology	Published
13.5. Interferon β-1b					
	April 13, 2021	Alavi Darazam	Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial	Nature	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	August 24, 2020	Rahmani	Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial	International Immunopharmacology	Published
	May 08, 2020	Hung	Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial (also reported under 'ribavirine')	The Lancet	Published
13.6. Peginterferon Lambda					
	February 5, 2021	Feld	Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial	The Lancet	Published
13.7. Peginterferon Lambda-1a					
	March 30, 2021	Jagannathan	Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial	Nature Communications	Published
13.8. Pegylated Interferon-2b					
	August 19, 2021	Bhushan	Efficacy and Safety of Pegylated Interferon-2b in Moderate COVID-19: A phase 3, randomized, comparator-controlled, open-label study	International Journal of Infectious Diseases	Journal Pre-proof
14. JAK-inhibitors					
14.1. Baricitinib (selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)					
	February 03, 2022	Ely	Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial	The Lancet Respiratory Medicine	Published
	September 1, 2021	Marconi	Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial	The Lancet Respiratory Medicine	
	December 11, 2020	Kalil, 2020	Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19	The England Journal of Medicine	
14.2. Fedratinib					
NA	NA	NA	NA	NA	NA

Medication/treatment	Published	1st author	Title	Journal	Status
14.3. Filgotinib					
NA	NA	NA	NA	NA	NA
14.4. Nezulcitinib					
NA	NA	NA	NA	NA	NA
14.5. Oclacitinib					
NA	NA	NA	NA	NA	NA
14.6. Peficitinib					
NA	NA	NA	NA	NA	NA
14.7. Ruxolitinib (Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)					
	March 29, 2022	Han	Ruxolitinib in addition to standard of care for the treatment of patients admitted to hospital with COVID-19 (RUXCOVID): a randomised, double-blind, placebo-controlled, phase 3 trial	The Lancet	Published
	May 26, 2020b	Cao	Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial	Journal of Allergy and Clinical Immunology	Published
14.8. Tofacitinib					
	December, 2021	Murugesan	An Evaluation of Efficacy and Safety of Tofacitinib, A JAK Inhibitor in the Management of Hospitalized Patients with Mild to Moderate COVID-19 - An Open-Label Randomized Controlled Study	Journal of The Association of Physicians of India	Published
	16 June, 2021	Guimarães	Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia	The New England Journal of Medicine	Published online
14.9. Upadacitinib					
NA	NA	NA	NA	NA	NA
15. IL1-remmers					
15.1. Anakinra (humane interleukine-1-receptorantagonist)					

Medication/treatment	Published	1st author	Title	Journal	Status
	October 29, 2021	Declercq	Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial (also reported under 'Siltuximab' and 'Tocilizumab')	The Lancet Respiratory Medicine	
	October 25, 2021	Kharazmi	A randomized controlled clinical trial on efficacy and safety on anakinra in patients with severe COVID-19	Immunity, Inflammation and Disease	
	September 3, 2021	Kyriazopoulou	Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial	Nature Medicine	
	January 22, 2021	Mariette	Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial	The Lancet Respiratory Medicine	
15.2. Canakinumab					
	July 20th, 2021	Caricchio	Effect of Canakinumab vs Placebo on Survival Without Invasive Mechanical Ventilation in Patients Hospitalized With Severe COVID-19: A Randomized Clinical Trial	JAMA	
16. IL6-remmers					
16.1. Clazakisumab					
NA	NA	NA	NA	NA	NA
16.2. Levilimab (Monoclonal antibody- IL-6 inhibitor-BCD-089; IIsira)					
	September 29, 2021	Lomakin	The efficacy and safety of levilimab in severely ill COVID-19 patients not requiring mechanical ventilation: results of a multicenter randomized double-blind placebo-controlled phase III CORONA clinical study	Inflammation Research	Epub ahead of print
16.3. Olokizumab					
NA	NA	NA	NA	NA	NA
16.4. Sarilumab (human monoclonal antibody; against the interleukin-6 receptor; sold under the brand name Kevzara)					
	February 23, 2022	García-Vicuña	Subcutaneous IL-6 Inhibitor Sarilumab vs. Standard Care in Hospitalized Patients With Moderate-To-Severe COVID-19: An Open Label Randomized Clinical Trial	Frontiers in Medicine	Published
	February 10, 2022	Sivapalasingam	Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19: A Randomized Clinical Trial	Clinical Infectious Diseases	Published
	December 13, 2021	Merchante	Early Use of Sarilumab in Patients Hospitalised with COVID-19 Pneumonia and Features of Systemic Inflammation	Antimicrobial Agents and Chemotherapy	Published

Medication/treatment	Published	1st author	Title	Journal	Status
	November 17, 2021	CORIMUNO-19 Collaborative Group	Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial	The Lancet Rheumatology	
	September 27, 2021	Sancho-López	Efficacy and Safety of Sarilumab in patients with COVID19 Pneumonia: A Randomized, Phase III Clinical Trial (SARTRE Study)	Infectious Diseases and Therapy	
	March 4, 2021	Lescure	Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial	The Lancet Respiratory Medicine	
	February 25, 2021	The REMAP-CAP Investigators	Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 DOI: 10.1056/NEJMoa2100433 <i>(also reported under 'Tocilizumab')</i>	The new england journal of medicine	
16.5. Siltuximab					
	October 29, 2021	Declercq	Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial <i>(also reported under 'Anakinra' and 'Tocilizumab')</i>	The Lancet Respiratory Medicine	
16.6. Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor)					
	May, 2022	Rosas	Tocilizumab in patients hospitalised with COVID-19 pneumonia: Efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA)	The Lancet	Published online
	March 04, 2022	Broman	Early administration of tocilizumab in hospitalized COVID-19 patients with elevated inflammatory markers; COVIDSTORM – a prospective, randomized, single center, open label study	Clinical Microbiology and Infection	Published
	February 04, 2022	Hermine	Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: two Randomised Controlled Trials of the CORIMUNO-19 Collaborative Group	European Respiratory Journal	Early view
	October 29, 2021	Declercq	Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial <i>(also reported under 'Anakinra' and 'Siltuximab')</i>	The Lancet Respiratory Medicine	
	October 5, 2021b	Rosas	Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial	Intensive Care Medicine	
	May 01, 2021a	Horby (Recovery Collaborative Group)	Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial	The Lancet	
	March 09, 2021	Wang	Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial	Frontiers of Medicine	

Medication/treatment	Published	1st author	Title	Journal	Status
	March 04, 2021	Soin	Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial	The Lancet Respiratory Medicine	
	February 25, 2021a	Rosas	Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia	New England Journal of Medicine	
	February 25, 2021	The REMAP-CAP Investigators	Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 DOI: 10.1056/NEJMoa2100433 <i>(also reported under 'Sarilumab')</i>	The new england journal of medicine	
	January 20, 2021	Veiga	Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial	British Medical Journal	
	December 17, 2020	Salama	Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia	The New England Journal of Medicine	
	October 21, 2020	Stone	Efficacy of Tocilizumab in Patients Hospitalized with Covid-19	The New England Journal of Medicine	
	October 20, 2020	Salvarani	Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia - A Randomized Clinical Trial	JAMA Internal Medicine	
	October 20, 2020	Hermine	Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial	Journal of the American Medical Association	
17. Other immunomodulators					
17.1. Auxora (potent and selective small molecule inhibitor of calcium release-activated calcium (CRAC) channels)					
	April 08, 2022	Bruen	Auxora vs. placebo for the treatment of patients with severe COVID-19 pneumonia: a randomized-controlled clinical trial	Critical Care	Published
	August 14, 2020	Miller	Auxora versus standard of care for the treatment of severe or critical COVID-19 pneumonia: results from a randomized controlled trial	Critical Care	Published
17.2. Colchicine (anti-inflammatory and analgesic medication)					
	March, 2022	Dorward	Colchicine for COVID-19 in the community: a randomised, controlled, adaptive platform trial	British Journal of General Practice	Epub ahead of print

Medication/treatment	Published	1st author	Title	Journal	Status
	April 10, 2022	Gorial	A Randomized Controlled Trial of Colchicine add on to the Standard Therapy in Moderate and Severe Corona Virus Disease-19 Infection	Annals of Medicine & Surgery	Published (journal pre-proof)
	February 02, 2022	Pourdowlat	Efficacy and safety of colchicine treatment in patients with COVID-19: A prospective, multicenter, randomized clinical trial	Phytotherapy Research	Published
	December 29, 2021	Diaz	Effect of Colchicine vs Usual Care Alone on Intubation and 28-Day Mortality in Patients Hospitalized With COVID-19 A Randomized Clinical Trial	JAMA Network Open	Published
	November 9, 2021	Absalón-Aguilar	Colchicine Is Safe Though Ineffective in the Treatment of Severe COVID-19: a Randomized Clinical Trial (COLCHIVID)	Journal of General Internal Medicine	Epub ahead of print
	October 18, 2021	RECOVERY Collaborative Group	Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial	The Lancet Respiratory Medicine	Epub ahead of print
	September 11, 2021	Pascual-Figal	Colchicine in Recently Hospitalized Patients with COVID-19: A Randomized Controlled Trial (COL-COVID)	International Journal of General Medicine	Published
	May 27, 2021	Tardif	Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial	The Lancet Respiratory Medicine	Epub ahead of print
	January 18, 2021	Lopes	Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial	RMD Open	Published
	June 24, 2020	Deftereos	Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019 The GRECCO-19 Randomized Clinical Trial	Jama Network	Peer-reviewed (published)
17.3. Fostamatinib					
	NA	NA	NA	NA	NA
17.4. Imatinib					
	17 June 2021	Aman	Imatinib in patients with severe COVID-19: a randomized, double-blind, placebo-controlled, clinical trial	Lancet Respir Med	Published online
17.5. Leflunomide (immunosuppressive disease-modifying antirheumatic drug, DMARD)					
	02 July 2021	Wang	Efficacy and Safety of Leflunomide for Refractory COVID-19: A Pilot Study	Frontiers in Pharmacology	Published online

Medication/treatment	Published	1st author	Title	Journal	Status
	September 21, 2020b	Wang	Treatment of COVID-19 Patients with Prolonged Post-Symptomatic Viral Shedding with Leflunomide – a Single-Center, Randomized, Controlled Clinical Trial	Clinical Infectious Diseases	Accepted Manuscript
17.6. Mycobacterium W					
	April 12, 2021	Sehgal	A randomised trial of Mycobacterium w in critically ill patients with COVID-19: ARMY-1	ERJ open research	Published online
17.7. Tractolimus					
	June 14, 2021	Solanich	Methylprednisolone Pulses Plus Tacrolimus in Addition to Standard of Care vs. Standard of Care Alone in Patients With Severe COVID-19. A Randomized Controlled Trial. <i>(also reported under 'methylprednisolone')</i>	Frontiers in Medicine	Published
18. SSRI					
18.1. Fluvoxamine					
	March 03, 2022	Seo	Fluvoxamine Treatment of Patients with Symptomatic COVID-19 in a Community Treatment Center: A Preliminary Result of Randomized Controlled Trial	Infection & Chemotherapy	Published

Studieresultaten Medicamenteuze behandeling COVID-19

Deze tabel vat de resultaten van studies naar medicamenteuze behandeling bij COVID-19 samen. De studies staan gerangschikt op middel en datum van publicatie. De literatuur wordt dagelijks bekeken en zo nodig wordt de tabel aangevuld. De kwaliteit van deze studies is beoordeeld, zie tabel 'Studiekwaliteit Medicamenteuze behandeling COVID-19'.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
1. Remdesivir							
Pan, 2022 <i>(Final results of the WHO Solidarity trial. See also Pan, 2020 for more detailed information)</i>	<p><u>Type of study:</u> RCT (open-label, non-blinded)</p> <p><u>Setting & country:</u> 405 hospitals in 30 countries; WHO Solidarity Trial</p> <p><u>Source of funding:</u> Funded by the World Health Organization;</p> <p>ISRCTN Registry nr, ISRCTN83971151; ClinicalTrials.gov nr, NCT04315948.)</p>	<p>Hospitalized COVID-19 patients with moderate-to-severe disease</p> <p><i>(See Pan, 2020)</i></p> <p><u>Remdesivir</u> <u>N total at baseline:</u> N = 8320 Intervention: N=4146 Control: N=4129</p> <p><u>Important characteristics:</u> <u>Age, n/N (%):</u> I: <50y: 1310/4146 (31.6%) 50-69y: 1920/4146 (46.3%) ≥70y: 916/4146 (22.1%) C: <50y: 1326/4129 (32.1%) 50-69y: 1908/4129 (46.2%) ≥70y: 895/4129 (21.7%)</p> <p><u>Sex, n/N (%) male:</u> I: 2601/4146 (62.7%) C: 2639/4129 (63.9%)</p> <p>Disease severity <u>Respiratory support</u> I: No suppl. Oxygen at entry: 896/4146 (21.6%) Suppl. Oxygen at entry 2918/4146 (70.4%) Already receiving ventilation 359/4146 (8.7%)</p>	<p>Remdesivir</p> <p>Intravenous; 200 mg on day 0 and 100 mg on days 1 through 9.</p>	<p>Standard of care</p>	<p><u>Length of follow up:</u> 28 days, or up to discharge</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: Died in hospital 602/4146 (14.5%), Consent to FU withdrawn 51/4146 (1.2%), Not yet reported on, FU censored at day 28 23/4146 (0.6%)</p> <p>Control: Died in hospital 643/4129 (15.6%), Consent to FU withdrawn 50/4129 (1.2%) Not yet reported on, FU censored at day 28 24/4129 (0.6%)</p>	<p><u>Clinical outcomes</u> <u>In-hospital mortality, n/N%</u> I: 602/4146 (14.5%) C: 643/4129 (15.6%) RR: 0.91 (95% CI 0.82-1.02), p=0.12</p> <p><u>Duration of hospitalization</u> Time-to-discharge is depicted in figure 4. ("Solidarity randomly allocated 8275 patients to remdesivir or open control, and has reliably shown that allocation of patients to open-label remdesivir infusions did not reduce time-to-discharge")</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Progression to ventilation, n/N (%)</u> I: 535/3787 (14.1%) C: 593/3782 (15.7%) RR: 0.88 (95% CI 0.77-1.00), p=0.04</p> <p><u>Safety</u> <u>Serious adverse events</u></p>	<p>Primary outcome: • In-hospital mortality, subdivided by disease severity</p> <p>Secondary outcome(s): • Progression to ventilation if not already ventilated • Time-to-discharge from hospital</p> <p><u>Definitions</u></p> <p><u>Remarks:</u> Lopinavir, hydroxychloroquine, and interferon (IFN)-β1a were discontinued for futility but randomisation to remdesivir continued.</p> <p><u>Authors conclusion:</u> Remdesivir has no significant effect on patients with COVID-19 who are already being ventilated. Among other hospitalised patients, it has a small effect against death or progression to ventilation (or both).</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: No suppl. Oxygen at entry: 861/4129 (20.9%) Suppl. Oxygen at entry 2921/4129 (70.7%) Already receiving ventilation 347/4129 (8.4%)</p> <p>Groups comparable at baseline</p>				<p>Not reported.</p> <p><u>Adverse events</u> Not reported.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Abd-Elsalam, 2021a	<p><u>Type of study:</u> Multicenter, randomized, controlled, open-label parallel study.</p> <p><u>Setting:</u> Two major hospitals.</p> <p><u>Country:</u> Egypt.</p> <p><u>Source of funding:</u> Not reported.</p> <p><u>Conflicts of interest:</u> Not reported.</p>	<p><u>Hospitalized with mild or moderate COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with mild or moderate symptoms; • Patients aged 18 to 80 years. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with history of renal impairment; • Patients with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels > 5 times the upper limit or normal; • Patients who had allergy or contraindication to remdesivir; • Pregnant or lactating mothers. <p><u>N total at baseline:</u> N = 209 Intervention: N = 105 Control: N = 104</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 55.04 y (14.15) C: 52.02 y (16.25) P=0.164</p> <p>Sex, n/N (%) male: I: 66/100 (66.0%)</p>	<p>Remdesivir</p> <p>Remdesivir 200 mg in the first day followed by 100 mg daily for the next 9 days (10-day course) intravenously infused over 30 to 60 minutes in addition to the standard care.</p>	<p>Control</p> <p>Standard of care alone.</p>	<p><u>Length of follow-up:</u> Unclear.</p> <p><u>Loss-to-follow-up:</u> Intervention: N = 5 Reasons: transferred to another hospital.</p> <p>Control: N = 4 Reasons: transferred to another hospital.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p>Clinical outcomes <u>Mortality*</u>, defined as fate, n/N (%)</p> <p><u>Died</u> I: 9/100 (9.0%) C: 7/100 (7.0%)</p> <p><u>Survived</u> I: 91/100 (91.0%) C: 93/100 (93.0%) P=0.602</p> <p><u>Duration of hospital stay in days, mean (SD)</u> I: 12.37 (8.96) days. C: 16.72 (5.78) days. P<0.001</p> <p><u>Duration of hospital stay in days, median (IQR)</u> I: 10 (8.0 to 13.75) days. C: 16 (12.0 to 21.0) days.</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> <u>Need for mechanical ventilation, n/N (%)</u> I: 11/100 (11.0%) C: 8/100 (8.0%) P=0.469</p>	<p><u>Definitions:</u> Standard of care: The standard care was composed of zinc, acetyl cysteine, lactoferrin, and vitamin C. Paracetamol and a prophylactic anticoagulant were prescribed when indicated.</p> <p><u>Remarks:</u> *The study also reported univariate and multivariate logistic regression of the possible risk of the patients' mortality for multiple risk factors (see table 3 and 4 of the study).</p> <p><u>Authors conclusion:</u> In conclusion, remdesivir had a positive influence on length of hospital stay with no mortality benefit in Egyptian patients with COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: 53/100 (53.0%) P=0.06</p> <p>Disease severity: <i>Not reported.</i></p> <p>Groups comparable at baseline? Yes.</p>				<p>Safety <u>Serious adverse events</u> I: 0/100 (0%) C: 0/100 (0%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Ader, 2021	<p><u>Type of study:</u> phase 3, open-label, adaptive, multicentre, randomised, controlled trial</p> <p><u>Setting:</u> 48 sites in Europe, Between March 22, 2020, and Jan 21, 2021</p> <p><u>Country:</u> France, Belgium, Austria, Portugal, Luxembourg</p> <p><u>Source of funding:</u> European Union's Horizon 2020 research and innovation programme (Europe); Austrian Group Medical Tumor (Austria); Belgian Health Care Knowledge Centre (Belgium); Fonds Erasme-COVID-Université Libre de</p>	<p>Hospitalized patients with confirmed SARS-CoV-2</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age ≥ 18 years, clinical assessment (evidence of rales or crackles on examination) oxygen saturation (SpO2) of 94% or less on room air; or requirement of supplemental oxygen, high-flow oxygen devices, non-invasive ventilation, or mechanical ventilation <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> liver enzymes (alanine aminotransferase or aspartate aminotransferase) more than five times the upper limit of normal a stage 4 severe chronic kidney disease or requiring dialysis (estimated glomerular filtration rate less than 30 mL/min), if a transfer within 72 h to another hospital that was not a study site was anticipated. pregnant or breastfeeding, contraindication to any study medication including allergy 	Remdesivir was administered intravenously at a loading dose of 200 mg on day 1 followed by a 100 mg, 1-h infusion once-daily for a total duration of 10 days	standards of care	<p><u>Length of follow-up:</u> 29 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention: N = 0</p> <p>Control: N = 0</p>	<p>Clinical outcomes</p> <p>Death within 28 days I: 34 (8%) C: 37 (9%) OR 0.93 (95% CI: 0.57 to 1.52); p=0.77</p> <p>7-point ordinal scale at day 15 (Primary Outcome) OR 0.98 (95% CI: 0.77 to 1.25); p=0.85</p> <p>7-point ordinal scale at day 29 OR 1.11 (95% CI: 0.87 to 1.42); p=0.39</p> <p>Duration of hospitalisation <u>Days to hospital discharge within 29 days</u> I: 15 (10 to 29) C: 13 (8 to 29) HR 0.94 (95% CI: 0.80 to 1.11); p=0.49</p> <p><u>New mechanical ventilation, ECMO, or death within 29 days*</u> I: 60/339 (18%) C: 87/344 (25%)</p>	<p><u>Definitions:</u> WHO Master Protocol:(1) not hospitalised, no limitation on activities; (2) not hospitalised, limitation on activities; (3) hospitalised, not requiring supplemental oxygen; (4) hospitalised, requiring supplemental oxygen; (5) hospitalised, on non-invasive ventilation or high flow oxygen devices; (6) hospitalised, on invasive mechanical ventilation or ECMO; and (7) dead.</p> <p><u>Remarks:</u> It was open-label and not placebo-controlled. Indeed, several treatments were concomitantly evaluated at the beginning of the trial, and masking was thus impossible due to the different modes of administration (intravenous, subcutaneous, or oral) of the different treatment groups.</p> <p><u>Authors conclusion:</u> In this randomised controlled trial, the use of remdesivir for the treatment of hospitalised patients with COVID-19 was not associated with clinical improvement at day 15 or day 29, nor with a reduction in mortality, nor with a reduction in SARS-CoV-2 RNA.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Bruxelles (Belgium); REACTing, a French multi-disciplinary collaborative network working on emerging infectious diseases (France); Ministry of Health (France); Domaine d'intérêt majeur One Health Île-de-France (France); European Regional Development Fund (Luxembourg); Ministry of Health (Portugal); Agency for Clinical Research and Biomedical Innovation (Portugal). We thank all participants who consented to enrol in the trial, as well as all study and site staff whose indispensable assistance made the conduct of the DisCoVeRy trial possible (all listed in the appendix 2 pp 35–47).</p> <p><u>Conflicts of interest:</u></p>	<ul style="list-style-type: none"> treated with one of the evaluated antiviral drugs in the past 29 days used ribavirin either in the past 29 days or concomitantly to random assignment <p><u>N total at baseline:</u> Total:= 857 Intervention: = 429 Control: N = 428</p> <p><u>ITT population:</u> I: 414 C: 418</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 63 (55–73) C: 64 (54–72)</p> <p>Sex, n/N (%) male: I: 291/414 (70%) C: 288/418 (69%)</p> <p><u>7-point ordinal scale at baseline:</u> 3: hospitalised, not requiring supplemental oxygen: I:8 (2%) C: 8 (2%) 4: hospitalised, requiring supplemental oxygen I: 241 (58%) C: 244 (58%) 5: hospitalised, on non-invasive ventilation or high flow oxygen devices I: 90 (22%) C: 93 (22%) 6: hospitalised, on invasive mechanical ventilation or ECMO I: 75 (18%) C: 73 (18%)</p> <p>Groups were comparable at baseline.</p>				<p>HR 0.66 (95% CI: 0.47 to 0.91); p=0.010</p> <p><u>Time to symptom resolution</u></p> <p><u>Respiratory support</u> <u>Oxygenation-free days until day 29</u> I: 17 (2 to 22) C: 17 (0 to 23) Least-square mean difference (LSMD) 0.35 (–0.90 to 1.60); p=0.59</p> <p><u>Ventilator-free days until day 29</u> I: 29 (20 to 29) C: 29 (16 to 29) LSMD 1.08 (–0.15 to 2.30); p=0.080</p> <p><u>Safety</u> <u>Any Serious adverse events</u> I: 135 (33%) C: 130 (31%) OR 1.11 (0.83–1.50); p=0.48</p> <p><u>Any adverse events</u> I: 241 (59%) C: 236 (57%) OR 1.14 (0.86–1.50); p=0.37</p> <p><u>Virological outcomes</u> The median decrease in viral loads between baseline and day 3 was similar in the remdesivir and control groups</p>	

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	DC reports grants and lecture fees from Janssen and lecture fees from Gilead, outside the submitted work.... Please refer to full text for the full conflicts of interest.					(appendix 2 pp 12–13). There was no significant effect of remdesivir on the viral kinetics (figure 3; appendix 2 pp 14, 29).	
Barratt-Due, 2021	<p><u>Type of study:</u> Independent, add-on RCT to WHO Solidarity trial, an open-label, adaptive RCT</p> <p><u>Setting:</u> 23 hospitals, between 28 March and 5 October 2020</p> <p><u>Country:</u> Norway</p> <p><u>Source of funding:</u> National Clinical Therapy Research, no role in RCT</p> <p><u>Conflicts of interest:</u> JTA reports grant from South-Eastern Norway Regional Health Authority. ABD reports paid lecture by Allergan Norden AB and participation in</p>	<p>Hospitalized patients with confirmed SARS-CoV-2 infection</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ≥18 years • SARS-CoV-2 confirmed by PCR • Hospitalized (ward or intensive care) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Severe comorbid conditions with life expectancy <3 months • Aspartate aminotransferase or alanine aminotransferase levels >5x normal upper limit • Rate-corrected QT interval > 470 ms • Pregnancy or breastfeeding • Acute occurrence comorbid condition >7 days before inclusion • Known intolerance to study drugs • Participation confounding trial • Concomitant medications interfering with study drugs <p><u>N total at baseline:</u> N = 181 Remdesivir: n=42 Hydroxychloroquine: n=52 Control remdesivir: n=57</p>	<p>R: standard of care plus 200 mg intravenous remdesivir on day 1, 100 mg daily up to day 9</p> <p>H: standard of care plus 800 mg oral hydroxychloroquine 2x day on day 1, 400 mg 2x day up to day 9</p> <p>All study treatment were discontinued at discharge.</p>	Standard of care according to WHO guidelines recommending systemic steroids	<p><u>Length of follow-up:</u> 3 months</p> <p><u>Loss-to-follow-up:</u> R: 9 (21%) - n=1: no post-randomization data - n=3: death - n=3: loss to follow-up - n=2: other CR: 9 (16%) - n=1: no post-randomization data - n=1: voluntary discontinuation - n=4: death - n=1: loss to follow-up - n=2: other H: 13 (24%) - n=2: no post-randomization data - n=5: voluntary discontinuation - n=4: death - n=1: loss to follow-up - n=1: other CH: 8 (15%)</p>	<p><u>Clinical outcomes</u> <u>Mortality (28 day)</u> R: 2.4 (0.1; 10.1) CR: 5.2 (1.3-13.1) RD: -2.9 (-10.3; 4.5) H: 7.5 (2.4; 16.7) CH: 1.8 (0.1; 7.6) RD: 5.8 (-2.2; 13.7) <u>Mortality (60 day)</u> R: 7.1 (1.8; 17.5) CR: 5.3 (1.3; 13.1) RD: 1.9 (-7.8; 11.6) H: 7.5 (2.4; 16.7) CH: 1.8 (0.1; 7.6) RD: 5.8 (-2.2; 13.7) <u>In-hospital mortality</u> R: 7.1 (1.8; 17.5) CR: 7.0 (2.2; 15.6) RR: 1.0 (0.2; 4.6) H: 7.5 (2.4; 16.7) CH: 3.6 (0.6; 10.6) RR: 2.2 (0.4; 10.8)</p> <p><u>Duration of hospitalization</u> Not reported <u>Admission to ICU during hospitalization</u> R: 19.0 (9.2; 32.6) CR: 19.3 (10.5; 30.8) RD: -0.3 (-15.9; 15.4) H: 22.6 (12.8; 35.0) CH: 16.1 (8.1; 27.1)</p>	<p><u>Definitions:</u> not applicable</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Randomization to remdesivir started on 7 April 2020. Hydroxychloroquine was removed on 8 June 2020. The trial was stopped on 5 October because of low mortality, potential adverse events and little effect of remdesivir. • 185 were randomly assigned, 4 excluded due of absence of post-randomization information • The groups are not well balanced, see table 1 • No blinding was performed • Some participants receiving SoC act as controls for both active treatment groups, whereas some act in one or the other, giving a partial overlap of the 2 control groups. <p><u>Authors conclusion:</u> The overall lack of effect of remdesivir and HCQ on the clinical course of patients hospitalized for COVID-19 was accompanied by a paucity of effect on SARS-CoV-2 viral clearance in the oropharynx. Our findings question the antiviral potential of these drugs in hospitalized patients with COVID-19.</p>

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	<p>advisory board meeting SANOFI-AVENTIS Norway. SGD reports grant from Research Council of Norway. FLJ reports funding from Oslo University Hospital and Helse SørØst. MT reports participation in European advisory board for Eli Lilly and coordinator of National reference group on COVID-19 treatment in Norway.</p>	<p>Control HSQ: n=54 (some controls were in both groups)</p> <p><u>Important characteristics:</u> Age, mean (SD): 59.8 (15.3) R: 59.7 y (16.5) CR: 58.1 y (15.7) H: 60.3 y (13.3) CH: 59.2 y (16.4)</p> <p>Sex, n/N (%) male: R: 29/42 (69%) CR: 43/57 (75%) H: 31/52 (60%) CH: 34/54 (63%)</p> <p>Disease severity, mean (SD): Defined by Viral load (log₁₀ count/1000 cells) R: 1.6 (1.6) CR: 2.3 (1.8) H: 2.3 (1.5) CH: 2.0 (1.5)</p> <p>Anti-SARS-CoV-2 antibodies, seroconverted (RDB ≥5) n/N (%) R: 14/42 (42.4%) CR: 18/57 (46.2%) H: 15/52 (42.9%) CH: 20/54 (54.1%)</p> <p>Groups are not comparable on baseline regarding sex, comorbid conditions, ICU admission, P-F ratio less than 40 kPa, ACE and ARB medication, LDH level, D-dimer level, AST level, ALT, level.</p>			<ul style="list-style-type: none"> - n=1: voluntary discontinuation - n=2: death - n=1: loss to follow-up - n=4: other <p><u>Incomplete outcome data:</u> Missing data due to discharge or participant withdrawal were imputed with best outcome. Not reported how many.</p>	<p>RD: 6.6 (-8.2; 21.4)</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> <u>Mechanical ventilation</u> R: 9.5 (3.1; 20.8) CR: 7.0 (2.2; 15.6) RD: 2.5 (-8.6; 13.6) H: 15.1 (7.2; 26.3) CH: 10.7 (4.4; 20.5) RD: 4.4 (-8.2; 17.0)</p> <p><u>Time to receipt mechanical ventilation</u> RR R vs CR: 1.4 (0.4; 5.8) RR H vs CH: 2.1 (0.7; 6.2)</p> <p><u>Duration of mechanical ventilation</u> Reported in appendix figure 1</p> <p>Safety <u>Adverse events n/N (%)</u> R: 34/42 (81%) H: 26/52 (50%) C: 33/87 (n=38%)</p> <p><u>Serious adverse events n/N (%)</u> R: 13/42 (31%) H: 12/52 (23%) C: 20/87 (n=23%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported <u>Viral load</u> Reported in a figure 2 and appendix figure 2 <i>Subgroup analysis based on symptom duration before hospitalization, the</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<i>presence of ARS-CoV-2 antibodies, high or low viral load at hospital admission, degree of inflammation, and age were performed.</i>	
Mahajan, 2021	<p>Type of study: RCT; not blinded</p> <p>Setting: June to December 2020;</p> <p>Country: India</p> <p>Source of funding: "Financial support and sponsorship Nil. Conflicts of interest There are no conflicts of interest."</p>	<p>Hospitalized COVID-19 patients with moderate-to-severe disease</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Hospitalised • 18-60 years of age • SARS-CoV-2 infection confirmed by PCR within the last 4 days • radiographic evidence of pneumonia, • respiratory rate >24/min • oxygen saturation ≤ 94% • creatinine clearance above 40 ml per minute <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • receiving mechanical ventilation • multi organ failure • Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 3x normal upper limit <p>N total at baseline: N = 82 Randomized: Intervention: 41 Control: 41 Included in analysis: Intervention: 34 (incl. 1 cross over) Control: 36</p> <p>Important characteristics: Age, mean (SD): I: 58.08±12.1</p>	<p>Remdesivir + standard of care</p> <p>IV 200 mg remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent four days</p>	<p>Standard of care</p> <p>supportive therapy throughout the duration of the study. Other drugs used for COVID treatment (off-label use and in the absence of written policy) were not allowed to be administered to the patients in the study period. Drugs like corticosteroids and heparin were given as per standard of care protocol.</p>	<p>Length of follow up: 12 days, or until discharge of death</p> <p>Loss to follow-up: I: 8/41 (19.5%) Reasons: 2 patients discharged, 1 patient died, 2 withheld treatment, 3 remdesivir C: 5/41 (12.2%) Reasons: 2 patients discharged, 2 patients died, 1 requested remdesivir treatment</p>	<p>Clinical outcomes</p> <p>Mortality Reported as 'death', score 6, on ordinal scale. Unclear at which moment in time (1 result for 12 to 24 days): Death I: 5 (14.7) C: 3 (8.3)</p> <p>Duration of hospitalization No data reported</p> <p>Symptom resolution Nausea, vomiting I: Baseline: 7 After treatment: 3 C: Baseline: 9 After treatment: 2</p> <p>Need for respiratory support Clinical status from day 12 to 24 Did not require hospitalisation* I: 2 (5.9) C: 3 (8.3) Hospitalised, but did not require supplemental oxygen I: 0 (0) C: 0 (0) Hospitalised, required supplemental oxygen</p>	<p>Definitions: <i>Clinical status day 1 – 12; assessed on 4-point ordinal scale:</i> 1), receiving low-flow oxygen supplementation; 2), receiving non-invasive ventilation or high-flow oxygen; 3), not receiving supplemental oxygen but requiring medical care; 4), receiving invasive mechanical ventilation</p> <p><i>Clinical status day 12 – 24; assessed on 6-point ordinal scale:</i> 1), Do not require hospitalisation, 2), hospitalised, but not requiring supplemental oxygen, 3), hospitalised, requiring supplemental oxygen; 4), Patients requiring high-flow oxygen or non-invasive ventilation; 5), Requiring or receiving mechanical ventilation; 6), Death</p> <p>Remarks:</p> <ul style="list-style-type: none"> • Concerns about study quality / risk of bias • High drop-out rate; 1 patient crossed-over to treatment group upon request • Unclear how results of clinical status are reported (1 result for ordinal status from day 12 to 24) <p>Authors conclusion:</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: 57.41±14.1 Sex, n/N (%) male: I: 13 (38.3) C: 9 (25.0) Duration of symptoms before involvement in trial (days); mean±SD I: 6.26±2.49 C: 7.38±0.99 Receiving low flow supplemental oxygen I: 27 (79.4) C: 26 (72.2) Receiving non-invasive ventilation or high-flow oxygen I: 7 (20.6) C: 10 (27.8) Receiving invasive mechanical ventilation I: 0 (0) C: 0 (0)</p> <p>Groups comparable at baseline? No, time from symptoms to enrolment longer in the control group, less patient in intervention group received non-invasive ventilation or high-flow oxygen in stead of low flow oxygen compared to the control group.</p>				<p>I: 4 (11.8) C: 6 (16.7) Required high-flow oxygen or non-invasive ventilation I: 19 (55.9) C: 22 (61.1) Required or received mechanical ventilation I: 4 (11.8) C: 2 (5.6) Death I: 5 (14.7) C: 3 (8.3)</p> <p><i>Also reported: AST levels, ALT levels and creatinine levels at baseline and after treatment</i></p> <p>Safety <u>Adverse events</u></p> <p>Virological outcomes <u>Viral clearance</u> not reported</p>	Remdesivir therapy for five days did not produce improvement in clinical outcomes in moderate to severe COVID-19 cases.
Pan, 2020	<p><u>Type of study:</u> RCT (open-label, non-blinded)</p> <p><u>Setting & country:</u> 405 hospitals in 30 countries; WHO Solidarity Trial</p> <p><u>Source of funding:</u> Funded by the World Health Organization;</p>	<p><u>N total at baseline:</u> N = 11,330</p> <p><i>Remdesivir arm</i> I: 2743 C: 2708</p> <p><u>Important characteristics:</u> <u>Age, n/N (%)</u> I: <50y: 961/2743 (35%) 50-69y: 1282/2743 (47%) ≥70y: 500/2743 (18%)</p>	<p>Remdesivir</p> <p>Intravenous; 200 mg on day 0 and 100 mg on days 1 through 9.</p> <p><u>Taking trial drug midway through scheduled duration*:</u> I: 96% C: 2%</p>	Standard of care	<p><u>Length of follow up:</u> 28 days, or up to discharge</p> <p><u>Loss to follow-up:</u> I: 7/2750 (0.3%) Reasons: no or unknown consent C: 17/2725 (0.6%) Reasons: no or unknown consent</p>	<p>Clinical outcomes</p> <p><u>All-cause in-hospital mortality, regardless of whether death occurred before or after day 28:</u> I: 301/2743 (12.5%) C: 303/2708 (12.7%) RR 0.98 (95% CI 0.84 to 1.14) HR=0.95 (95% CI 0.81-1.11)</p>	<p><u>Definitions/information:</u></p> <p><i>*Taking trial drug midway through scheduled duration, %, calculated only among patients who died or were discharged alive, % patients who were taking the trial drug midway through its scheduled duration (or midway through the time from entry to death or discharge, if this was shorter).</i></p> <p><i>**Adjusted model all-cause mortality: some overlap between the 4 control</i></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	ISRCTN Registry nr, ISRCTN83971151; ClinicalTrials.gov nr, NCT04315948.)	<p>C: <50y: 952/2708 (35%) 50-69y: 1287/2708 (48%) ≥70y: 469/2708 (17%) <u>Sex, n/N (%) male:</u> I: 1706/2743 (62%) C: 1725/2708 (64%) <u>Respiratory support</u> I: No suppl. Oxygen at entry: 661/2743 (24%) Suppl. Oxygen at entry 1828/2743 (67%) Already receiving ventilation 254/2743 (9%) C: No suppl. Oxygen at entry: 664/2708 (25%) Suppl. Oxygen at entry 1811/2708 (67%) Already receiving ventilation 233/2708 (9%) <u>Previous days in hospital</u> I: 0 days: 724/2743 (26%) 1 day: 917/2743 (33%) ≥2 days: 1102/2743 (40%) C: 0 days: 712/2708 (26%) 1 day: 938/2708 (35%) ≥2 days: 1058/2708 (39%)</p>	<p><u>Use of non-study drug, n/N (%)</u>: Corticosteroids I: 1310 (47.8%) C: 1288 (47.6%) Convalescent plasma I: 52 (1.9%) C: 58 (2.1%) Anti-IL-6 drug I: 133 (4.9%) C: 143 (5.3%) Non-trial interferon I: 3 (0.1%) C: 25 (0.9%) Non-trial antiviral I: 65 (2.4%) C: 152 (5.6%)</p>			<p>Adjusted** HR=0.95 (95% CI 0.81-1.11)</p> <p><u>All-cause in-hospital mortality, stratified by randomization:</u> Ventilated: HR 1.20 (95% CI 0.89-1.64) Not ventilated: HR 0.86 (95% CI 0.72-1.04)</p> <p><u>Initiation of mechanical ventilation, in those not receiving ventilation at baseline:</u> I: 295/2489 (11.6%) C: 284/2475 (11.5%) RR 1.03 (95% CI 0.89 to 1.20)</p> <p><u>Composite death or initiation ventilation:</u> I: 479/2743 (18.5%) C: 479/2708 (18.9%) RR 0.99 (95% CI 0.88 to 1.11) Publication: RR 0.97 [0.85-1.10]</p> <p><u>Hospitalized, not discharged:</u> <i>Percentage of patients (rather than number of patients) ever reported as discharged who were still in the hospital:</i> Day 7, % I: 69% C: 59% Day 14 I: 22% C: 19%</p>	<p>groups; an exploratory sensitivity analysis used multivariate Cox regression to fit all 4 treatment effects simultaneously; adjusted for several prognostic factors (age, sex, diabetes, bilateral lung lesions at entry (no, yes, not imaged at entry), and respiratory support at entry (no oxygen, oxygen but no ventilation, ventilation).</p> <p><u>Authors conclusion:</u> These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Day 21 I: 9% C: 8%	
Beigel, 2020	<p>Type of study: Double-blind, randomized placebo-controlled trial</p> <p>Setting + Country: There were 60 trial sites and 13 subsites in the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1).</p> <p>Source of funding: Funded by the National Institute of Allergy and Infectious Diseases and others; ACCT-1 ClinicalTrials.gov number, NCT04280705</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Male / non-pregnant female Age ≥18y Diagnostic specimen positive for SARS-CoV-2 on RT-PCR [more detailed information can be found in the supplementary file] <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Allergy to product Anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrolment. [more detailed information can be found in the supplementary file] <p>N total at baseline: N = 1062 Intervention: 541 Control: 521</p> <p>Important characteristics:</p> <p>Intervention group: Age (mean (SD)): 58.6 (14.6) Male: 352 (65.1%)</p> <p>Control group: Age (mean (SD)): 59.2 (15.4) Male: 332 (63.3%) Groups comparable at baseline.</p>	Remdesivir: intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death	Placebo: Matching placebo was administered according to the same schedule and in the same volume as the active drug.	28 days	<p>Remdesivir versus control</p> <p>Median recovery time: Remdesivir: 10 days (95% CI 9 – 11) Placebo: 15 days (95% CI 13 – 18)</p> <p>Recovery HR for recovery: 1.29; 95% CI, 1.12 to 1.49; P<0.001).</p> <p>Mortality by 14 days Remdesivir: 6.7% Placebo 11.9% HR for death: 0.55; 95% CI, 0.36 to 0.83)</p> <p>Serious adverse events Remdesivir: 24.6% Placebo: 31.6%</p>	<p>Comments: /</p> <p>Authors conclusion: Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.</p>
Spinner, 2020	<p>Type of study: Randomized open-label multicentre clinical trial</p>	<p>Inclusion criteria: Willing and able to provide written informed consent; aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing</p>	I1: Remdesivir for 10 days. 73 (38%) patients completed the assigned treatment duration; the median number of doses	Standard care (not specified)	28 days (in person for hospitalized patients or by phone for discharged patients)	<p>Difference in clinical status distribution versus standard care (OR (95%CI)) I1: not reported * P=0.18</p>	<p>Remarks: Patients who had sufficiently improved in the judgment of the investigator could be discharged from</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> 105 hospitals</p> <p><u>Country:</u> US, Europe and Asia</p> <p><u>Source of funding:</u> Gilead Sciences, which designed and conducted the study in consultation with the FDA and the investigators.</p>	<p>≥ 40 kg; SARS-CoV-2 infection confirmed by PCR ≤ 4 days before randomization; currently hospitalized; SpO2 > 94% on room air at screening; radiographic pulmonary infiltrates; men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception.</p> <p><u>Exclusion criteria:</u> Participation in any other clinical trial of an experimental agent treatment for COVID-19; concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing; Requiring mechanical ventilation at screening; ALT or AST > 5 x ULN; creatinine clearance < 50 mL/min, pregnant or breastfeeding woman; known hypersensitivity to the study drug, the metabolites, or formulation excipient.</p> <p><u>N total at baseline:</u> N = 596 Intervention1: 197* Intervention2: 199* Control: 200*</p> <p>Of which respectively 193 (I1), 191 (I2) and 200 (C) patients were included in primary analysis.</p>	<p>for the group was 6 (range, 1-10). Reasons were hospital discharge (n=98), withdrawal (n=8) or adverse events (n=6).</p> <p>I2: Remdesivir for 5 days. 145 (76%) patients completed the assigned treatment duration (median, 5 doses; range, 1-5). Reasons were hospital discharge (n=35), withdrawal (n=5) or adverse events (n=4).</p> <p>Remdesivir was dosed intravenously (30-60 minutes) at 200 mg on day 1 followed by 100 mg/d.</p> <p>Remdesivir treatment was to be discontinued in any patient experiencing severe elevations in liver enzymes or decreases in estimated creatinine clearance to less than 30 mL/min.</p>			<p>I2: 1.65 (1.09 to 2.48) P=0.02 *The proportional odds assumption was not met.</p> <p><u>Clinical improvement day 11 (n/N, %)**</u> I1: 126/193 (65) I2: 134/191 (70) C: 121/200 (61) Difference I1-C (95%CI): 4.8 (-5.0 to 14.4) Difference I2-C (95%CI): 9.7 (0.1 to 19.1) <u>Clinical improvement day 28 (n/N, %)**</u> I1: 174/193 (90) I2: 171/191 (90) C: 166/200 (83) Difference I1-C: not reported Difference I2-C: not reported **Defined as ≥2-point improvement from baseline on the 7-point ordinal scale.</p> <p><u>Recovery at day 11 (n/N, %)**</u> I1: 132 (68) I2: 141 (74) C: 128 (64) Difference I1-C (95%CI): 4.4 (-5.0 to 13.8) Difference I2-C (95%CI): 9.8 (0.3 to 19.0)</p> <p><u>Recovery at day 28 (n/N, %)**</u> I1: 178 (92) I2: 175 (92) C: 170 (85)</p>	<p>the hospital before finishing their assigned course of treatment.</p> <p>Data on clinical improvement and recovery are also reported for other days. Furthermore, data on other exploratory outcome measures and details on adverse events were reported, but data is not shown here.</p> <p>Peaks in discharge rates were observed in the remdesivir groups following the end of their assigned duration of treatment (i.e., there were increased rates of discharge on day 6 in the 5-day remdesivir group and on day 11 in the 10-day group), suggesting that discharges were delayed for some patients to allow them to complete full courses of assigned remdesivir treatment.</p> <p>Original protocol was amended on the basis of emerging understanding of the clinical presentation and assessment of COVID-19.</p> <p><u>Authors conclusion:</u> Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>Important characteristics:</u> Age, median (IQR): I1: 56 (45-66) I2: 58 (48-66) C: 57 (45-66) P=not reported Sex, n/N (%) male: I1: 118/193 (61) I2: 114/191 (60) C: 125/200 (63) P=not reported</p> <p>Groups comparable at baseline? Patients in standard care group were more commonly prescribed with other COVID-19 agents.</p>				<p>Difference I1-C: not reported Difference I2-C: not reported ***Defined as improvement from a baseline score of 2-5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7, on the 7-point ordinal scale.</p> <p><u>All-cause mortality at day 28 (n/N, %)</u> I1: 3/193 (2) I2: 2/191 (1) C: 4/200 (2) HR (95%CI) I1 vs C: 0.76 (0.17 to 3.40) HR (95%CI) I2 vs C: 0.51 (0.09 to 2.80)</p> <p><u>Adverse events (n/N, %)</u> Any adverse event I1: 113/193 (59) I2: 98/191 (51) C: 93/200 (47) Any serious adverse event I1: 10/193 (5) I2: 9/191 (5) C: 18/200 (9)</p> <p>There were no significant differences between the remdesivir and standard care groups in duration of oxygen therapy or hospitalization (data not reported).</p>	
Wang, 2020a	<u>Type of study:</u> Randomised, double-blind,	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Men and non-pregnant women with COVID-19 Aged at least 18 years 	Remdesivir <i>Treatment regimens</i>	Placebo <i>Treatment regimens</i>	<u>Follow-up period:</u> 28 days	<p>Primary clinical endpoint <u>Clinical improvement</u> Defined as a 2-point reduction in patients'</p>	<p><u>Remarks:</u> - number of patients needed according to power calculation was not reached, because no patients were enrolled after</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>placebo-controlled, multicentre trial</p> <p><u>Setting:</u> 10 hospitals in Wuhan, Hubei, between Feb 6 and March 12, 2020</p> <p><u>Country:</u> China</p> <p><u>Source of funding:</u> Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project</p> <p><u>Conflicts of interest:</u> One author has served as non-compensated consultant to Gilead Sciences on its respiratory antiviral program, outside the submitted work. All other authors declare no competing interests.</p>	<ul style="list-style-type: none"> RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less within 12 days of symptom onset <p>Eligible patients of child-bearing age (men and women) agreed to take effective contraceptive measures (including hormonal contraception, barrier methods, or abstinence) during the study period and for at least 7 days after the last study drug administration</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1.73 m²) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; enrolment into an investigational treatment study for COVID-19 in the 30 days before screening 	Intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) for a total of 10 days (both provided by Gilead Sciences, Foster City, CA, USA).	The same volume of placebo infusions for a total of 10 days (provided by Gilead Sciences, Foster City, CA, USA)		<p><i>admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first.</i></p> <p>n/N (%)</p> <p>Day 7: I: 4/158 (3%) C: 2/78 (3%)</p> <p>Day 14: I: 42/158 (11%) C: 18/78 (23%)</p> <p>Day 28: I: 103/158 (65%) C: 45/78 (58%)</p> <p><u>Time to clinical improvement</u> Median (IQR) days I: 21 (13–28) C: 23 (15–28) HR 1.23 (95% CI: 0.87 to 1.75)</p> <p>Subgroup analysis ≤10 days from symptom onset: I: 18 (12–28) C: 23 (15–28) HR 1.52 (95% CI: 0.95 to 2.43)</p> <p><u>Secondary outcomes</u> <u>Proportion of patients in each category of the 6-point scale</u> Day 7 OR: 0.69 (0.41–1.17)</p> <p>Day 14 OR: 1.25 (0.76–2.04)</p>	<p>March 12, because of the control of the outbreak in Wuhan. Based on the termination criteria specified in the protocol, the data safety and monitoring board recommended that the study be terminated.</p> <p>- At this stage, the interim analysis was abandoned. When all the other assumptions stayed the same, with the actual enrolment of 236 participants, the statistical power was reduced from 80% to 58%.</p> <p><u>Authors conclusion:</u> Our trial found that intravenous remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo. We found that this dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reductions in some clinical parameters.</p> <p>In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.</p> <p>[See also the study by Shih, 2020: Remdesivir is Effective for Moderately</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>N total at baseline:</u> N = 237 Intervention: 158 Control: 79</p> <p><u>Important characteristics:</u> Age, median (IQR) I: 66 (57–73) C: 64 (53–70) Sex, n/N (%) male: I: 89/158 (56%) C: 51/78 (65%) Time from symptom onset to starting study treatment, n/N (%) of ≤10 days I: 71/155 (46%) C: 47/78 (60%)</p> <p><u>Groups comparable at baseline?</u> More patients with hypertension, diabetes, or coronary artery disease in the remdesivir group than the placebo group. More patients in the control group than in the remdesivir group had been symptomatic for 10 days or less at the time of starting remdesivir or placebo treatment, and a higher proportion of remdesivir recipients had a respiratory rate of more than 24 breaths per min. No other major differences in symptoms, signs, laboratory results, disease severity, or treatments were observed between groups at baseline.</p>				<p><u>Day 28</u> OR 1.15 (0.67–1.96)</p> <p><u>All-cause mortality at day 28, n/N (%)</u> I: 22/158 (14%) C: 10/78 (13%) Difference: 1.1% (95% CI: -8.1 to 10.3)</p> <p><u>Duration of invasive mechanical ventilation, median (IQR) days</u> I: 7·0 (4·0 to 16·0) C: 15·5 (6·0 to 21·0) Difference: -4·0 (-14·0 to 2·0)</p> <p><u>Duration of oxygen support, median (IQR) days</u> I: 19·0 (11·0 to 30·0) C: 21·0 (14·0 to 30·5) Difference: -2·0 (-6·0 to 1·0)</p> <p><u>Duration of hospital admission, median (IQR) days</u> I: 25·0 (16·0 to 38·0) C: 24·0 (18·0 to 36·0) Difference: 0·0 (-4·0 to 4·0)</p> <p>Virological measures <u>Proportions of patients with viral RNA detected and viral RNA load</u> <i>Measured by quantitative RT-PCR</i> Viral load decreased over time similarly in both</p>	<p>Severe Patients: A Re-Analysis of the First Double-Blind, Placebo-Controlled, Randomized Trial on Remdesivir for Treatment of Severe COVID-19 Patients Conducted in Wuhan City]</p> <p><u>Note:</u> 6-point ordinal scale: 6 = death; 5 = hospital admission for extracorporeal membrane oxygenation or mechanical ventilation; 4 = hospital admission for non-invasive ventilation or high-flow oxygen therapy; 3 = hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation); 2 = hospital admission but not requiring oxygen therapy; 1 = discharged or having reached discharge criteria (defined as clinical recovery—ie, normalisation of pyrexia, respiratory rate <24 breaths per minute, saturation of peripheral oxygen >94% on room air, and relief of cough, all maintained for at least 72 h)</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>groups. When adjusted for baseline sputum viral load at enrolment, the remdesivir group showed no significant difference at day 5 from placebo, but a slightly more rapid decline in load (p=0.0672). The cumulative rate of undetectable viral RNA of nasopharyngeal and oropharyngeal swabs by day 28 was 153 (78%) of 196 patients, and the negative proportion was similar among patients receiving remdesivir and those receiving placebo.</p> <p>Safety outcomes</p> <p><u>Treatment-emergent adverse events</u> I: 102/155 (66%) C: 50/78 (64%)</p> <p><u>Serious adverse events</u> I: 28/155 (18%) C: 20/78 (26%)</p> <p><u>Premature discontinuations of study drug</u> I: 18/155 (12%) C: 4/78 (5%)</p>	
2. Corticosteroids							
2.1. Dexamethasone							
Jamaati, 2021	<u>Type of study:</u> RCT, clinical trial <u>Setting:</u> Conducted in	Hospitalized patients with mild to moderate acute respiratory distress syndrome (ARDS) due to COVID-19	Intravenous dexamethasone at a dose of 20 mg/day from day 1–5 and then at 10 mg/day	Standard care only	<u>Length of follow up:</u> 28 days <u>Loss to follow-up:</u> I: 0/25 (%)	Clinical outcomes <u>Mortality (n (%)/N) within 28 days</u> I: 16/25 (64%) C: 15/25 (60%)	<u>Definitions:</u> <u>Remarks:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>March 2020 at Dr. Masih Daneshvari Hospital: primary referral center for patients with COVID-19.</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> None</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age > 18y; • Confirmed SARS-CoV-2 infection; • PaO₂/FiO₂ between 100 and 300 mmHg; • Bilateral lung infiltration; • Written informed consent by the patient. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Chronic kidney disease; • Chronic liver disease; • Hyperglycemia; • Pregnant or breastfeeding. <p><u>N total at baseline:</u> N = 50 Intervention: 25 Control: 25</p> <p><u>Important characteristics:</u></p> <p>Age, median (IQR): I: 62 y (52-71) C: 62 y (54-68)</p> <p>Sex, n/N (%) male: I: 18/25 (72%) C: 18/25 (72%)</p> <p>Disease severity: <i>Defined by symptoms, n (%) / N</i></p> <p><i>Fever</i> I: 16 (64%) / 25 C: 18 (72%) / 25</p> <p><i>Cough</i> I: 15 (60%) / 25 C: 14 (56%) / 25</p> <p><i>Dyspnea</i> I: 7 (28%) / 25 C: 20 (80%) / 25</p>	from day 6–10 + standard care		C: 0/25 (%)	<p>RR: 1.07 [95% CI 0.69 to 1.65]</p> <p><u>Discharged patients within 28 days</u> I: 9/25 (37%) C: 10/25 (40%) RR: 0.90 [95% CI 0.44 to 1.83]</p> <p><u>Duration of hospitalization (days), median (IQR)</u> <i>Overall</i> I: 11 (6–16) C: 6 (4–9) <i>Survivors (sub-group)</i> I: 16 (9-21), n=9 C: 8.5 (5-13), n=10 <i>Non-survivors (sub-group)</i> I: 9.5 (5.5-13), n=16 C: 6 (3-7), n=15</p> <p><u>Duration of ICU stay (days), median (IQR)</u> <i>Overall</i> I: 7 (4–11) C: 3 (2–5) <i>Survivors (sub-group)</i> I: 7 (4-12), n=9 C: 4.5 (3-5), n=10 <i>Non-survivors (sub-group)</i> I: 7 (4.5-10), n=16 C: 3 (2-3), n=15</p> <p><u>Symptom resolution</u> Not reported</p> <p><u>Need for non-invasive ventilation, n(%) / N</u> <i>Overall</i> I: 23 (92%) / 25 C: 24 (96%) / 25</p>	<ul style="list-style-type: none"> • At baseline, more patients in the control group suffered from pulmonary diseases. The authors do not address this result in the text. • Authors do not state whether the patients, caretakers or outcome assessors were blinded to treatment allocation, except for the radiologist who judged the CT scans (this person was blinded to the lab data and clinical findings). • Sample size was adjusted based on the study results: authors state they halted their study because they did not achieve a clinical response in fifty patients. • Small sample size (N=50) <p><u>Authors conclusion:</u> The current study showed that there was no clinical benefit in high dose administration of corticosteroid for the treatment of mild to moderate ARDS in patients with COVID-19. However, dexamethasone administration may shorten the duration of hospitalization.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Myalgia</i> I: 1 (4%) / 25 C: 8 (32%) / 25</p> <p><i>Nausea or vomiting</i> I: 1 (4%) / 25 C: 1 (4%) / 25</p> <p>Groups were comparable at baseline, with the exception of the number of patients with pulmonary diseases as part of their medical history. This number was higher in the control group (I: 1, C: 9).</p>				<p><i>Survivors (sub-group)</i> I: 9 (100%), n=9 C: 10 (100%), n=10</p> <p><i>Non-survivors (sub-group)</i> I: 14 (88%), n=16 C: 14 (93%), n=15</p> <p>Among the patients who required non-invasive ventilation, the following numbers of patients required invasive mechanical ventilation: <u>Need for invasive ventilation</u></p> <p><i>Overall</i> I: 13 (52%) / 25 C: 11 (44%) / 25</p> <p><i>Survivors (sub-group)</i> I: 2 (22%), n=9 C: 1 (10%), n=10</p> <p><i>Non-survivors (sub-group)</i> I: 11 (69%), n=16 C: 10 (67%), n=15</p> <p><u>SOFA-score, mean (SD)</u></p> <p><i>Overall</i> I: 4.68 (1.38) C: 4.56 (1.36)</p> <p><i>Survivors (sub-group), median (IQR)</i> I: 4 (4-5) n=9 C: 4 (4-5), n=10</p> <p><i>Non-survivors (sub-group), median (IQR)</i> I: 5 (4-6), n=16 C: 4 (4-6), n=15</p> <p><u>Improvements in lung CT scan images</u> I: 40% of patients C: 12% of patients</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Safety <u>Adverse events</u> Not reported Virological outcomes <u>Viral clearance</u> Not reported	
Tomazini, 2020	<u>Type of study:</u> Multicenter, randomized, open-label, clinical trial <u>Setting:</u> 41 intensive care units (ICUs) <u>Country:</u> Brazil <u>Source of funding:</u> This trial was funded and supported by the Coalition COVID-19 Brazil. The Laboratórios Farmacêuticos provided the study drug, distribution logistics, and insurance for the study patients.	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> Age ≥ 18 yrs; Probable or confirmed infection by SARS-CoV2; Intubated and mechanically ventilated; Moderate or severe ARDS according to Berlin criteria; Within 48 hours of meeting criteria for moderate or severe ARDS. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Pregnancy or active lactation; Known history of dexamethasone allergy; Corticosteroids use in non hospitalized patients in the past 15 days; Indication for corticosteroids use for other clinical conditions; Patients who used corticosteroids during hospital stay for more than one day; Use of immunosuppressive drugs; Cytotoxic chemotherapy in the past 21 days; Neutropenia due to hematological or solid malignancies with bone marrow invasion; 	dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first, plus standard care.	Standard care only	28 days after randomization or until hospital discharge, whichever occurred first.	Clinical outcomes <u>All-cause mortality, n/N (%)</u> I: 85/151 (56.3%) C: 91/148 (61.5%) Adj. HR= 0.97 (95% CI= 0.72 to 1.31) P=0.85 Unadj. HR= 0.86 (95% CI= 0.64 to 1.15) P=0.31 <u>Days alive and ventilator free at 28 days, mean (95% CI)</u> I: 6.6 (95% CI 5.0 to 8.2) C: 4.0 (95% CI= 2.9 to 5.4) Adj. MD= 2.26 (95% CI = 0.2 to 4.38) P=0.04 Unadj. MD= 2.55 (95% CI= 0.46 to 4.6) P=0.02 <u>ICU free days, mean (95% CI)</u> I: 2.1 (95% CI= 1.0 to 4.5) C: 2.0 (95% CI= 0.8 to 4.2) Adj. MD= 0.28 (95% CI= -0.49 to 1.02) P=0.50 Unadj. MD= 0.14 (95% CI= -0.92 to 1.27) P=0.78	<u>Remarks:</u> <u>Authors conclusion:</u> In patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care, compared with standard care alone, resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> Patients expected to die in the next 24 hours; Consent refusal for participation. <p><u>N total at baseline:</u> N = 299 Intervention: 151 Control: 148</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 60.1 yrs (15.8) C: 62.7 yrs (13.1)</p> <p>Sex, n/N (%) male: I: 90/151 male (59.6%) C: 97/148 male (65.6%)</p>				<p><u>Mechanical ventilation days, mean (95% CI)</u> I: 12.5 (95% CI= 11.2 to 13.8) C: 13.9 (95% CI= 12.7 to 15.1) Adj. MD= -1.54 (95% CI= -3.24 to 0.12) P=0.11 Unadj. MD= -1.46 (95% CI = -3.10 to 0.57) P=0.18</p> <p><u>Serious adverse events, n/N (%)</u> I: 5/151 (3.3%) C: 9/148 (6.1%) AD= 2.8 (95% CI= -2.7 to 8.2)</p> <p>*AD = absolute difference</p>	
Horby, 2020a	<p><u>Type of study:</u> randomized, controlled, open-label, adaptive, platform trial</p> <p><u>Setting:</u> hospitalized COVID-19 patients; 176 National Health Service (NHS) hospital organizations</p> <p><u>Country:</u> UK</p> <p><u>Source of funding:</u> <u>Conflicts of interest:</u> The authors have no conflict of</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Hospitalized clinically suspected or laboratory confirmed SARS-CoV-2 infection no medical history that might, in opinion of attending clinician, put patient at significant risk <i>NOTE: pregnant or breast-feeding women were eligible</i> <p><u>Exclusion criteria:</u> Not further specified</p> <p><u>N total at baseline:</u> Intervention: 2104 Control: 4321</p> <p><u>Important characteristics:</u> <u>Mean age (SD):</u></p>	<p>Usual care + dexamethasone [6 mg given once daily for up to 10 days]</p> <p>Remark: 95% of the intervention group received at least 1 dose dexamethasone [median = 6 days]</p>	<p>Usual care</p> <p>Remark: 7% of control group received dexamethasone</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up data handling:</u> 4.8% of patients not followed for 28 days: by the time of data cut (10 June 2020) were either censored on 8 June 2020 or, if they had already been discharged alive, were right-censored at day 29 (in the absence of any information to the contrary they were assumed to have survived 28 days).</p>	<p><u>28-day mortality</u> I: 454/2104 (21.6%) C: 1065/4321 (24.6%) Rate ratio = 0.83 (0.74-0.92)</p> <p><u>Time to discharge from hospital</u> I: 1360/2104 (64.6%) C: 2639/4321 (61.1%) Rate ratio = 1.11 (1.04-1.19)</p> <p><u>Receipt of invasive mechanical ventilation (including extra-corporeal membrane oxygenation; among patients not receiving invasive mechanical ventilation at randomization)</u> I: 92/1780 (5.2%)</p>	<p><u>Remarks:</u> Trial design</p> <ul style="list-style-type: none"> This was a randomized controlled trial The trial was open label / not blinded Participants It is assumed that the effect of corticosteroid treatment is different for different phases of COVID-19 infection. The phase of COVID-19 of the participants was not specified Treatment 95% of the intervention group received at least 1 dose dexamethasone [median = 6 days] 7% of control group received dexamethasone and not all patients randomized to the intervention group received dexamethasone. This means cross-over between treatment groups took place. <p>Analyses</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	interest or financial relationships relevant to the submitted work to disclose; this work was supported by the National Institute for Health Research Clinical Research Network	I: 66.9y (15.4) C: 65.8y (15.8) <u>Male/N (%)</u> : I: 1338/2104 (64%) C: 2750/4321 (64%) Intervention group 1.1y older than control group; rate ratios and risk ratios were adjusted for baseline age				C: 258/3638 (7.1%) Rate ratio: 0.76 (0.61-0.96) <u>Death</u> (among patients not receiving invasive mechanical ventilation at randomization) I: 360/1780 (20.2%) C: 787/3638 (21.6%) Rate ratio: 0.91 (0.82-1.01) Also described: 28-day mortality in all patients, and separately according to level of respiratory support received at randomization	<ul style="list-style-type: none"> Analyses were performed according to intention-to-treat protocol. Results should be interpreted keeping cross-over between groups in mind. <p><u>Author's conclusion:</u> The RECOVERY trial provides clear evidence that treatment with dexamethasone 6 mg once daily for up to 10 days reduces 28-day mortality in patients with COVID-19 who are receiving respiratory support. Based on these results, 1 death would be prevented by treatment of around 8 patients requiring invasive mechanical ventilation or around 25 patients requiring oxygen (which, in the UK, is recommended when oxygen saturations on room air are 92-94%) without invasive mechanical ventilation. There was no benefit (and the possibility of harm) among patients who did not require oxygen. Prior to the completion of this trial, many COVID-19 treatment guidelines have stated that corticosteroids are either 'contraindicated' or 'not recommended' in COVID-19. These should now be updated, as has already happened within the UK. Dexamethasone provides an effective treatment for the sickest patients with COVID-19 and, given its low cost, well understood safety profile, and widespread availability, is one that can be used worldwide.</p>
2.2. Hydrocortisone							
Munch, 2021	<u>Type of study:</u> Multicentre, parallel-group,	Patients with COVID-19 and severe hypoxia	Hydrocortisone i.v. (200 mg/day) for 7 days or until hospital discharge in	Placebo (0.9% isotonic saline) i.v. for 7 days or	<u>Length of follow-up:</u> 90 days	The researchers planned to conduct statistical analyses of subgroup	<u>Definitions:</u> -

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>placebo-controlled, blinded, centrally randomised, stratified clinical trial</p> <p><u>Setting:</u> Hospital-based, between April 15 and June 16, 2020</p> <p><u>Country:</u> 12 trial sites in Denmark</p> <p><u>Source of funding:</u> Funded by the Novo Nordisk Foundation, Grant/Award Number: 0062998 and supported by Rigshospitalet's Research Council, Grant/Award Number: E-22703-06 and Pfizer, Grant/Award Number: 60473019. The funding sources were not involved in designing, conducting, analysing or reporting of the trial.</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • confirmed COVID-19 requiring hospitalisation • use of one of the following: <ul style="list-style-type: none"> ○ invasive mechanical ventilation, OR ○ non-invasive ventilation or continuous use of CPAP for hypoxia, OR ○ oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • use of systemic corticosteroids • invasive mechanical ventilation > 48 hrs prior to screening • invasive fungal infection. • fertile woman (< 60 y) with positive urine-hCG or plasma-hCG • known hypersensitivity to hydrocortisone • a patient for whom the clinical team has decided not to use invasive • mechanical ventilation • previously randomised into the COVID STEROID trial • informed consent not obtainable <p><u>N total at baseline:</u> Randomized: N = 30</p> <p>Intervention: N = 16 Control: N = 14</p>	<p>addition to standard care; continuous infusion over 24 hrs or as bolus injections every 6 hrs (50 mg per bolus)</p>	<p>until hospital discharge; continuous infusion over 24 hrs or as bolus injections every 6 hrs (50 mg per bolus)</p>	<p><u>Loss-to-follow-up:</u> I: 0/16 (0%) <i>Reasons:</i> -</p> <p>Control: 0/14 (0%) <i>Reasons:</i> -</p>	<p>differences on the primary outcome (i.e. days alive without life support at day 28) in the ITT population, but refrained from this due to the reduced sample size.</p> <p>Clinical outcomes <u>Mortality</u> <u>Days alive without life support at day 28</u> Days, median (IQR) I: 7 (2-24) C: 10 (3-26) aMD -1.1 (95%CI: -9.5-7.3)</p> <p><u>Days alive without life support at day 90</u> Days, median (IQR) I: 41 (6-86) C: 72 (52-88) aMD -14.7 (95%CI: -40.4-10.9)</p> <p><u>All-cause mortality at day 28</u> n/N (%) I: 6/16 (38%) C: 2/14 (14%) RR 2.63 (95%CI: 0.74-16.03)</p> <p><u>All-cause mortality at day 90</u> n/N (%) I: 7/16 (44%) C: 3/14 (21%) RR 2.04 (95%CI: 0.71-8.16)</p> <p><u>Days alive and out of hospital at day 90</u> Days, median (IQR)</p>	<p><u>Remarks:</u> The researchers planned to randomise 1000 adult patients with COVID-19 and severe hypoxia in Denmark, Sweden, Switzerland and India. The trial was commenced on April 15, 2020; paused on June 16, 2020; and terminated early on September 4, 2020, after 30 patients had been enrolled at 12 trial sites in Denmark. The trial was terminated very quickly after starting enrollment, due to unexpected (at trial design) inability to enroll participants.</p> <p><u>Authors conclusion:</u> In this early terminated randomised clinical trial of adult patients with COVID-19 and severe hypoxia, we were unable to provide any precise estimates on the benefits and harms of hydrocortisone versus placebo for any outcomes as only 3% of the planned sample size had been enrolled.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	extensively reported.	<p><u>Important characteristics:</u> Age, median (IQR): I: 59 y (52-74) C: 62 y (55-71)</p> <p>Sex, n/N (%) male: I: 14/16 (88%) C: 10/14 (71%)</p> <p>Unclear whether groups were (statistically) comparable at baseline.</p>				<p>I: 31 (8-78) C: 53 (42-68) aMD -6.5 (95%CI: -29.6-16.7)</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p><u>Safety</u> <u>≥ 1 serious adverse reactions</u> n/N (%) I: 1/16 (6%) C: 0/14 (0%)</p> <p><u>Virological outcomes</u> <u>Viral clearance</u> Not reported.</p>	
Angus, 2020	<p><u>Type of study:</u> Ongoing, international, multicenter, open-label trial</p> <p><u>Setting:</u> An intensive care unit for respiratory or cardiovascular organ support at 121 sites in Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United Kingdom,</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age >18; presumed or confirmed SARS-CoV-2 infection; admitted to intensive care unit. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment; 	<p>I: Patients received a fixed dose of intravenous hydrocortisone, 50 mg, every 6 hours for 7 days.</p> <p>II: intravenous hydrocortisone, 50 mg, every 6 hours while in shock for up to 28 days.</p>	No hydrocortisone	Up to day 21	<p><u>Organ support-free days: Median (IQR)</u> I: 0 (-1 to 15) II: 0 (-1 to 3) C: 0 (-1 to 11)</p> <p><u>Subcomponents of organ support-free days</u> <i>In hospital deaths; N (%)</i> I: 41/137 (30%) II: 37/141 (26%) C: 33/101 (33%)</p> <p><i>Organ support-free days among survivors, Median (IQR)</i> I: 11.5 (0 to 17)</p>	<p><u>Remarks:</u> For an additional 11 patients, of whom 5 were in the corticosteroid domain, follow-up data were unavailable. Thus, the final cohort available for outcome analysis comprised 576 participants in the REMAP-CAP severe COVID-19 cohort (whose data are used for covariate adjustment in the primary analysis), of whom 379 were randomized within the corticosteroid domain (after removing 5 patients in the shock-dependent hydrocortisone group whose outcomes were not available).</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>and the United States.</p> <p><u>Source of funding:</u> Hele lange lijst. Niet zinvol om hier weer te geven mijn inziens.</p>	<ul style="list-style-type: none"> • Patient is expected to be discharged from hospital today or tomorrow; • More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection; • Previous participation in this REMAP within the last 90 days. <p><u>N total at baseline:</u> N = 614 Intervention (I): 137 Intervention (II): 146 Control: 101</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 60.4y (11.6) II: 59.5y (12.7) C: 59.9y (14.6)</p> <p>Sex, n/N (%) male: I: 98/137 male (71.5%) II: 103/146 male (70.6%) C: 72/101 male (71.3%)</p>				<p>II: 9.5 (0 to 16) C: 6 (0 to 12)</p> <p><u>Time to death; adjusted hazard ratio (mean (SD))</u> I: 0.97 (0.22) II: 1.01 (0.23) C: 1 (reference)</p> <p><u>Time to death; adjusted hazard ratio (median (95%CI))</u> I: 0.94 (0.61 – 1.46) II: 0.98 (0.63 – 1.54) C: 1 (reference)</p> <p><u>Respiratory support-free days; adjusted odds-ratio (mean (SD))</u> I: 1.45 (0.34) II: 1.31 (0.30) C: 1 (reference)</p> <p><u>Respiratory support-free days; adjusted odds-ratio (median/95%CrI)</u> I: 1.42 (0.90 – 2.24) II: 1.28 (0.81 – 2.00) C: 1 (reference)</p> <p><u>Length of ICU stay; adjusted hazard ratio (mean (SD))</u> I: 0.93 (0.14) II: 0.86 (0.13) C: 1 (reference)</p> <p><u>Length of ICU stay; adjusted hazard ratio (median (95% CI))</u> I: 0.92 (0.68 – 1.24) II: 0.85 (0.62 – 1.15) C: 1 (reference)</p>	<p>Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93% and 80% probabilities of superiority with regard to the odds of improvement in organ support-free days within 21 days. However, the trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>Length of hospital stay; adjusted hazard ratio (mean (SD))</u> I: 0.99 (0.16) II: 0.94 (0.15) C: 1 (reference)</p> <p><u>Length of hospital stay; adjusted hazard ratio (median (95% CI))</u> I: 0.97 (0.72 – 1.32) II: 0.93 (0.69 – 1.26) C: 1 (reference)</p> <p><u>Free of invasive mechanical ventilation at baseline; N</u> I: n= 50 II: n= 70 C: n= 48</p> <p><u>Serious adverse events (>1) N (%)</u> I: 4/137 (3%) II: 5/141 (4%) C: 1/101 (1%)</p>	
Dequin, 2020 <i>CAPECOVID trial = Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease</i>	<p><u>Type of study:</u> RCT; randomized double-blind sequential trial</p> <p><u>Setting:</u> Multicentre; 9 ICUs; embedded in the ongoing Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPECOD) trial.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age ≥18 years • admitted to participating ICU for ARDS • confirmed (RT-PCR) or suspected (suggestive CT chest) COVID-19 • experimental treatment administered < 24 hours of the onset of first severity criterion (see below) or < 48 hours for patients referred from another hospital. • 1 of 4 severity criteria had to be present: 1) need for mechanical ventilation with positive end- 	<p>Hydrocortisone</p> <p>Continuous IV infusion Initial dose of 200mg/d</p> <p>Treatment was continued at 200mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days.</p> <p>If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment</p>	<p>Placebo (Saline)</p> <p>Continuous IV infusion Initial dose of 200mg/d</p> <p>Treatment was continued at 200mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3</p>	<p><u>Length of follow-up:</u> 28 days or to death</p> <p><u>Loss-to-follow up:</u> I: 0/76 C: 0/73 1 patient in the intervention group withdrew consent; for the primary outcome this patient was considered to have experienced treatment failure on day 21.</p>	<p><u>Treatment failure on day 21</u>, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy I: 32/76 (42.1%) C: 37/73 (50.7%) RD: -8.6% (95% CI -24.9% to 7.7%)</p> <p><u>Need for tracheal intubation</u> (among patients not intubated at baseline); I: 8/16 (50%)</p>	<p><u>Remarks:</u> -the study was stopped early after release of the RECOVERY trial and might therefore be underpowered</p> <p><u>Authors conclusion:</u> In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study was stopped early and likely was underpowered</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Start inclusion COVID-19 patients in parent trial: March 7, 2020; ethical committee approval: April 9, 2020; discontinuation of trial: July 3, 2020.</p> <p><u>Country:</u> France</p> <p><u>Source of funding:</u> This study was funded by the French Ministry of Health, Programme Hospitalier de Recherche Clinique (PHRC) (2014 [CAPE COD parent trial], 2020 [CAPE COVID subtrial]).</p>	<p>expiratory pressure (PEEP) of 5 cm H2O or more; 2) a ratio of PaO2 to fraction of inspired oxygen (Fio2) < 300 on high-flow oxygen therapy with an FIO2 value of at least 50%; 3) for patients receiving oxygen through a reservoir mask, a PaO2:FIO2 ratio less than 300, estimated using prespecified charts; 4) or a Pulmonary Severity Index > 130</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • septic shock • do-not-intubate orders. <p><u>N total at baseline:</u> N = 149 Intervention: 76 Control: 73</p> <p><u>Important characteristics:</u> Age, median (IQR), y: I: 63.1 (51.5-70.8) C: 66.3 (53.5-72.7) Sex, n/N (%) male: I: 54/76 (71.1%) C: 50/73 (68.5%)</p> <p>Groups comparable at baseline.</p>	<p>regimen was used (200mg/d for 4 days, followed by 100mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days). [see publication for criteria that allowed considering adaptive scheme)</p> <p>Adjunctive treatments could be administered at the discretion of the patients' primary physicians.</p> <p>Median duration treatment: 10.5 days (IQR 6.0 to 14.0)</p>	<p>days, for a total of 14 days.</p> <p>If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200mg/d for 4 days, followed by 100mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days). [see publication for criteria that allowed considering adaptive scheme)</p> <p>Adjunctive treatments could be administered at the discretion of the patients' primary physicians.</p> <p>Median duration treatment: 12.8 days (IQR 8.0 to 13.0)</p>		<p>C: 12/16 (75%)</p> <p><u>Cumulative incidences of prone position sessions (until day 21)</u> I: 36/76 (47.4%) C: 39/73 (53.4%) HR 0.85 (95% CI 0.55 to 1.32)</p> <p><u>Extracorporeal membrane oxygenation / Inhaled nitric oxide:</u> "Too few patients were treated with extracorporeal membrane oxygenation or inhaled nitric oxide to allow statistical testing."</p> <p><u>PaO2:FIO2 ratio</u> measured daily from day 1 to day 7, day 14 and day 21: "Daily evolution of PaO2:FIO2 ratio during the first week and on days 14 and 21 did not significantly differ between the groups (P = .37."</p> <p><u>At least 1 episode of nosocomial infection:</u> I: 28 of 75 (37.3%) C: 30 of 73 (41.1%)</p> <p><u>At least 1 episode of ventilator-associated pneumonia</u> I: 22/75 patients (29.0%) C: 20/73 patients (27.4%)</p>	to find a statistically and clinically important difference in the primary outcome.
2.3. Inhaled corticosteroids (budesonide, ciclesonide)							

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Agustí, 2022 (TACTI)	<p>Type of study: multicentre, randomized, open-label trial</p> <p>Setting: Hospitalized, between April 20, 2020, until March 16, 2021</p> <p>Country: 7 centers in Argentina 7 centers in Spain (obtained from NCT04355637)</p> <p>Source of funding: TACTIC was an investigator-initiated trial supported by AstraZeneca</p> <p>Conflicts of interest: Conflicts of interest were transparently and extensively reported.</p>	<p>Hospitalized patients with symptomatic COVID-19 infection, status 3-4 WHO scale</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Aged 18 to 79 years • PCR confirmed SARS-CoV-2 infection • Radiological evidence of pneumonia • No contraindication to the study drug <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Treatment with inhaled or systemic steroids and/or other immunomodulator drugs • High flow-oxygen or mechanical ventilation • pregnancy <p>N total at baseline: Randomized: N = 120</p> <p>Intervention: N = 58 Control: N = 62</p> <p>Important characteristics:</p> <p>Age, mean (SD) I: 50.6 y (13.7) C: 51.6 y (13.8)</p> <p>Sex, n/N (%) male I: 24/58 (42.1%) C: 32/62 (51.6%)</p> <p>Disease severity: Defined by chest x-ray findings Bilateral pneumonia I: 49/58 (86%) C: 48/62 (77.4%)</p>	<p>Inhaled budesonide 400µg/12 h via Pulmicort Turbuhaler®</p> <p>(duration of treatment unknown) +</p> <p>Usual care</p>	<p>Usual care: dynamically established by the institutional protocol of each participating centre during the course of the pandemic</p>	<p>Length of follow-up: 90 days</p> <p>Incomplete outcome data & loss-to-follow-up: <i>Diseased:</i> I: 1/58 (1.8%) (due to COVID-19) C: 1/62 (1.6^) (due to liver cirrhosis)</p>	<p>Clinical outcomes Mortality <u>All-cause mortality by day 30</u> I: 0/58 (0%) C: 0/62 (0%)</p> <p><u>All-cause mortality by day 30</u> I: 1/58 (1.8%) C: 1/62 (1.6%)</p> <p>Duration of hospitalisation Not reported.</p> <p>Time to symptom resolution Not reported.</p> <p>Disease progression I: 2/N (3.7%) C: 4/N (6.6%) <i>N=not reported</i> Difference: 2.88% (95%CI - 10.48% to 4.72%), p=0.458</p> <p>Respiratory support Not reported.</p> <p>Safety <u>Any severe adverse event</u> I: 2/58 (3.6%) C: 3/52 (4.8%)</p> <p>Virological outcomes Not reported</p>	<p>Primary outcome: • Disease progression</p> <p>Secondary outcomes†: • ICU admission • ICU refusal • Occurrence of complications • LDH, CRP, ferritin, D-dimer, leukocyte counts</p> <p>† not reported in the article (obtained from obtained NCT04355637)</p> <p>Definitions: Disease progression defined by a composite outcome that included treatment with non-invasive ventilation of high flow oxygen devices (WHO stage 5), invasive ventilation (WHO stage 6) and/or death from any cause (WHO stage 7) during the first 15 days after randomization.</p> <p>Remarks: 13 patients (21%) in the usual care arm were treated with dexamethasone after randomization at the discretion of the attending physician, whereas only 6 patients (10.7%) in the intervention group were.</p> <p>Stopped prematurely, because of the progressive and generalized use of dexamethasone to treat hospitalized patients with COVID-19.</p> <p>This RCTs lacks statistical power because it had to be terminated prematurely.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Oxygen requirements at admission, low flow O₂ I: 18/58 (31%) C: 13/62 (21%)</p> <p>Groups not comparable at baseline: The proportion of patients without supplemental oxygen at entry was nominally higher in the usual care group</p>					<p><u>Authors conclusion:</u> Results suggest that the addition of inhaled budesonide to usual care in patients hospitalized because of COVID19 pneumonia is safe and showed an encouraging trend towards a reduction in disease progression</p>
Clemency, 2022	<p><u>Type of study:</u> multicentre, randomized, double-blind, placebo-controlled, phase 3 trial</p> <p><u>Setting:</u> outpatient-based, between June 11, 2020 and November 3, 2020</p> <p><u>Country:</u> 10 centers in the USA</p> <p><u>Source of funding:</u> The study was sponsored and funded by Covis Pharma GmbH. Research at the primary site was also supported by the National Center for Advancing Translational Sciences and the National Heart, Lung, and Blood</p>	<p>non-hospitalized patients with symptomatic COVID-19 infection</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 12 y • positive SARS-CoV-2 molecular or antigen diagnostic sample obtained during the previous 72 h • not hospitalized or under consideration for hospitalization • O₂ saturation level ≥ 93% on room air • able to demonstrate successful use of a metered-dose inhaler • ≥ 1 of the following symptoms of COVID-19: fever, cough, or dyspnea <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • hypersensitivity to ciclesonide • use of an inhaled or intranasal corticosteroid within 14 days • use of oral corticosteroids within 90 days • participated in any other clinical trial or use of any investigational agent within 30 days • history of cystic fibrosis • history of idiopathic pulmonary fibrosis 	ciclesonide metered-dose inhaler (160 µg per actuation for a total of 2 actuations twice a day; total daily dose of 640 µg) + standard supportive care	placebo + standard supportive care	<p><u>Length of follow-up:</u> 30 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> I: 16/197 (8%) <i>Reasons</i></p> <ul style="list-style-type: none"> • lost to follow-up (n = 11) • withdrawal by patient (n = 5) <p>C: 14/203 (7%) <i>Reasons</i></p> <ul style="list-style-type: none"> • lost to follow-up (n = 9) • withdrawal by patient (n = 4) <p>physician discretion (n = 1)</p>	<p>Clinical outcomes</p> <p>Mortality <u>All-cause mortality by day 30</u> I: 0/197 (0%) C: 0/203 (0%)</p> <p><u>COVID-19-related mortality by day 30</u> I: 0/197 (0%) C: 0/203 (0%)</p> <p>Duration of hospitalisation Not reported.</p> <p>Time to symptom resolution <u>Time to alleviation of all COVID-19-related symptoms (primary endpoint)</u> Days, median I: 19.0 (95%CI: 14.0-21.0) C: 19.0 (95%CI: 16.0-23.0) HR 1.08 (95%CI:0.84-1.38)</p> <p><u>Participants with alleviation of COVID-19-related symptoms by day 7</u> I: 28/197 (14%)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Ciclesonide did not achieve the primary efficacy endpoint of reduction of time to alleviation of all COVID-19-related symptoms. Future studies of inhaled steroids are needed to explore their efficacy in patients with a high risk for disease progression and in reducing the incidence of long-term COVID-19 symptoms or postacute sequelae of SARS-CoV-2.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Institute of the NIH. Covis Pharma GmbH had a role in the design and conduct of the study. Covis Pharma GmbH approved the plan for, but did not participate in, the collection, management and analysis of the data. Covis Pharma GmbH approved the decision to submit the manuscript for publication. Changes to the primary end point were made by the study sponsor in consultation with the study steering committee and the US Food and Drug Administration. The NIH had no role in the study design, data collection, data analysis, or decision to publish.</p> <p><u>Conflicts of interest:</u> Two authors reported grants from Covis Pharma, GmbH during the conduct of the study. Two</p>	<ul style="list-style-type: none"> receiving treatment with hydroxychloroquine/chloroquine pregnant <p><u>N total at baseline:</u> Randomized: N = 400 ITT population: N = 400</p> <p>Intervention: N = 197 Control: N = 203</p> <p><u>Important characteristics:</u> Age, mean (SD/range) I: 43.7 y (17.53/13-87) C: 42.9 y (16.28/14-83)</p> <p>Sex, n/N (%) male I: 85/197 (43%) C: 94/203 (46%)</p> <p>Symptom severity <u>≥ 1 severe symptoms</u> I: 5/197 (3%) C: 9/203 (4%)</p> <p><u>≥ 1 moderate or severe symptoms</u> I: 80/197 (41%) C: 74/203 (36%)</p> <p>The ciclesonide arm had higher rates of type 2 diabetes (22 participants [11.2%] in the ciclesonide arm and 8 participants in the placebo arm [3.9%]; p = 0.01) and asthma (18 participants [9.1%] in the ciclesonide arm and 8 participants in the placebo arm [3.9%]; p = 0.04).</p>				<p>C: 29/203 (14%) HR 0.92 (95%CI:0.51-1.66)</p> <p><u>Participants with alleviation of COVID-19-related symptoms by day 14</u> I: 81/197 (41%) C: 76/203 (37%) HR 1.19 (95%CI:0.78-1.81)</p> <p><u>Participants with alleviation of COVID-19-related symptoms by day 30</u> I: 139/197 (71%) C: 129/203 (64%) HR 1.28 (95%CI:0.84-1.97)</p> <p>Respiratory support Not reported.</p> <p>Other <u>Participants with subsequent emergency department visit or hospital admission for reasons related to COVID-19 by day 30</u> I: 2/197 (1%) C: 11/203 (5%) HR 0.18 (95%CI:0.04-0.85)</p> <p><u>Participants with hospital admission or death by day 30</u> I: 3/197 (2%) C: 7/203 (3%) HR 0.45 (95%CI:0.11-1.84)</p> <p>Safety <u>Adverse events</u> <u>Any</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	authors reported personal fees from Covis Pharma GmbH during the conduct of the study.					<p>I: 22/197 (11%) C: 29/203 (14%)</p> <p><u>Dyspnoea</u> I: 1/197 (1%) C: 4/203 (2%)</p> <p><u>Dysphonia</u> I: 2/197 (1%) C: 0/203 (0%)</p> <p><u>Hypoxia</u> I: 0/197 (0%) C: 2/203 (1%)</p> <p><u>Cough</u> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><u>Nasal congestion</u> I: 1/197 (1%) C: 0/203 (0%)</p> <p><u>Productive cough</u> I: 1/197 (1%) C: 0/203 (0%)</p> <p><u>Sinus pain</u> I: 1/197 (1%) C: 0/203 (0%)</p> <p><u>Throat tightness</u> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><u>Wheezing</u> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><u>COVID-19</u> I: 1/197 (1%) C: 3/203 (1%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>COVID-19 pneumonia</u> I: 1/197 (1%) C: 2/203 (1%)</p> <p><u>Oral candidiasis</u> I: 1/197 (1%) C: 1/203 (< 1%)</p> <p><u>Cellulitis</u> I: 1/197 (1%) C: 0/203 (0%)</p> <p><u>Conjunctivitis</u> I: 1/197 (1%) C: 0/203 (0%)</p> <p><u>Urinary tract infection</u> I: 1/197 (1%) C: 0/203 (0%)</p> <p><u>Varicella-zoster virus infection</u> I: 0/197 (1%) C: 1/203 (< 1%)</p> <p><u>Dry mouth</u> I: 3/197 (2%) C: 1/203 (< 1%)</p> <p><u>Dyspepsia</u> I: 0/197 (0%) C: 2/203 (1%)</p> <p><u>Diarrhoea</u> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><u>Intestinal obstruction</u> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><u>Nausea</u> I: 0/197 (0%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 1/203 (< 1%)</p> <p><i>Headache</i> I: 1/197 (1%) C: 0/203 (0%)</p> <p><i>Dizziness</i> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><i>Hypoaesthesia</i> I: 1/197 (1%) C: 0/203 (0%)</p> <p><i>Paraesthesia</i> I: 1/197 (1%) C: 0/203 (0%)</p> <p><i>Piriformis syndrome</i> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><i>Chest discomfort</i> I: 1/197 (1%) C: 1/203 (< 1%)</p> <p><i>Fatigue</i> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><i>Atrial fibrillation</i> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><i>Bradycardia</i> I: 0/197 (0%) C: 1/203 (< 1%)</p> <p><i>Animal bite</i> I: 1/197 (1%) C: 0/203 (0%)</p> <p><i>Tendon injury</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I: 1/197 (1%) C: 0/203 (0%) <u>Back pain</u> I: 1/197 (1%) C: 0/203 (0%) <u>Neck pain</u> I: 1/197 (1%) C: 0/203 (0%) <u>Insomnia</u> I: 0/197 (0%) C: 1/203 (< 1%) <u>Panic attack</u> I: 0/197 (0%) C: 1/203 (< 1%) <u>Renal and urinary disorders</u> I: 2/197 (2%) C: 0/203 (0%) Virological outcomes Not reported	
Song, 2021	<p><u>Type of study:</u> Randomized, open-label, multicenter clinical trial.</p> <p><u>Setting:</u> Six hospitals in South Korea</p> <p><u>Country:</u> South Korea</p> <p><u>Source of funding:</u> This work was supported by the National Research Foundation of</p>	<p><u>Mild-to-moderate COVID-19 patients.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with confirmed RT-PCR within three days of diagnosis or within seven days from symptom onset; • Patients with a low National Early Warning Score (NEWS) rang from 0 to 4. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Oxygen saturation <95% breathing room air; • Pregnancy or breastfeeding; 	<p><u>Intervention 1:</u> Ciclesonide (320 µg inhalation twice per day for 14 days).</p> <p><u>Intervention 2:</u> Ciclesonide-HCQ (320 µg inhalation twice per day for 14 days/400 mg daily for 10 days).</p>	<p>Standard of care</p> <p>Standard care comprised intravenous fluid, supplementary oxygen, and antibiotics, as necessary</p>	<p><u>Length of follow-up:</u> 14 days.</p> <p><u>Loss-to-follow-up:</u> None.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p>Clinical outcomes</p> <p><u>Mortality (28-30 day)</u> Not reported.</p> <p><u>Duration of hospitalization, mean days (SD)</u> I: 19.1 (7.7) C: 19.5 (7.4) P=0.839</p> <p><u>Clinical failure rate, n/N (%)</u> I: 1/35 (2.9%) C: 5/26 (19.2%) P=0.034</p>	<p><u>Definitions:</u></p> <p>- NEWS is a scoring system based on routine physiological parameters (respiratory rate, oxygen saturation, supplemental oxygen, body temperature, systolic blood pressure, heart rate, and level of consciousness), which can be obtained easily at the bedside. For each parameter, a score of zero is considered normal, and simple addition allows a total score from 0 to 20. A score of ≥5 represents the key threshold for urgent response, and patients with a score of ≥7 would be deemed to have a high-risk clinical condition requiring emergency response.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Korea (NRF) grant [2020M3A9I20816 99] and Korea University Guro Hospital grant (I2000171) that was underwritten by the SK Chemicals Corporation, Seongnam, Republic of Korea.</p> <p><u>Conflicts of interest:</u> The authors declare no conflict of interest.</p>	<ul style="list-style-type: none"> Renal impairment (estimated creatine clearance <30 mL/min); Hepatic dysfunction (alanine aminotransferase or aspartate aminotransferase levels more than five times the upper limit of normal); Immunocompromising conditions; Severe uncontrolled comorbidities; Chronic airway diseases (asthma and chronic obstructive lung disease); Contraindications for use of ciclesonide inhaler. <p><u>N total at baseline:</u> N = N = 61 Intervention: N = 35 Control: N = 26</p> <p><u>Important characteristics:</u> Age, mean days (SD): I: 44.9 (17.9) C: 49.0 (16.8) P=0.362</p> <p>Sex, n/N (%) male: I: 11/35 (31.4%) C: 9/26 (34.6%) P=0.503</p> <p>Disease severity, mean (SD): <i>Defined by NEWS at enrolment, median (IQR)</i> I: 0 (0) C: 0 (0 to 1) P=0.519</p> <p>Groups comparable at baseline? Yes.</p>				<p>aOR 0.026 (95% CI 0.001 to 0.845)</p> <p><u>Clinical improvement rate at day 14, n/N (%)</u> I: 26/35 (74.3%) C: 14/26 (53.8%) P=0.794</p> <p><u>Clinical improvement rate at day 7, n/N (%)</u> I: 19/35 (54.3%) C: 15/26 (57.7%) P=0.793</p> <p><u>Clinical improvement rate at day 10, n/N (%)</u> I: 21/35 (60%) C: 14/26 (53.8%)</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u> I: 3/35 (8.6%) C: 0/26 (0%)</p> <p>*No serious adverse event was reported in any patients.</p> <p>Virological outcomes <u>SARS-CoV-2 eradication rate at day 14, n/N (%)</u> I: 10/31 (32.3%) C: 1/20 (5%) P=0.021 aOR 12.194 (95% CI 1.187 to 125.240)</p> <p><u>SARS-CoV-2 eradication rate at day 10, n/N (%)</u></p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, our results indicate that ciclesonide shortened SARS-CoV-2 viral shedding duration. Ciclesonide may inhibit the progression to acute respiratory failure in patients with mild-to-moderate COVID-19. Ciclesonide inhalation could be a useful therapeutic option for mild-to-moderate COVID-19 in an outpatient setting.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I: 4/33 (12.1%) C: 0/22 (0%) P=0.090 <u>SARS-CoV-2 eradication rate at day 7, n/N (%)</u> I: 2/34 (5.9%) C: 0/22 (0%) P=0.247	
Yu, 2021	<p>Type of study: RCT, open-label, multi-arm, adaptive platform trial</p> <p>Setting: Enrolment between Nov 2020 and March 2021, recruitment in general medical practices, from May 2020 people could enrol online or by telephone, several outreach strategies were applied (e.g. expert working with ethnic minorities, collaboration with e.g. religious organisations)</p> <p>Country: United Kingdom</p> <p>Source of funding: National Institute of Health Research</p>	<p>Non-hospitalized patients with COVID-19 at high risk of an adverse outcome.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≥65 y or ≥50 y with comorbidities* • Ongoing symptoms from PCR-confirmed or suspected COVID-19, started ≤ 14 days <p>*heart disease, hypertension, asthma or lung disease, diabetes, hepatic impairment, stroke or neurological problems, weakened immune system and self-reported obesity/BMI ≥ 35 kg/m²</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Use of inhaled budesonide was contraindicated <p>N total at baseline: N = 1959 Intervention: 833 Control: 1126</p> <p>Important characteristics: Age, mean (SD):</p>	<p>Inhaled budesonide + usual care</p> <p>Inhaled budesonide: 800 µg twice daily for 14 days (Pulmicort Turbohaler, AstraZeneca). The breath-actuated inhaler was either prescribed or issued directly by the participant's general medical practitioner, or issued centrally by the study team and delivered to the Participant.</p>	<p>Usual care</p> <p>Usual care in the UK National Health Service for suspected COVID-19 in the community is largely focused on managing symptoms with antipyretics, with antibiotics only recommended if bacterial pneumonia is suspected.</p>	<p>Length of follow-up: 28 days through an online daily symptom diary, supplemented with telephone calls to non-responders at day 7, 14 and 28.</p> <p>Loss-to-follow-up: Intervention: NR*</p> <p>Control: NR*</p> <p><i>*It is only mentioned that 95% of the participants were included in analysis, since they provided follow-up data.</i></p> <p>Incomplete outcome data: Intervention: NR</p> <p>Control: NR</p>	<p>Clinical outcomes <u>Hospital admission or death at 28 days, % (95%CI)</u> I: 6.8 (4.1 to 10.2) C: 8.8 (5.5 to 12.7) Estimated benefit death rate (95%CI): 2.0% (-0.2 to 4.5) OR (95%CI): 0.75 (0.55 to 1.03) P= 0.963</p> <p>Mortality (28-30 day), n/N (%)* I: 6/787 (1) C: 10/799 (1) Effect (95%CI): NR P= NR</p> <p><i>*Based on WHO ordinal scale of clinical progression. It is not sure whether this is 28-30 day mortality.</i></p> <p>Intensive care unit admission I: 10/771 (1%) C: 21/779 (3%)</p>	<p>Definitions: <i>Time to first reported recovery:</i> The first instance that a participant reports feeling recovered.</p> <p>Remarks: PRINCIPLE is an adaptive platform trial. The interventions assessed in PRINCIPLE were hydroxychloroquine, azithromycin, doxycycline, colchicine, favipiravir and, reported here, inhaled budesonide.</p> <p>At the beginning of the trial participants with suspected COVID-19 were included in the primary analysis population, irrespective of confirmatory testing. When testing became more accessible, the trial steering committee recommended restricting the primary analysis population to those with confirmed COVID-19. This population includes participants randomly assigned to usual care before the budesonide group opened, who might differ from concurrently assigned participants because of changes in the inclusion or exclusion</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>and United Kingdom Research Innovation</p> <p><u>Conflicts of interest:</u> Several authors report grants/ personal fees from e.g. pharmaceutical companies.</p>	<p>I: 64.7 y (7.3) C: 64.5 y (7.7)</p> <p>Sex, n/N (%) male: I: 404/833 (48%) C: 431/886 (49%)</p> <p>Disease severity, mean (SD): <i>Not reported (only data available on presence of symptoms (e.g. fever, shortness of breath))</i></p> <p>Vaccine doses received (one dose), n/N (%) I: 105/833 (13) C: 100/886 (11)</p> <p>Groups comparable at baseline? Yes</p>				<p>Effect (95%CI): 0.48 (0.23 to 1.01) P= 0.068</p> <p><u>Duration of hospitalization</u> I: 9.5 (5 to 28) (n=70) C: 10 (4 to 29) (n=95) Effect (95%CI): -0.70 (-6.34 to 4.94) P=0.81</p> <p><u>Time to first reported recovery in days (median (95%CI))</u> I: 11.8 (10.0 to 14.1) C: 14.7 (12.3 to 18.0) Estimated benefit median time to recovery (95%CI): 2.94 (1.19 to 5.11) HR (95%CI): 1.21 (1.08 to 1.36) P= >0.999</p> <p><u>Alleviation of all symptoms, n/N (%)</u> I: 630/701 (90) C: 666/732 (91) Effect (95%CI): NR P= NR</p> <p><u>Time to symptom resolution in days, median (IQR)</u> I: 4 (2 to 9) C: 5 (2 to 10) Effect (95%CI): 1.07 (0.96 to 1.19) P= 0.26</p> <p><u>Respiratory support Oxygen administration</u> I: 50/774 (7%) C: 73/785 (9%)</p>	<p>criteria and changes over time in usual care. Primary analysis was adjusted for this temporal drift. Furthermore, sensitivity analysis was performed using the concurrent assigned population. For the primary outcomes (hospital admission or death at 28 days and time to first reported recovery) we reported the results of the corrected primary analysis in the confirmed COVID-19 subjects. For secondary outcomes, analysis was restricted to those with confirmed COVID-19 and concurrent randomisation (analyses in all confirmed COVID-19 subjects was not available).</p> <p><u>Authors conclusion:</u> Our study provides evidence that inhaled budesonide is an effective and safe treatment for people with COVID-19 in the community who are at increased risk of adverse outcomes.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Effect (95%CI): 0.69 (0.49 to 0.98) P= 0.039</p> <p><i>Mechanical ventilation</i> I: 13/776 (2%) C: 14/784 (2%) Effect (95%CI): 0.94 (0.44 to 1.98) P= >0.99</p> <p>Safety <u>Adverse events</u> 2 hospital admissions unrelated to COVID-19 in the budesonide group and 4 in the usual care group</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p> <p>Also available: sustained alleviation of all symptoms in n/days, sustained recovery in n/days, initial reduction of severity of symptoms in n/days, illness severity rating on day 7, 14, 21 and 28, WHO Well-Being Index, contact with health care services or GP (self-reported), new infections in household, prescription of antibiotics, hospital assessment without admission, WHO ordinal scale of clinical progression. Subgroup analyses (for: age, comorbidity, duration of illness, symptom severity score, lung disease, more than one dose of</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						vaccination) were performed for the outcome measures time to first reported recovery and COVID-19-related hospital admission or death.	
Ramakrishnan, 2021	<p>Type of study: RCT; open-label</p> <p>Setting: Recruitment: July 16 to Dec 9, 2020;</p> <p>Country: Oxfordshire, UK</p> <p>Source of funding: "The study was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre and AstraZeneca (Gothenburg, Sweden). The funders had no role in study design, data collection, data analysis, data interpretation, writing of the article, or the decision to publish the study."</p>	<p>Non-hospitalized COVID-19 patients; out-patients</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Age > 18 years symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days <p>Exclusion criteria:</p> <ul style="list-style-type: none"> recent use (within 7 days) of inhaled or systemic glucocorticoids known allergy or contraindication to inhaled budesonide <p>N total at baseline: N = 146 Intervention: 73 Control: 73</p> <p>Important characteristics: Age, mean (SD): I: 44 (19–71) y C: 46 (19–79) y Sex, n/N (%) male: I: 31 (44%) C: 28 (41%) Duration of symptoms, days, at randomization, mean (SD) I: 3 (2–5) C: 3 (2–4) Evidence of COVID-19-positive status I: 66 (94%) C: 65 (94%)</p>	<p>Budesonide dry powder inhaler</p> <p>Pulmicort Turbuhaler, AstraZeneca, Gothenburg, Sweden) at a dose of 400 µg per actuation (two puffs to be taken twice per day; total dose 1600 µg.</p> <p>Participants allocated to budesonide were asked to stop taking the inhaler when they felt they had recovered (self-reported symptom recovery) or if they hit the primary outcome; <i>Budesonide was taken for a median duration of 7 days (4–10).</i></p>	<p>Usual care</p> <p>Usual care was supportive therapy, with the National Health Service (NHS) advising patients with COVID-19 symptoms to take anti-pyretics for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and honey for symptoms of cough</p>	<p>Length of follow up: 28 days</p> <p>Loss to follow-up: <i>ITT protocol</i> No loss to FU</p> <p>Per protocol analysis: I: 4/73 (5.5%) <i>Reasons: 3 withdrew consent due to allocation, 1 needed urgent care before visit</i> C: 3/73 (4.1%) <i>Reasons: 1 withdrew consent due to allocation, 1 needed urgent care before visit</i></p>	<p>Clinical outcomes</p> <p>Mortality not reported</p> <p>Duration of hospitalization not reported</p> <p>Symptom resolution</p> <p>COVID-19-related urgent care visits, including emergency department assessment or hospitalisation (reasons for care visits described in publication) ITT analysis I: 2 (3%) C: 11 (15%) difference in proportion 0-123, 95% CI 0-033–0-213; p=0-009 Per protocol analysis I: 1 (1%) C: 10 (14%) difference in proportions 0-131, 95% CI 0-043–0-218; p=0-004 NNT: 8</p> <p>Time to clinical recovery, as defined by self-reported time to symptom resolution, median [95% CI]; mean (SD) <i>Per protocol analysis</i></p>	<p>Definitions: -</p> <p>Remarks: • Open-label trial; no role of sponsor in design and analysis</p> <p>Authors conclusion: Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline.				<p>I: 7 days [6–9]; 8 days (SD 5) C: 8 days [7–11]; 12 days (SD 8) log-rank test for median, p=0.007</p> <p><u>Presence self-reported symptoms at day 14</u> I: 7 (10%) C: 21 (30%) difference in proportion 0.204 (95% CI 0.075–0.334); p=0.003</p> <p><u>Viral symptoms; Symptom resolution, day 14, defined by InFLUenza Patient-Reported Outcome (FLUPro) questionnaire; 37 items, score 0–4 per item; higher scores indicates more severe symptoms</u> I: 55 (82%) C: 49 (72%) difference in proportions 0.100, 95% CI –0.040 to 0.241; p=0.166 Time to symptom resolution; as measured by the FLUPro I: 3 days (95% CI 2 to 5) C: 4 days (3 to 6) (log-rank test p=0.080) <u>Common Cold Questionnaire (CCQ); total score of 27; higher score indicates more severe symptoms; mean change in CCQ total score between days 0 – 14</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I: -0.49 (95% CI -0.63 to -0.35) C: -0.37 (-0.51 to -0.24) MD -0.12, 95% CI -0.21 to -0.02; p=0.016).</p> <p><u>Need for antipyretics</u> (paracetamol, aspirin, or ibuprofen), median proportion of days I: 27% (IQR 0-50) C: 50% (15-71; Wilcoxon test p=0.025).</p> <p>Blood oxygen saturation; proportion of days with oxygen saturations of 94% or less, during the first 14 days, I: 19% (SD 24) C: 22% (27) (Wilcoxon test p=0.627; Hodge-Lehmann median 0, 95% CI -0.07 to 0). <u>at least 1 day with oxygen saturations of 94% or less during first 14 days</u> I: 41 (59%) C: 40 (58%) (difference in proportions 0.006, 95% CI -0.158 to 0.170; p=0.943).</p> <p><u>Fever ($\geq 37.5^{\circ}\text{C}$)</u> number of days in first 14 days, mean (SD) <i>Per protocol analysis</i> I: 2% (SD 6) in the budesonide C: 8% (18) Wilcoxon test p=0.051; Hodge-Lehmann median 0%, 95% CI 0 to 0). <u>At least 1 day of fever</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I: 8 (11%) C: 16 (23%) participants difference in proportion 0.067 (95% CI -0.678 to 0.242), p=0.076</p> <p><u>Need for respiratory support</u> not reported</p> <p>Safety <u>Adverse events</u> I: 5 (4 sore throat; 1 dizziness; all self-limiting and fully resolved on cessation of budesonide) C: 0</p> <p>Virological outcomes <u>Cycle threshold reduction between visits 1 and 2</u> I: 3.20 [95% CI 0.46 to 5.94] C: 3.75 [1.00 to 6.50] MD -0.55 (95% CI -2.39 to 1.29) p=0.554</p>	
2.4. Methylprednisolone							
Solanich, 2021	<p><u>Type of study:</u> Randomized, single-center, open-label, phase II trial</p> <p><u>Setting:</u> One public hospital for adults, between 1 April and 2 May 2020</p> <p><u>Country:</u> Spain</p> <p><u>Source of funding:</u></p>	<p>Severe COVID-19 patients with lung injury and systemic hyperinflammatory syndrome</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • COVID-19 confirmed by nasopharyngeal RT-PCR • New pulmonary infiltrates • Respiratory failure (PaO₂/FiO₂ <300 or SpO₂/FiO₂ <220) • High analytical inflammatory parameters: CRP >100 mg/L, D- Dimer >1000 µg/L, ferritin > 1000 µg/L <p><u>Exclusion criteria:</u></p>	<p>Methylprednisolone pulses and tracolimus added to standard of care</p> <p>methylprednisolone pulses of 120 mg/day had to be administered on 3 consecutive days after randomization (if not previously administered). The administration of higher doses or longer duration of corticosteroids was allowed if their treating physicians considered it appropriate.</p>	<p>Standard of care</p> <p>SoC included measures of supplemental oxygen and respiratory support, fluid therapy, antipyretic treatment, postural measures, low molecular weight</p>	<p><u>Length of follow-up:</u> 56 days</p> <p><u>Loss-to-follow-up:</u> Intervention: 3/27 (11.1%) Reasons (describe) n=3: treatment compliance</p> <p>Control: 2/28 (7.1%) Reasons (describe) n=2: deceased with <5 days of follow-up</p>	<p>Clinical outcomes <u>COVID-19-related mortality (28 day)</u> I: 3/27 (11.1%) C: 4/28 (14.3%) OR: 0.76 [0.13-4.02] <u>COVID-19-related mortality (56 day)</u> I: 4/27 (14.8%) C: 4/28 (14.3%) OR: 1.04 [0.21-5.13] <u>All-cause mortality (28 day)</u> I: 4/27 (14.8%) C: 6/28 (21.4%) OR: 0.65 [0.14-2.67]</p>	<p><u>Definitions:</u> Clinical stability was defined as fulfilling all of the following criteria for 48 consecutive hours: body temperature ≤37.5°C; PaO₂/FiO₂ >400 and/or SpO₂/FiO₂ > 300; and respiratory rate ≤ 24 rpm. Treatment failures were defined as: 1) not hospitalized and no limitations of activities; 2) not hospitalized, with limitation of activities, home oxygen requirement, or both; 3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>COVID-19 funding from the Departament de Salut de la Generalitat de Catalunya</p> <p><u>Conflicts of interest:</u> No conflict of interest</p>	<ul style="list-style-type: none"> Life expectancy ≤ 254h Glomerular filtration ≤ 30 ml/min/1.73m² Leukopenia ≤ 4000 cells/μl or other immunosuppression conditions Concomitant potential serious infections Contraindication for corticosteroids or tacrolimus Known hypersensitivity to study drugs, their metabolites or formulation excipient Previous participation in RCT <3 months before <p><u>N total at baseline:</u> N = 55 Intervention: 27 Control: 28</p> <p><u>Important characteristics:</u> Age, mean (SD): I: .61.5 y (13.9) C: 64.8 y (12.1)</p> <p>Sex, n/N (%) male: I: 23/27 (85.2%) C: 21/28 (75.0%)</p> <p>Disease severity, mean (SD): <i>Defined by ordinal scale</i> I: 5 (5-5) C: 5 (5-6) <i>Score 5:</i> I: 23/27 (85.2%) C: 16/28 (57.1%) <i>Score 6:</i> I: 4/27 (14.8%) C: 12/28 (42.9%)</p> <p>Groups are not completely balanced, especially regarding</p>	<p>Tacrolimus starting dose was 0.05 mg/kg (Adoport®) twice daily. Patients using lopinavir-ritonavir received 0.2 mg (Modigraf®) every 48 h. Thereafter, tacrolimus dosing was individualized through therapeutic drug monitoring to achieve blood trough levels of 8–10 ng/ml. In addition, patients in the experimental arm could receive standard of care (SoC) for their management in accordance with treating physicians.</p>	<p>heparins, and could also include treatments with unproved antiviral (lopinavir-ritonavir, hydroxichloroquine, etc.) or immunosuppressive (any regimen of corticosteroids, tocilizumab, anakinra, etc.) drugs, or those necessary at the discretion of the treating physician, except for cyclosporine and/or tacrolimus.</p>	<p><u>Incomplete outcome data:</u> Some incomplete data regarding viral load, however, reasons not clear.</p>	<p><u>COVID-19-related mortality (28 day)</u> I: 5/27 (18.5%) C: 6/28 (21.4%) OR: 0.84 [0.21-3.28] <i>Also reported: mortality rates at day 10, time to COVID-19 related death, and time to all-cause death.</i></p> <p><u>Duration of hospitalization</u> I: 13.0 (8.5-21.0) C: 14.0 (9.0-22.5) <u>Discharge at day 65</u> I: 21/27 (77.8%) C: 21/28 (75.0%) OR: 1.16 [0.32-4.28]</p> <p><u>Time to symptom resolution/clinical stability within 56 days</u> I: 21/27 (77.8%) C: 22/28 (78.6%) OR: 0.96 [0.25-3.61] <i>Also reported: clinical stability at 10 and 28 days, ordinal scale at day 5, day 10, day 28 and day 58, time to body temperature normalization, PaO₂/FIO₂ >400 or SpO₂/FIO₂ >300, and respiratory rate <24 bpm.</i></p> <p><u>Respiratory support Duration of oxygen support (days)</u> I: 11.0 (8.0-19.5) C: 13.0 (7.75-23.0) p=0.953 <u>High-flow or ventilatory support therapies</u></p>	<p>nonmedical reasons); 4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions); 5) hospitalized, requiring any supplemental oxygen; 6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8) death.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Groups are not comparable on baseline (see patient characteristics) <p><u>Authors conclusion:</u> The combined use of methylprednisolone pulses and tacrolimus, in addition to the SoC did not significantly improve the time to clinical stability or other secondary outcomes compared with SoC alone in hospitalized patients with severe COVID-19. Although not statistically significant, patients receiving the experimental therapy had numerically lower all-cause mortality than those receiving SoC. No relevant differences were observed in the clearance of the virus or in the rate of adverse events between the two groups. The reason why the largest and longest corticosteroid doses were used in the control group remains unclear.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		time between symptom onset and randomization, the need for non-invasive ventilation or high-flow oxygen devices, corticosteroids use, CRP and creatinine kinase.				<p>I: 14/27 (51.9%) C: 18/28 (64.3%) p=0.509 <i>Also reported: duration of high-flow or ventilatory support</i></p> <p>Safety <u>Adverse events</u> I: 23/27 (85.2%) C: 23/28 (82.1%) <u>Serious adverse events</u> I: 9/27 (33.3%) C: 10/28 (35.7%)</p> <p>Virological outcomes <u>SARS-CoV-2 positive test at day 56</u> <u>Upper respiratory tract samples</u> I: 1/17 (5.8%) C: 1/20 (5.0%) <u>Blood samples</u> I: 1/22 (4.5%) C: 2/19 (10.5%) <i>OR/RR not reported</i> <i>Also reported: positive test at day 28, viral load.</i></p>	
Tang, 2021	<p><u>Type of study:</u> prospective, multicentre, single-blind, clinical RCT</p> <p><u>Setting:</u> Conducted between February and April 2020 in respiratory departments or infectious disease department of 7 tertiary hospitals in</p>	<p>Patients with COVID-19 pneumonia admitted to general wards for less than 72h.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Laboratory confirmed SARS-CoV-2 infection and had pneumonia; Age ≥ 18 y; Admitted to general wards for less than 72 h; Able to sign informed consent. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Severe immunosuppression; 	1 mg/kg per day of methylprednisolone dissolved in 100 mL 0.9% normal saline, administered intravenously for 7 days + standard care	100 mL 0.9% normal saline administered intravenously + standard care	<p><u>Length of follow up:</u> 14 days</p> <p><u>Loss to follow-up:</u> I: 0/43 (0%) C: 0/43 (0%)</p>	<p>Clinical outcomes <u>In-hospital mortality, n (%)</u> I: 0 (0%) / 43 C: 1 (2.3%) / 43 OR 0.977 [0.933 to 1.023] P = 0.314</p> <p><u>Duration of hospitalization, median (IQR), days</u> I: 17 (13–22) C: 13 (10–20) HR 1.300 [0.844 to 2.002] P = 0.235</p>	<p><u>Definitions:</u></p> <ul style="list-style-type: none"> Clinical deterioration: patient met at least one of the following criteria: the clinical symptoms and signs continue to deteriorate, new pulmonary or extrapulmonary lesions appear, the chest computed tomography indicates the progress, or the patient is transferred to the ICU or is dead. Clinical cure: patient met all of the following criteria: the clinical symptoms and signs of COVID-19 improved or alleviated (body temperature for 3 consecutive days, respiratory symptoms improved)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Beijing and Hubei province of China.</p> <p><u>Country:</u> China</p> <p><u>Source of funding:</u> Beijing Municipal Administration of Hospitals' Mission Plan, China; Excellence Program of Beijing Clinical Key Specialty (2018); Novel Coronavirus Pneumonia Key Technology Research and Development Funding of Beijing Municipal Administration of Hospitals.</p> <p>The authors declare no conflict of interest.</p> <p>Pfizer Manufacturing Belgium NV produced the methylprednisolone, but was not involved in analysis of the results.</p>	<ul style="list-style-type: none"> • Pregnant or breastfeeding women; • Corticosteroid needs for other diseases; • Refractory hypertension; • Epilepsy or delirium; • Glaucoma; • Active gastro-intestinal bleeding within 3 months; • Refractory hypokalemia; • Secondary bacterial or fungal infection; • Unwilling or unable to participate or complete the study; • Participation in other studies <p><u>N total at baseline:</u> N = 86 Intervention: 43 Control: 43</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 57 y (49-67) C: 55 y (38-65) Sex, n/N (%) male: I: 21/43 (48.8%) C: 20/43 (46.5%)</p> <p>Groups were comparable at baseline, with the exception of the number of patients who showed the symptom "sputum". In the intervention group, more patients showed this symptom (I: 17 vs. C: 6).</p>				<p><u>ICU admission, n (%)</u> I: 2 (4.8%) / 43 C: 2 (4.8%) / 43 OR 1.000 [0.134 to 7.442] P = 1.000</p> <p><u>Clinical deterioration 14 days after randomization, n (%)</u> I: 2 (4.8%) / 43 C: 2 (4.8%) / 43 OR 1.000 [0.134 to 7.442] P = 1.000</p> <p><u>Clinical cure 14 days after randomization, n (%)</u> I: 22 (51.2%) / 43 C: 25 (58.1%) / 43 OR 1.326 [0.566 to 3.106] P = 0.516</p> <p><u>Time from randomization to clinical cure, median (IQR), days</u> I: 14 (10–19) C: 12 (9–17) HR 1.043 [0.673 to 1.617] P = 0.850</p> <p><u>Need for respiratory support</u> Not reported</p> <p><u>Safety</u> <u>Adverse events</u> Not reported</p> <p><u>Virological outcomes</u> <u>Time from virus shedding of SARS-CoV-2, median (IQR), days</u> I: 11 (6–16) C: 8 (2–12)</p>	<p>significantly, and computed tomographic images showed obvious absorption of bilateral extensive ground-glass opacification and/or consolidation), and no additional or alternative treatments were needed.</p> <ul style="list-style-type: none"> • Virus shedding: SARS-CoV-2-negative result of the nucleic acid tests from throat swabs for 2 consecutive times (sampling interval of at least 1 day). RT-PCR was used to test SARS-CoV-2. <p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Pfizer pharmaceuticals produced the intervention drug. • Single-blinded RCT: physicians were aware of treatment randomization • Trial was terminated prematurely (because the number of patients with COVID-pneumonia decreased). <p><u>Authors conclusion:</u> Due to early termination of this trial, most outcomes were difficult to estimate because of the low statistical power. However, the short-term early use of corticosteroid could suppress the immune cells, which may prolong SARS-CoV-2 shedding in patients with COVID-19 pneumonia, especially for the patients without acute respiratory failure. It was suggested that corticosteroids should not be added to standard therapy as a general treatment for the patients of COVID-19 patients; moreover, it should be evaluated according to the severity and necessity. The interpretation still needs to be further verified by a large sample size and randomized clinical trials.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						HR 1.782 [1.057 to 3.003] P = 0.030	
Corral-Gudino, 2021	<p>Type of study: Randomized, open-label, controlled, two-arm, parallel-group, trial</p> <p>Setting: 5 hospitals (Hospital Universitario Marqués de Valdecilla, Hospital Hortega, Hospital El Bierzo, Hospital Laredo, and Hospital Sierrallana) in Spain in April-May 2020</p> <p>Country: Spain</p> <p>Source of funding: The authors received no specific funding for this work.</p>	<p>Inclusion criteria: Eligible patients were hospitalized subjects over 18 years of age, with a laboratory confirmed diagnosis of SARS-CoV2 infection. Additional inclusion criteria were all the following: 1) Symptom duration ≥ 7 days 2) Radiological evidence of lung disease in chest X-ray or CT-scan 3) Moderate-to-severe disease with abnormal gas exchange: PaFi (PaO₂/FIO₂) < 300, or SAFI (SAO₂/FIO₂) < 400, or at least 2 criteria of the BRESCIA-COVID Respiratory Severity Scale (BCRSS) 4) Laboratory parameters suggesting a hyper-inflammatory state: serum C-Reactive Protein (CRP) >15 mg/dl, D-dimer > 800 mg/dl, ferritin > 1000 mg/dl or IL-6 levels > 20 pg/ml.</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> intubated or mechanically ventilated hospitalized in the ICU treated with corticosteroids or immunosuppressive drugs at the time of enrolment chronic kidney disease on dialysis pregnant <p>N total at baseline: N = 86,</p>	<p>Methylprednisolone (MP)</p> <p>Patients in the experimental group received intravenous (iv) MP 40mg bid for 3 days and then 20mg bid for 3 more days. The initiation of MP occurred on the same day of inclusion in the trial. The clinical teams freely prescribed interleukin-blocking agents and other therapies as indicated.</p>	<p>Standard of care (SOC)</p> <p>SOC included symptomatic treatment with acetaminophen, oxygen therapy, thrombosis prophylaxis with low molecular weight heparin, and antibiotics for co-infections. Azithromycin, hydroxychloroquine and lopinavir plus ritonavir were frequently prescribed.</p>	<p>Patients were followed until hospital discharge or day 28 after inclusion.</p> <p>91 patients were included in GLUCOCOVID trial and 5 patients were later eliminated from the analysis (2 were previously on corticosteroids, 1 was on NIV, 1 was taken to the ICU after MP initiation, and 1 patient with initial suspicion of COVID-19 was finally diagnosed with vasculitis).</p>	<p>Composite end-point (included in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required noninvasive ventilation (NIV) (intention to treat analysis)) I: 14/35 (40%) C: 14/29 (48%) Relative risk (95%CI): 0.50 (0.13 – 1.93) P-value: 0.273</p> <p>Mortality at 28 days (intention to treat analysis) I: 7/35 (20%) C: 5/29 (17%) Relative risk (95%CI)*: 0.63 (0.25-1.62) P-value: 0.482</p> <p>Admission to ICU (intention to treat analysis) I: 6/35 (17%) C: 8/29 (28%) Relative risk (95%CI)*: 0.85 (0.27 – 2.66) P-value: 0.880</p> <p>Requirement of NIV (intention to treat analysis) I: 10/25 (29%) C: 7/29 (24%)</p>	<p>Remarks:</p> <ul style="list-style-type: none"> - Initial sample size was 90 patients in each study arm. In this paper we report the results of the interim analysis, which was planned a priori after inclusion of 90 patients to avoid delaying the communication of clinically useful data in the current pandemic scenario. - 86 patients were analyzed; 22 received MP according to the clinician's preference, and 64 were randomized. Although allowed by design, no patient was included in the control arm by clinician's preference. - More than 90% of the patients took hydroxychloroquine and/or azithromycin during hospital admission. - In two patients in the SOC group but none in the MP group, clinicians prescribed MP boluses after initial allocation because of deterioration of the patient's condition. - Percentage variation in biochemical markers of inflammation from baseline to six days after randomization, per protocol analysis of primary outcome, secondary outcome and adverse events in randomized and randomized plus preference patients and microbiology data of infections in randomized patients were available. <p>Authors conclusion: The planned sample size was not achieved, and our results should therefore be interpreted with caution. The use of MP had no significant effect</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>(22 received MP according to clinician's preference, and 64 were randomized) Intervention: 22 (preference) + 35 (randomized) Control: 29</p> <p><u>Important characteristics:</u> Age, mean (SD): I (randomized): 73±11 C: 66±12 Mean differences SOC vs MP (95% CI): -7 (-13 to -2)</p> <p>Sex, n/N (%) male: I (randomized): 23/35 (66%) C: 16/29 (55%) Mean differences SOC vs MP (95% CI): -11% (-33 to 13)</p> <p><i>Groups comparable at baseline?</i> Those in the MP arm were older, but the baseline characteristics were otherwise very similar across groups.</p>				<p>Relative risk (95%CI)*: 0.97 (0.34-2.79) P-value: 0.798</p> <p>Hyperglycaemia (intention to treat analysis) I: 9/35 (26%) C: 0/29 (0%) Relative risk (95%CI)*: 7.70 (1.10-40.4) P-value: 0.015</p> <p>Nosocomial infection (intention to treat analysis) I: 5/35 (14%) C: 1/29 (3%) Relative risk (95%CI)*: 2.12 (0.31-14.38) P-value: 0.637</p> <p>* Risk ratio were adjusted by age group (Mantel Haenszel) * Risk ratio were also published per stratified age group</p>	on the primary endpoint in ITT analysis; however, the PP analysis showed a beneficial effect due to MP, which consistent with other published trials support the use of glucocorticoids in severe cases of COVID-19.
Edalatifard, 2020	<p><u>Type of study:</u> RCT; single-blind, two-arm parallel, randomized, controlled trial</p> <p><u>Setting:</u> April 20, till Jun 20, 2020; multi-center; 2 university hospitals, Tehran</p>	<p>Severe hospitalized patients with confirmed COVID-19 (ARDS excluded)</p> <p><u>Diagnosis COVID-19:</u> 1. Positive RT-PCR for SARS-CoV-2 in nasopharyngeal swab or sputum samples 2. Abnormal CT scan finding (bilateral, subpleural, peripheral ground-glass opacities) with</p>	<p>Methylprednisolone pulse + standard of care</p> <p>(intravenous injection, 250mg/day for 3 days)</p>	<p>Standard of care, no methylprednisolone or other glucocorticoids</p> <p>Standard care: Hydroxychloroquine sulfate, Lopinavir, and Naproxen</p>	<p><u>Length of follow up:</u> For most outcomes 3 days of treatment and discharge time; primary outcomes: "All patients were followed-up from day 0 to day 3, improvement, hospital discharge or death and</p>	<p>Clinical outcomes Recovery, n (%) I: 32 (94.1) C: 16 (57.1) Death, n (%) I: 2 (5.9) C: 12 (42.9) Time to event (discharge or death), days, median±range I: 11.62±4.81 C: 17.61±9.84</p>	<p><u>Remarks:</u></p> <ul style="list-style-type: none"> Definitie van improvement niet duidelijk 6 patienten van controle groep kregen interventie behandeling en warden geëxcludeerd uit de analyse. Behandelaars niet blind voor behandeling <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> "This study was supported by a grant from Deputy of Research, Tehran University of Medical Sciences (Grant No. 99-1-101-47282)." "The authors declare that they have no competing interest.s"</p>	<p>oxygen saturation <90% at rest.</p> <p><u>Early pulmonary phase:</u> start of pulmonary involvement including hypoxia (SO₂<93%) tachypnea (RR> 18) and little dyspnea and based on CT scan findings.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age 18 years or older; • Confirmed COVID-19 with blood oxygen saturation <90%), elevated C-reactive protein (CRP >10), interleukin (IL)-6 (>6) at early pulmonary phase of disease before connecting to ventilator and intubation • agreed to give informed consent <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • intolerant or allergic to any therapeutic agents • Pregnant or lactating women • blood oxygen saturation <75% • positive pro-calcitonin (PCT) • troponin test • Acute Respiratory Distress Syndrome (ARDS) • uncontrolled hypertension (HTN) • uncontrolled diabetes mellitus (DM) • gastrointestinal problems or gastrointestinal bleeding (GIB) history • heart failure (HF) • active malignancies and received any immune-suppressor agents. <p>N total at baseline:</p>			<p>1 week after hospital discharge"</p> <p><u>Loss to follow-up:</u> I: 0 (0%) C: 0 (0%), n=6 excluded, received intervention therapy</p>	<p>Time to improvement, days, median±range I: 11.84±4.88 C: 16.44±6.93</p> <p>Survival rate, Kaplan–Meier Log-rank test: HR 0.293 (95% CI 0.154–0.556).</p> <p>Safety Severe adverse events I: 2 (5.8%) C: 2 (7.1%) Adverse events Infection, no (%) I: 1 (2.9%) C: 0 Edema, no (%) I: 1(2.9%) C: 0 Shock, no (%) I: 0 C: 2 (7.1%) Digestive bleeding, no (%) I: 0 C: 0 Others I: 0 C: 0 Of which events related to study treatment I: 0 C: 0 Psychiatric or delirium events I: 0 C: 0</p> <p>Also reported: Laboratory findings and clinical symptoms before</p>	<p>Our results suggest that methylprednisolone pulse could be an efficient therapeutic agent for hospitalised severe COVID-19 patients at the pulmonary phase.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>N = 68 Intervention: 34 Control: 34</p> <p><u>Important characteristics:</u> Age, mean \pm SD: I: 55.8y \pm 16.35 C: 61.7y \pm 16.62 Sex, n/N (%) male/female: I: 24 (70.6%)/ 10 (29.4%) C: 15 (53.5%)/ 13 (46.4%) Days from illness onset to Hospitalization, mean SD: I: 6.7 \pm 2.92 C: 6.9 \pm 3.09 Need for oxygen therapy: Nasal Cannula I: 4 (11.8%) C: 9 (32.1%) Simple Mask I: 5 (14.7%) C: 2 (7.1%) Reserve Mask I: 12 (35.3%) C: 6 (21.4%) Noninvasive ventilation I: 13 (38.2%) C: 10 (35.7%)</p> <p>Groups comparable at baseline? More males in the intervention group. More nasal cannula in control group, more simple mask and reserve mask in intervention group.</p>				and after treatment (comparison, repeated measures ANOVA)	
Jerônimo, 2020	<p><u>Type of study:</u> RCT</p> <p><u>Setting:</u> a tertiary care facility in Manaus, Brazil</p> <p><u>Country:</u> Brazil</p>	<p><u>Inclusion criteria:</u> hospitalized patients with clinical AND/OR radiological suspicion of COVID-19 (history of fever AND any respiratory symptom, e.g., cough or dyspnea AND/OR ground glass opacity OR pulmonary consolidation on CT scan),</p>	Intravenous sodium succinate MP (0.5 mg/kg), twice daily for 5 days	Placebo (saline solution)	Until discharge or death	<p><u>28-day mortality, %</u> I: 72/194 (37.1%) C: 76/199 (38.2%) P-value: 0.629</p> <p><u>7-day mortality, %</u> I: 32/194 (16.5%) C: 47/199 (23.6%)</p>	<p><u>Remarks:</u></p> <p><u>Authors conclusion:</u> "In conclusion, the use of MP during only 5 days in hospitalized patients with COVID-19 was not sufficient to improve prognosis, as opposed to RECOVERY</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> MVGL, WMM. No conflicts of interest.</p>	<p>aged ≥ 18 years, SpO₂ ≤ 94% at room air OR in use of supplementary oxygen OR under IMV.</p> <p><u>Exclusion criteria:</u> Patients were excluded if they had a history of hypersensitivity to MP, HIV/AIDS, chronic use of corticosteroids or immunosuppressive agents, pregnant or breastfeeding, decompensated cirrhosis or chronic renal failure.</p> <p><u>N total at baseline:</u> N = 416 Intervention: 194 Control: 199</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 54 (15) C: 57 (15) P= not reported</p> <p>Sex, n/N (%) male: I: 68/194 (35.1) C: 71/199 (35.7)</p> <p>Groups comparable at baseline? Yes</p>				<p>P-value: 0.089</p> <p><u>14-day mortality, %</u> I: 53/194 (27.3%) C: 63/199 (31.7%) P-value: 0.290</p> <p><u>Presence of viral RNA in the naso/oropharyngeal swab on day 5, %</u> I: 69/144 (47.9%) C: 66/139 (47.5%) P-value: 0.942</p>	<p>trial, in which dexamethasone was successfully used for 10 days. Our exploratory analysis showed that MP reduces mortality in hospitalized patients older than 60 years with COVID-19. Caution is needed in the use of steroids in less severe patients, as a trend towards more harm was seen in the lower age group."</p>
3. Hydroxychloroquine							
Barratt-Due, 2021	See evidence table of Barratt-Due (2021) by remdesivir.						
Arabi, 2021	<p><u>Type of study:</u> Randomized, embedded, multifactorial adaptive platform trial for community-acquired</p>	<p><u>Severe COVID-19 ICU patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • 18 years or older; • Admitted with suspected or confirmed COVID-19; • Receiving respiratory or cardiovascular organ failure 	<p><u>Lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir and hydroxychloroquine</u></p> <p>Lopinavir-ritonavir was administered for 5 days minimum, up to a</p>	<p><u>No antiviral agents against COVID-19</u></p>	<p><u>Length of follow-up:</u> 90 days</p> <p><u>Loss-to-follow-up:</u> Intervention 1: N = 6 (%) Reasons: not reported.</p>	<p><u>Clinical outcomes</u> <u>In-hospital deaths, n/N (%)</u> Intervention 1: 88/249 (35.3%) Intervention 2: 17/49 (34.7%) Intervention 3: 13/26 (50.0%) Control: 106/353 (30.0%)</p>	<p><u>Definitions:</u> - Organ support included the provision of invasive mechanical ventilation, non-invasive mechanical ventilation, high-flow nasal cannulae with a flow rate of at least 30 L per minute and a fractional inspired oxygen concentration of 0.4 or higher, or the infusion of vasopressor or inotropes for shock.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>pneumonia (REMAP-CAP).</p> <p><u>Setting:</u> 187 sites across 11 countries.</p> <p><u>Country:</u> United States of America, Canada, France, Germany, Ireland, Netherlands, Portugal, United Kingdom, Saudi Arabia, Australia, New Zealand.</p> <p><u>Source of funding:</u> Supported by the European Union; See the full-text publication of the study for the full description.</p> <p><u>Conflicts of interest:</u> See the full-text publication of the study for the full description.</p> <p>NCT02735707</p>	<p>support in an intensive care unit.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • If death was deemed to be imminent during the next 24 hours and one or more of the patients, substitute decision-maker, or attending physician are not committed to full active treatment; • Expected to be discharged from hospital the same day or the following day; • More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection; • Previous participation in this REMAP-CAP within the last 90 days; • Presence of any of the following exclusion criteria: known hypersensitivity to lopinavir-ritonavir and hydroxychloroquine, (2) receiving lopinavir-ritonavir or hydroxychloroquine as a usual medication prior to this hospitalization, (3) known human immunodeficiency (HIV) infection (an exclusion criterion from receiving lopinavir-ritonavir), (4) severe liver failure (an exclusion criterion from lopinavir-ritonavir), (5) known or suspected pregnancy, (6) receiving amiodarone as a usual medication prior to this hospitalization or any 	<p>maximum of 14 days or until ICU discharge whichever occurred frst. Lopinavir–ritonavir was administered at a dose of 400 mg of lopinavir and 100 mg of ritonavir every 12 h. For patients with a gastric tube who were unable to swallow tablets, lopinavir-ritonavir (at the same dose) was administered as a 5-ml suspension every 12 h or alternatively as two dissolved tablets or four crushed tablets (double dose), noting that systemic absorption is reduced by approximately 50% for crushed tablets</p> <p>Hydroxychloroquine</p> <p>Hydroxychloroquine was administered as two loading doses of 800 mg, 6-h apart, followed 6 h later by 400 mg 12 hourly for 12 doses. Tis dose regimen was supported by pharmacokinetic modelling and by guidance regarding safety from clinicians with experience with the use of hydroxychloroquine for the treatment of severe malaria. If a patient was unable to swallow, crushed hydroxychloroquine</p>		<p>Intervention 2: N = 1 (%) Reasons: not reported.</p> <p>Intervention 3: N = 1 (%) Reasons: not reported.</p> <p>Control: N = 9 (%) Reasons: not reported.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p><u>90-day survival (time-to-event analysis), adjusted HR (95% CI)</u> Intervention 1: aHR 0.83 (95% CI 0.65 to 1.07) Intervention 2: aHR 0.71 (95% CI 0.45 to 0.97) Intervention 3: aHR 0.58 (95% CI 0.36 to 0.92) Control: 1</p> <p><u>Duration of hospitalization</u> <i>Time to hospital discharge, adjusted HR, median (95% CI)</i> Intervention 1: aHR 0.83 (95% CI 0.68 to 0.99) Intervention 2: aHR 0.76 (95% CI 0.56 to 0.97) Intervention 3: aHR 0.63 (95% CI 0.42 to 0.89) Control: 1</p> <p><i>Time to ICU discharge, adjusted HR, median (95% CI)</i> Intervention 1: aHR 0.87 (95% CI 0.72 to 1.07) Intervention 2: aHR 0.74 (95% CI 0.52 to 0.94) Intervention 3: aHR 0.63 (95% CI 0.44 to 0.89) Control: 1</p> <p><u>Time to symptom resolution</u> <i>WHO scale at day 14, adjusted HR, median (95% CI)</i> Intervention 1: aHR 0.85 (95% CI 0.68 to 0.99)</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, among critically ill patients with COVID-19, treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy resulted in worse outcomes compared to no COVID-19 antiviral therapy</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>administration of amiodarone within the 72 h prior to the assessment of eligibility (an exclusion criterion from lopinavir-ritonavir), (7) high clinical risk of sustained ventricular dysrhythmia.</p> <p><u>N total at baseline:</u> N = 694; analysed: N = 677 Intervention 1: N = 255; N = 249 Intervention 2: N = 50; N = 49 Intervention 3: N = 27 ; N = 26 Control: N = 362; N = 353</p> <p><u>Important characteristics:</u> Age, mean (SD): Intervention 1: 61 y (13) Intervention 2: 56.3 y (13) Intervention 3: 60.3 y (8.9) Control: 60.8 y (12.9)</p> <p>Sex, n/N (%) male: Intervention 1: 182/254 (71.7%) Intervention 2: 35/50 (70%) Intervention 3: 19/27 (70.4%) Control: 252/362 (69.6%)</p> <p>Disease severity, mean (SD): <i>Defined by APACHE II score, median (IQR)</i> Intervention 1: 13.0 (8 to 18) Intervention 2: 12.5 (7.8 to 20.2) Intervention 3: 14 (10.2 to 20.8) Control: 13 (8 to 19)</p> <p>Groups comparable at baseline? Yes.</p>	<p>tablets were administered via an enteral tube.</p> <p>Combination therapy</p> <p>Combination of Lopinavir-ritonavir and hydroxychloroquine.</p>			<p>Intervention 2: aHR 0.76 (95% CI 0.56 to 0.97) Intervention 3: aHR 0.63 (95% CI 0.42 to 0.89) Control: 1</p> <p><u>Respiratory support</u> <i>Progression to invasive mechanical ventilation, ECMO, or death, restricted to those not intubated at baseline, n/N (%); adjusted OR, median (IQR)</i> Intervention 1: 89/176 (50.6%); aOR 0.75 Intervention 2: 17/24 (70.8%); aOR 0.58 (95% CI 0.24 to 1) Intervention 3: 11/14 (78.6%); aOR 0.42 (95% CI 0.16 to 0.95) Control: 107/239 (44.8%); aOR 1.00.</p> <p><i>Cardiovascular support-free days, median (IQR); adjusted OR (95% CI)</i> Intervention 1: 14 (-1 to 21); aOR 0.66 (95% CI 0.49 to 0.89) Intervention 2: 13 (-1 to 19); aOR 0.60 (95% CI 0.39 to 0.86) Intervention 3: -1 (-1 to 14); aOR 0.39 (95% CI 0.22 to 0.69) Control: 18 (-1 to 21); aOR 1.00.</p> <p><i>Respiratory support-free days, median (IQR); adjusted OR (95% CI)</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Intervention 1: 3 (-1 to 15); aOR 0.75 (95% CI 0.56 to 0.99)</p> <p>Intervention 2: 0 (-1 to 9); aOR 0.64 (95% CI 0.4 to 0.92)</p> <p>Intervention 3: -1 (-1 to 7); aOR 0.47 (95% CI 0.27 to 0.83)</p> <p>Control: 5 (-1 to 16); aOR 1.00.</p> <p>Safety</p> <p><u>Serious adverse events</u> <i>Patients with ≥1 serious adverse events, n/N (%); adjusted OR (95% CI)</i></p> <p>Intervention 1: 13/255 (5.1%); aOR 0.55 (95% CI 0.24 to 1.22)</p> <p>Intervention 2: 3/50 (6.0%); aOR 0.65 (95% CI 0 to 2.38)</p> <p>Intervention 3: 1/27 (3.7%); aOR 0.97 (95% CI 0.24 to 4.79)</p> <p>Control: 12/362 (3.3%) aOR 1.00.</p> <p><u>Serious ventricular arrhythmia or sudden unexpected death, n/N (%); adjusted OR (95% CI)</u></p> <p>Intervention 1: 6/239 (2.5%); aOR 1.30 (95% CI 0.56 to 3.28)</p> <p>Intervention 2: 2.49 (4.1%); aOR 0.88 (95% CI 0.27 to 3.55)</p> <p>Intervention 3: 2/26 (7.7%); aOR 0.62 (95% CI 0.18 to 2.60)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Control: 10/345 (2.9%); aOR 1.00. Virological outcomes <u>Viral clearance</u> Not reported.	
Schwartz, 2021	<p>Type of study: randomized, double-blind, placebo-controlled trial</p> <p>Setting: community-based in Alberta, with enrolment beginning April 15, 2020 and paused on May 22, 2020</p> <p>Country: Canada</p> <p>Source of funding: Calgary Health Trust, the University of Calgary, Alberta Innovates Health Solutions, Alberta Health Services and the Alberta Government provided funding. Hydroxychloroquine and matching placebo were provided by Apotex. Funders had no role in trial design, interpretation or</p>	<p>Community-dwelling individuals with confirmed COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adults SARS-CoV-2 infection confirmed by RT-PCR from a nasopharyngeal or pharyngeal swab within the previous 4 days symptom onset within the previous 12 days ≥ 1 risk factor for severe disease <p>Exclusion criteria:</p> <ul style="list-style-type: none"> hospitalized pregnant or breastfeeding unable to swallow pills unable to comply with the medical regimen used hydroxychloroquine, chloroquine, lumefantrine, mefloquine or quinine within the previous 30 days <p>N total at baseline: Randomized: N = 148 Intervention: N = 111 Control: N = 37</p> <p>Important characteristics: Age, mean (SD): I: .46.7 y (11.5) C: .46.9 y (11.0)</p> <p>Sex, n/N (%): male: I: 65/111 (58.6%)</p>	hydroxychloroquine 800 mg orally in divided doses on day 1 followed by 200 mg twice daily for 4 days (12 tablets over 5 days)	placebo	<p>Length of follow-up: 30 days</p> <p>Loss-to-follow-up: Based on the information presented in the flow chart (Fig. 2), no participants were lost to follow-up in the ITT population. However, the table of results (Tab. 2) shows that for most of the outcomes data was missing for ≥ 1 participants; the PP population consisted of 74/111 patients in the intervention group, and 31/37 patients in the control group.</p> <p>Incomplete outcome data: <u>Mortality within 30 days</u> I: 0/111 (0%) C: 0/37 (0%)</p> <p><u>Admission to ICU within 30 days</u> I: 1/111 (0.9%) C: 0/37 (0%)</p> <p><u>Hospitalization within 30 days</u> I: 4/110 (3.6%) C: 0/37 (0%)</p> <p>Time to symptom resolution <u>Time to COVID-19 recovery</u> Days, median I: 14 (95%CI: 10-20); data available for 89/111 participants C: 12 (95%CI: 7-18); data available for 35/37 participants p = 0.3</p>	<p>Primary outcome was the development of severe disease, defined as the composite of hospitalization, invasive mechanical ventilation, or death within 30 days.</p> <p>Clinical outcomes Mortality <u>Mortality within 30 days</u> I: 0/111 (0%) C: 0/37 (0%)</p> <p>Duration of hospitalization <u>Admission to ICU within 30 days</u> I: 1/110 (0.9%) C: 0/37 (0%)</p> <p><u>Hospitalization within 30 days</u> I: 4/110 (3.6%) C: 0/37 (0%)</p>	<p>Definitions: -</p> <p>Remarks: The trial recruited only 10% of the target sample size, stopping early because of a report on hydroxychloroquine safety (that was subsequently retracted) and a rapid decline in disease prevalence coinciding with control of the first wave of the COVID-19 pandemic.</p> <p>Authors' conclusion: There was no evidence that hydroxychloroquine reduced symptom duration or prevented severe outcomes among outpatients with proven COVID-19, but the early termination of our study meant that it was underpowered.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>publication decisions.</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported. Most importantly, the last author (MH) reports that Apotex Pharma provided the drug and placebo for the current trial as an in-kind contribution to the study. He was the main contact with Apotex Pharma and has no other relationship with the company; there were no obligations attached to this donation of drug and placebo.</p>	<p>C: 17/37 (45.9%)</p> <p>Participants in the intervention group less often had diabetes or asthma. Also, they less often had shortness of breath, malaise, myalgias, coryza, dysgeusia and diarrhea, but more often had nausea; unclear whether these differences are statistically significant.</p>			<p>I: 1/111 (0.9%) C: 0/37 (0%)</p> <p><u>Time to symptom resolution</u> Days, median I: 22/111 (19.8%) C: 2/37 (5.4%)</p> <p><u>Development of severe disease, defined as the composite of hospitalization, invasive mechanical ventilation or death within 30 days</u> I: 1/111 (0.9%) C: 0/37 (0%)</p> <p>The safety population consisted of 91/111 patients in the intervention group and 33/37 patients in the placebo group who took at least 1 tablet of the study drug.</p>	<p>Respiratory support Not reported.</p> <p>Other <u>Development of severe disease, defined as the composite of hospitalization, invasive mechanical ventilation or death within 30 days</u> I: 4/110 (3.6%) C: 0/37 (0%) p = 0.6</p> <p><u>Disposition at day 30</u> Recovered vs. Ongoing symptoms, not hospitalized vs. Unknown, not hospitalized or deceased I: 67/110 (60.9%) vs. 23/110 (20.9%) vs. 20/11020/ (18.2%); missing for 1 patient C: 29/37 (78.4%) vs. 5/37 (16.2%) vs. 2/37 (5.4%)</p> <p>Safety <u>Serious adverse events within 30 days</u> I: 3/91 (3.3%) C: 0/33 (0%) p = 0.6</p> <p><u>Emesis within 30 days</u> I: 5/91 (5.5%) C: 0/33 (0%) p = 0.3</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Ader, 2021	<p>Type of study: RCT, phase 3 open-label (DisCoVeRY)</p> <p>Setting: 30 sites in France and 2 in Luxembourg, between March 22nd and June 29th.</p> <p>Country: France and Luxembourg</p> <p>Source of funding: The study was founded by Programme Hospitalier de Recherche Clinique (PHRC-20-0351) (Ministry of Health), from the DIM One Health</p>	<p>Hospitalized patients, peripheral oxygen saturation $\leq 94\%$ (moderate) or requiring supplemental oxygen (severe)</p> <p>Inclusion criteria: adults (≥ 18-year-old) a PCR-proven (< 72 hours) SARS-CoV-2 infection pulmonary rales or crackles with a peripheral oxygen saturation $\leq 94\%$ or requiring supplemental oxygen</p> <p>Exclusion criteria: Enrolment in another investigative trial Use of other antivirals</p> <p>N total at baseline: N = 583</p> <p>Intervention: -L/r: 145</p>	<p>-lopinavir/ritonavir (L/r) (400 mg lopinavir and 100 mg ritonavir 234 orally twice on day for 14 days) + SoC</p> <p>- lopinavir/ritonavir plus IFN-β-1a (L/r + IFN) (44 μg of subcutaneous IFN-β-1a on days 1, 3, and 6 +SoC</p> <p>-hydroxychloroquine (HCQ) (400 mg orally, 236 twice on day 1 as a loading dose followed by 400 mg once daily for 9 days + SoC</p> <p>Supportive treatments corticosteroids, anticoagulants or immunomodulatory agents were allowed</p>	<p>Standard of care (SoC)</p> <p>Supportive treatments corticosteroids, anticoagulants or immunomodulatory agents were allowed.</p>	<p>Length of follow up: 29\pm3 days</p> <p>Loss to follow-up: L/r: 1/145 (0.7%)</p> <p>Reason: did not receive at least one dose of intervention.</p> <p>L/r + IFN: 1/145 (0.7%)</p> <p>Reason: did not receive at least one dose of intervention.</p> <p>HCQ: 2/145 (1.4%)</p> <p>Reason: did not receive at least one dose of intervention.</p> <p>C: 0/148 (0%)</p>	<p>All analyses were stratified by severity at randomization, and adjusted effect measures are reported.</p> <p>Clinical outcomes</p> <p>Mortality (within 28 days), n (%)</p> <p>Moderate subgroup L/r: 4 (4.3%) L/r + IFN: 4 (4.4%) HCQ: 6 (6.5%) C: 5 (5.3%)</p> <p>Severe subgroup L/r: 10 (19.6%) L/r + IFN: 13 (24.1%) HCQ: 5 (9.6%) C: 7 (13.0%)</p>	<p>Definitions: *7-point ordinal scale of the WHO Master Protocol (v3.0, March 3, 2020):</p> <p>1. Not hospitalized, no limitation on activities; 2. Not hospitalized, limitation on activities; 3. Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6. Hospitalized, on invasive mechanical ventilation or ECMO; 7. Death.</p> <p>Remarks: Based on interim analyses (see Supplementary Appendix), enrolment in the hydroxychloroquine arm was prematurely stopped on June 17th , and enrolment in lopinavir containing arms was stopped on June 29th 2020 (futility and safety concerns).</p> <p>The trial was performed in the early phase of the COVID-19 pandemics and the SoC underwent substantial changes over time</p> <p>Authors conclusion:</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Île-de-France (R20117HD), and from REACTing, a French multi-disciplinary collaborative network working on emerging infectious diseases. The funding sources had no role in the analysis of the data nor in the decision of publication.</p> <p>Conflicts of interest:</p> <p>F.R. reports personal fees from Gilead Sciences, personal fees from MSD, personal fees from Pfizer, personal fees from TheraTechnologies, personal fees from ViiV Healthcare, outside the submitted work. F.G. reports grants from BioMerieux, personal fees and non-financial support from</p>	<p>-L/r + IFN: 145</p> <p>-HCQ: 145</p> <p>Control: 148</p> <p>Important characteristics:</p> <p>Age, median [IQR]:</p> <p>L/r: 63 [55-71]</p> <p>L/r + IFN: 64 [53-71]</p> <p>HCQ: 65 [55-71]</p> <p>C: 62 [52-71]</p> <p>Sex, n/N (%) male:</p> <p>L/r: 106/145 (73.1%)</p> <p>L/r + IFN: 103/145 (71.0%)</p> <p>HCQ: 104/145 (71.7%)</p> <p>C: 105/148 (70.9%)</p> <p>Baseline severity of COVID-19, n/N (%):</p> <p>Moderate disease (receiving low-flow supplemental oxygen or not requiring oxygen)</p> <p>L/r: 94/145 (64.8%)</p>				<p>L/r vs control: OR=1.24 (0.55 to 2.82) [P=0.60]</p> <p>L/r + IFN vs control: OR=1.51 (0.69 to 3.34) [P=0.30]</p> <p>HCQ vs control: OR=0.93 (0.40 to 2.20) [P=0.88]</p> <p>Duration of hospitalization</p> <p>Time to hospital discharge within 29 days</p> <p>L/r vs control: HR=0.77 (0.58 to 1.02) [P=0.07]</p> <p>L/r + IFN vs control: HR=0.72 (0.54 to 0.96) [P=0.026]</p> <p>HCQ vs control: HR=0.83 (0.62 to 1.10) [P=0.20]</p> <p>Time to symptom resolution</p> <p>Clinical status at 7-point ordinal scale* at day 15</p> <p>L/r vs control: OR=0.83 (0.55 to 1.26) [P=0.39]</p>	<p>In patients admitted to hospital with COVID-19, lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine were not associated with clinical improvement at day 15 and day 29, nor reduction in viral shedding, and generated significantly more SAEs in lopinavir/ritonavir-containing arms. These findings do not support the use of these investigational treatments for patients hospitalized with COVID-19.</p>

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	<p>Gilead, non-financial support from Corevio, outside the submitted work.</p> <p>G.P. reports grants and personal fees from Gilead Sciences, grants and personal fees from Merck, grants and personal fees from ViiV Healthcare, grants and personal fees from TheraTechnologies, outside the submitted work.</p> <p>K.L. reports personal fees and non-financial support from Gilead, personal fees and non-financial support from Janssen, personal fees and non-financial support from MSD, personal fees and non-financial support from ViiV Healthcare, personal fees and non-financial support from</p>	<p>L/r + IFN: 91/145 (62.8%)</p> <p>HCO: 93/145 (64.1%)</p> <p>C: 94/148 (63.5%)</p> <p>Severe disease (requiring non-invasive ventilation or high-flow oxygen devices, invasive mechanical ventilation or ECMO)</p> <p>L/r: 51/145 (35.2%)</p> <p>L/r + IFN: 54/145 (37.2%)</p> <p>HCO: 52/145 (35.9%)</p> <p>C: 54/148 (36.5%)</p> <p>Groups comparable at baseline?</p> <p>Not reported.</p>				<p>L/r + IFN vs control: OR=0.69 (0.45 to 1.04) [P=0.08]</p> <p>HCO vs control: OR=0.93 (0.62 to 1.41) [P=0.75]</p> <p>Clinical status at 7-point ordinal scale* at day 29</p> <p>L/r vs control: OR=0.93 (0.62 to 1.41) [P=0.74]</p> <p>L/r + IFN vs control: OR=0.76 (0.50 to 1.15) [P=0.19]</p> <p>HCO vs control: OR=1.16 (0.77 to 1.75) [P=0.49]</p> <p>Respiratory support</p> <p>Ventilator-free days until day 29</p> <p>L/r vs control: LSMD=-0.98 (-2.96 to 1.00) [P=0.33]</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Abbvie, during the conduct of the study. Y.Y. has nothing to disclose. He has been a board member receiving consultancy fees from ABBVIE, BMS, Gilead, MSD, J&J, Pfizer, and ViiV Healthcare, however all these activities have been stopped in the 03 past years. F.L. reports personal fees from Gilead personal fees and non-financial support from MSD, non-financial support from Astellas, non financial support from Eulmedica, outside the submitted work. A.K. reports personal fees from Baxter, personal fees from Aspen, personal fees from Aguettant, outside the submitted work. S.N. reports personal fees from</p>					<p>L/r + IFN vs control:LSMD=-2.01 (-4.03 to 0.00) [P=0.05]</p> <p>HCQ vs control: LSMD=0.09 (-1.93 to 2.10) [P=0.93]</p> <p>Safety</p> <p>Adverse events, n/N (%)</p> <p>Any adverse events</p> <p>L/r: 119/144 (82.6%); p=0.02</p> <p>L/r + IFN: 117/144 (81.3%); p=0.04</p> <p>HCQ: 109/143 (76.2%); p=0.35</p> <p>C: 105/148 (70.9%)</p> <p>Any serious adverse events</p> <p>L/r: 76/144 (52.8%); p=0.02</p> <p>L/r + IFN: 78/144 (54.2%); p=0.01</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>MSD, personal fees from Pfizer, personal fees from Gilead, personal fees from Biomérieux, personal fees from BioRad, outside the submitted work. F.D. reports personal fees from Gilead, outside the submitted work. J.N. reports non448 financial support from MSD France, non-financial support from GILEAD Sciences, personal fees from PASCALEO, outside the submitted work. J.M. reports non-financial support from GILEAD, outside the submitted work. A.M. reports personal fees from MSD, personal fees from GILEAD, personal fees from JANSSEN, personal fees from Viiv Healthcare, outside the</p>					<p>HCQ: 63/143 (44.1%); p=0.34</p> <p>C: 57/148 (38.5%)</p> <p>Virological outcomes</p> <p>Viral clearance</p> <p>The slope of the decrease of the viral loads in Nasopharyngeal swab (NPS) over time was not significantly affected by any of the investigational treatments. No significant difference in the proportion of participants with detectable viral loads at each sampling time was observed in the NPS nor in the lower respiratory tract (LRT) specimens.</p> <p>Also available:</p> <p>Secondary efficacy outcome measures were the clinical status at day 29 and the time to an improvement of 2 categories as measured on the 7-point ordinal scale or hospital discharge until</p>	

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	<p>submitted work. M.H. reports grants from Fonds Erasme- COVID- Université Libre de Bruxelles, grants from Belgian health Care Knowledge Center, during the conduct of the study; personal fees from Gilead advisory board on education on invasive fungal infections, personal fees from Pfizer: moderator for session on Isavuconazole, outside the submitted work. D.C. reports personal fees from Gilead, grants and personal fees from Janssen, outside the submitted work. C.B. reports personal fees from Da Volterra, personal fees from Mylan</p> <p>Pharmaceuticals, outside the submitted work.</p>					<p>day 29, the time to National Early Warning Score 2 (NEWS2) ≤ 2 or hospital discharge until day 29, the time to hospital discharge until day 29, oxygenation- and ventilator-free days until day 29, 29-day mortality, and the SARS-CoV-2 detection and quantitative normalized viral loads. Trough plasma concentrations of lopinavir, ritonavir and hydroxychloroquine were measured at days 1 and 3. Secondary safety outcomes included the cumulative incidence of any grade 3 or 4 AE, or of any serious adverse event (SAE, according to the DAIDS Table</p> <p>264 for Grading the Severity of Adult and Paediatric Adverse Events, v2.1, July 2017) and the proportion of patients with a premature suspension or discontinuation for any reason of the investigational treatments.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	F.M. reports grants from Sanofi, grants and personal fees from Da Volterra, outside the submitted work. All other authors have nothing to disclose.						
Réa-Neto, 2021	<p>Type of study: RCT (open-label)</p> <p>Setting: 6 hospitals in Curitiba, Brazil April 16 to August 06, 2020</p> <p>Country: Brazil</p> <p>Source of funding: Not reported.</p> <p>Conflicts of interest: No competing interest.</p> <p>clinicaltrials.gov nr, NCT04420247, "Retrospectively Registered"</p>	<p>Patients admitted to ICU</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Age ≥ 18 with flu symptoms (runny nose, dry or productive cough, sore throat and/or fever) associated with: clinical need for supplemental oxygen for dyspnea, pulse oxygen saturation ≤ 94% on room air, pulmonary CT findings compatible with COVID-19 the necessity of mechanical ventilation (MV) and a diagnosis of SARS-CoV-2 infection confirmed by molecular analysis or RT-PCR performed at admission <p>Exclusion criteria:</p> <ul style="list-style-type: none"> History of cardiopathy or any kind of arrhythmia psoriasis seizure G6PD deficiency myasthenia gravis ALT/AST > 5* ULN creatinine clearance < 30 ml/min/1.73 m² pregnancy or lactation 	<p>Chloroquine or hydroxychloroquine for 5 days plus standard treatment</p> <p>Chloroquine: 450 mg twice a day on day 1 and 450 mg once daily from days 2-5</p> <p>Hydroxychloroquine: 400 mg twice a day on day 1 and 400 mg once daily from days 2-5</p>	standard treatment only	<p>Length of follow up: 28 days</p> <p>Loss to follow-up: I: 0/53 (0%) C: 1/52 (1.9%)</p>	<p>The modified intention-to-treat analysis was restricted to 105 patients. Results also reported for Clq and HClq separately (see supplement of article)</p> <p>Clinical outcomes Mortality (28 day) I: 16 (30%) C: 10 (19%) (Difference (95% CI): 1.57 (0.79 to 3.13), p= 0.236) RR 1.57 [95% CI 0.79 to 3.13], p=0.196</p> <p>Duration of hospitalization ICU LOS (Length of stay) among survivors, median (IQR), days: I: 3.5 (1–12) C: 3 (0–7) (Difference (95% CI): 1 (– 2.6 to 4.6), p= 0.368)</p> <p>Hospital LOS among survivors, median (IQR), days: I: 7.5 (5–16) C: 7 (4–12) (Difference (95% CI): 1 (– 2.9 to 4.9), p= 0.257)</p>	<p>Primary outcome: Clinical status measured on day 14 after randomization with a WHO 9-point ordinal scale.</p> <p>Secondary outcomes: all-cause mortality; invasive MV use; the incidence of acute renal dysfunction in 28 days; clinical status of patients on days 5, 7, 10 and 28</p> <p>Definitions: *WHO Score on nine-point ordinal scale: (0) non-hospitalized and no clinical or virological evidence of infection; (1) non-hospitalized and no limitation on activities; (2) non-hospitalized, but with limitation on activities; (3) hospitalized, but not requiring supplemental oxygen; (4) hospitalized and on oxygen via mask or nasal prongs; (5) hospitalized, on non IVM or high-flow oxygen or pressure support ventilation in weaning mode; (6) hospitalized, intubated and on MV; (7) hospitalized on MV and additional organ support (renal replacement therapy, vasoactive drugs or extracorporeal membrane oxygenation), and (8) dead</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> known Clq/HClq allergy <p><u>N total at baseline:</u> N = 142 Intervention: 71 Control: 71 The modified intention-to-treat analysis: N=105 I: 53 C: 52</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 54.7 y (12.1) C: 52.8 y (12.6) Sex, n/N (%) male: I: 36/53 (67.9%) C: 34/52 (65.4%)</p> <p>Disease severity: <i>according to ventilatory support</i> <u>Intensive mechanical ventilation at baseline, no. (%):</u> I: 9/53 (17) C: 10/52 (19.2) <u>Score on nine-point ordinal scale*, no. (%):</u> 3: I: 1 (1.9), C: 0 (0) 4: I: 43 (81.1), C: 42 (80.8) 5: I: 0 (0), C: 0 (0) 6: I: 1 (1.9), C: 3 (5.8) 7: I: 8 (15.1), C: 7 (13.5)</p> <p>Groups were comparable at baseline, with the exception of the number of patients with hypertension (I: 19 vs. C: 21), DM (I: 11 vs. C: 16) and Immunocompromised state (I: 2 vs. C: 4). No p values reported.</p>				<p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> Mechanical ventilation - free days, median (IQR), days: I: 25 (3–28) C: 28 (4–28) (Difference (95% CI): – 3 (– 11.7 to 5.7), p= 0.236)</p> <p>Invasive mechanical ventilation incidence, no (%): I: 18 (41) C: 8 (19) (Difference (95% CI): 2.15 (1.05 to 4.40), p= 0.03)</p> <p><u>WHO 9-point ordinal score*, n(%):</u> <u>day 14</u> Score 0 : I: 11 (20.8) C: 22 (42.3) Score 1: I: 5 (9.4) C: 6 (11.5) Score 2: I: 10 (18.9) C: 6 (11.5) Score 3: I: 0 (0) C: 0 (0) Score 4: I: 6 (11.3) C: 2 (3.8) Score 5: I: 2 (3.8) C: 3 (5.8) Score 6: I: 3 (5.7) C: 3 (5.8) Score 7: I: 6 (11.3) C: 3 (5.8) Score 8: I: 10 (18.9) C: 7 (13.5) OR (95% CI): 2.41 (1.17 to 4.93; odds for worse clinical condition)</p>	<p><u>Remarks:</u> Open-label trial; The trial was stopped before reaching the planned sample size due to harmful effects; Retrospectively Registered protocol.</p> <p><u>Authors conclusion:</u> In conclusion, the addition of Clq/HClq to standard care in patients admitted to the hospital with severe COVID-19 resulted in clinical worsening and higher incidences of IMV and renal dysfunction, even though there was no difference in mortality. According to these findings, the use of Clq/HClq in patients with more severe forms of COVID-19 pneumonia is strongly contraindicated, and these results can inform clinical practice and guidelines.</p>

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						<p>P=0.016 Day 28 OR 2.47 (1.15-5.30), p=0.020</p> <p>Safety <u>Arrhythmias, no (%)</u> I: 4/68 (5.9) C: 1/70 (1.9) (Difference (95% CI): 3.92 (0.45 to 33.9), p= 0.176) One patient in the Clq/HClq group stopped treatment on the third day owing to severe arrhythmia</p> <p>Virological outcomes Not reported.</p> <p>Also available: Coagulopathy incidence, Acute renal dysfunction incidence, clinical status on days 5, 7, 10 and 28.</p>	
Reis, 2021	<p><u>Type of study:</u> RCT TOGETHER Trial</p> <p><u>Setting:</u> local public health authorities in Brazil, participants enrolled between June 2 and September 30, 2020.</p> <p><u>Country:</u> Brazil</p>	<p>High-risk adult outpatients (see inclusion criteria)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • 18 years or older • reported less than 8 days since onset of flulike symptoms or chest computerized tomography scan consistent with COVID-19 • at least one additional criterion for high risk: aged 50 years or older; presence of pulmonary disease, specifically moderate or severe persistent asthma, chronic 	<p><u>hydroxychloroquine group</u> loading dose of 800 mg at the time of randomization and then 400 mg in daily doses at 8:00 AM for 9 days.</p> <p><u>lopinavir-ritonavir group</u> a loading dose of 800 mg of lopinavir and 200 mg of ritonavir at the first 2 intakes, followed by 400 mg of lopinavir and 100 mg of ritonavir every 12 hours for the next 9 days.</p>	<p><u>placebo group</u> corresponding tablets of inert material (talc). Placebo bottles were matched for the same number of tablets as active hydroxychloroquine (placebo of hydroxychloroquine) and active lopinavir-ritonavir</p>	<p><u>Length of follow up:</u> 90 days</p> <p><u>Loss to follow-up:</u> I hydro: 16/214 (7.5%) Reasons: -7 Did not receive assigned Treatment -9 Had adhered <80% to assigned treatment</p> <p>I lopi-rito: 44/244 (18.0%) Reasons:</p>	<p>Clinical outcomes <u>Mortality</u> At the end of the trial, we recorded 3 fatalities, 1 in the placebo group and 2 in the lopinavir-ritonavir intervention group.</p> <p><u>Duration of hospitalization</u> COVID-19 hospitalization, n/N (%) I hydro: 8/214 (3.7) HR 0.76 (95% CI 0.30-1.88) I lopi-rito: 14/244 (5.7) HR 1.16 (95% CI 0.53-2.56) C: 11/227 (4.8)</p>	<p><u>Remarks:</u> The independent DSMB, based on interim analysis results, made the decision to stop enrollment to the hydroxychloroquine and lopinavir-ritonavir groups because of a low number of emerging events. This study reports on the final results inclusive of patients who had been randomized to hydroxychloroquine or lopinavir-ritonavir between the time of data-cut for interim analysis to the time of the DSMB meeting.</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> The trial was supported by the Bill and Melinda Gates Foundation. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.</p> <p><u>Conflicts of interest:</u> None reported by the authors.</p>	<p>obstructive pulmonary disease, pulmonary hypertension, or emphysema; diabetes requiring oral medication or insulin; hypertension requiring treatment; known cardiovascular diseases (congestive heart failure of any etiology, documented coronary artery disease, clinically manifest miscellaneous heart disease); symptomatic lung disease on chronic treatment; history of transplantation; obesity (body mass index ≥ 30 [calculated as weight in kilograms divided by height in meters squared]); immunocompromised status due to disease (eg, those living with HIV with a CD4 T-cell count of <200 cells/mm³, confirmed malignant neoplasm); immunocompromised status due to medication (eg, people taking 10 mg or more of prednisone equivalents a day); and patients with cancer</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • use of any of study drugs in 30 days prior to screening • clinical evidence of progression of COVID-19 (ie, use of oxygen supplementation; arterial oxygen saturation less than 94%; use of noninvasive positive-pressure ventilation support) • history of known lifethreatening cardiac arrhythmias; 		(placebo of lopinavir-ritonavir).	<p>-12 Did not receive assigned Treatment -32 Had adhered $<80\%$ to assigned treatment</p> <p>C: 19/227 (8.4%) Reasons: -7 Did not receive assigned Treatment -12 Had adhered $<80\%$ to assigned treatment</p> <p>At the end of the trial, 79 participants (11.5%) did not complete all phases of the study. The lopinavir-ritonavir intervention group had 44 participants (18%) who did not complete the study, which was more than either of the other 2 groups.</p>	<p>HR 1 [reference]</p> <p><u>Time to hospitalization, median (IQR), d</u> I hydro: 4.8 (1.40-6.12) I lopi-rito: 3.6 (2.50-4.76) C: 2.4 (0.76-3.20)</p> <p>All-cause hospitalization, n/N (%) I hydro: 11/214 (5.1) HR 0.96 (95% CI 0.42-2.17) I lopi-rito: 16/244 (6.6) HR 1.22 (95% CI 0.58-2.57) C: 12/227 (5.3) HR 1 [reference]</p> <p><u>Time to hospitalization, median (IQR), d</u> I hydro: 3.8 (1.88-6.43) I lopi-rito: 3.1 (2.31-4.75) C: 2.2 (0.79-3.12)</p> <p><u>Time to symptom resolution</u> WURSS Scale (Wisconsin Upper Respiratory Symptom Survey) We found no difference in the resolution of combined symptoms using the WURSS scale between either hydroxychloroquine and placebo or lopinavir-ritonavir and placebo, or for individual symptoms.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u></p>	<p>This randomized clinical trial found no clinical benefit to support the use of either hydroxychloroquine or lopinavir-ritonavir in an outpatient population. This adds to the growing evidence that these drugs should not be used for the treatment of COVID-19. While evidence emerges to evaluate these drugs as prophylaxis, as treatment for both outpatients and inpatients, hydroxychloroquine and lopinavir-ritonavir do not appear to confer any clinical benefit.</p>

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		<ul style="list-style-type: none"> • long QT syndrome • known allergy to study drugs <p><u>N total at baseline:</u> N = 685 Intervention hydro: 214 Intervention lopi-rito: 244 Control: 227</p> <p><u>Important characteristics:</u> Age, median (IQR): I hydro: 53 y (18-84) I lopi-rito: 54 y (18-94) C: 53 y (18-80) Sex, n/N (%) male: I hydro: 92/214 (43.0 %) I lopi-rito: 110/244 (45.1%) C: 106/227 (46.7 %) Participants with multiple risk factors, n/N (%) I hydro: 121/214 (56.5%) I lopi-rito: 134/244 (54.9%) C: 134/227 (59.0%)</p> <p>Groups comparable at baseline? With respect to covariates of age, body mass index, and comorbidities, the groups were generally well balanced.</p>				<p>Any Treatment-Emergent Adverse Events (TEAE), n/N (%) I hydro: 46/207 (22.2) I lopi-rito: 92/232 (39.7) C: 46/220 (20.9)</p> <p>Serious TEAE, n/N (%) I hydro: 11 (5.3) I lopi-rito: 20 (8.6) C: 12 (5.5)</p> <p>Virological outcomes <u>Virological clearance</u> Defined as 1 negative swab since Baseline.</p> <p>In the mixed-effect logistic model, the clearance for the hydroxychloroquine (odds ratio [OR], 0.91; 95% CI, 0.82-1.02) and lopinavir-ritonavir (OR, 1.04; 95% CI, 0.94-1.16) groups did not differ in comparison with the control group.</p> <p>Neither hydroxychloroquine nor lopinavir-ritonavir showed difference in viral clearance across all prespecified subgroups based on ITT analysis.</p>	
Gupta, 2021a	<u>Type of study:</u> Open-label randomized controlled trial	<u>Patients with moderate to severe COVID-19 infections who require hospitalized care.</u> <u>Inclusion criteria:</u>	Hydroxychloroquine + standard of care Patients in the HCQ arm received the drug as per	Standard of care Standard of care included	<u>Length of follow-up:</u> Four days. <u>Loss-to-follow-up:</u> Intervention:	Clinical outcomes <u>Mortality (28-30 day), n/N (%)</u> I: 10/55 (18.2%) C: 2/55 (3.6%)	<u>Definitions:</u> SOC: Standard of care included intravenous (IV) antibiotics to cover respiratory pathogens, IV dexamethasone at a dose of 4 mg every

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>with unblinded assessment.</p> <p><u>Setting:</u> Tertiary care centre of Indian Armed Forces Medical Services located in a metropolitan city.</p> <p><u>Country:</u> India.</p> <p><u>Source of funding:</u> No information.</p> <p><u>Conflicts of interest:</u> All authors have none to declare.</p>	<ul style="list-style-type: none"> Patients who were COVID-19 positive based on real time reverse transcription polymerase chain reaction (rRT PCR); Patients who were symptomatic for the disease for <5 days; Patients who were willing to participate in the trial and satisfied at least two of the following four criteria: (i) oxygen saturation (SaO₂) less than 95% as measured by digital pulse oximetry; (ii) respiratory rate more than 20/min; (iii) pulse rate more than 90/min or; (iv) imaging evidence of lung infection in the form of reticulonodular opacities, ground glass opacities, consolidation or acute respiratory distress syndrome. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients who were 14 years or less in age. <p><u>N total at baseline:</u> N = 110 Intervention: N=55 Control: N=55</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 57.8 y (12.6) C: 57.3 y (14.1) P=0.72</p> <p>Sex, n/N (%) male: I: 43/55 (76.8%) C: 37/55 (68.5%) P=0.20</p>	the following schedule: 400 mg twice on day 1, followed by 400 mg once daily from day 2 today 5.	intravenous (IV) antibiotics to cover respiratory pathogens, IV dexamethasone at a dose of 4 mg every 8 h for 5 days and subcutaneous low-molecular-weight heparin(LMWH) enoxaparin in dose of 40 mg (0.4 ml) once a day for 5days.	<p>N (%) Reasons (describe)</p> <p>Control: N (%) Reasons (describe)</p> <p><u>Incomplete outcome data:</u> Intervention: N (%) Reasons (describe)</p> <p>Control: N (%) Reasons (describe)</p>	<p>P=0.01</p> <p><u>Duration of hospitalization</u> <i>Days of hospitalization, mean (SD)</i> I: 13.89 (5.85) C: 13.67 (5.83) P=0.98</p> <p><u>Time to symptom resolution</u> <i>Days to normalization of SaO₂, mean (SD)</i> I: 6.54 (4.48) C: 7.59 (5.06) P=0.26</p> <p><u>Respiratory support</u> <i>Days on oxygen, mean (SD)</i> I: 8.49 (6.38) C: 7.98 (5.45) P=0.26</p> <p><i>Number of needing ventilator, n/N (%)</i> I: 10/55 (18.2%) C: 4/55 (7.27%) P=0.09</p> <p><i>Days from admission to ventilator, mean (SD)</i> I: 4.90 (4.88) C: 1.5 (2.38) P=0.18</p> <p><i>Days on ventilator, mean (SD)</i> I: 8.33 (8.60) C: 8.75 (3.09) P=0.37</p> <p>Safety <u>Adverse events</u></p>	<p>8 h for 5 days and subcutaneous low-molecular-weight heparin(LMWH) enoxaparin in dose of 40 mg (0.4 ml) once a day for 5days.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, in the rapidly changing world of COVID-19therapeutics, our open-label, parallel group, unblinded ran-domized control trial suggests that HCQ does not changeoutcomes in moderate to severe COVID-19 infection. It sup-ports some of the other observational studies and trials con-ducted in the last few months. We could not comment on thetoxicity of HCQ as trial was not designed to assess it. Thestrength of our trial is that it was randomized and therandomization was good as seen by the well matched baselinecharacteristics; we recruited more patients than our calcu-lated sample size and this helped us perform the adjustedanalysis without losing the strength of the study and ouroutcomes were both clinical and laboratory based. The chieflimitation of our trial is that there was no blinding atrandomization or at assessment. Our trial is relevant becauseit is one of the first few from India. It will help clinicians in notprescribing a drug which does not change outcomes in moderate to severe COVID-19 infection and may be potentiallylytoxic. It will help policy makers in closing the chapter on arepurposed drug which had gained a lot of popularity and spotlight at the beginning of the pandemic.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Disease severity, mean (SD): <i>Defined by SOFA score at admission (SD)</i> I: 2.6 (1.7) C: 2.4 (1.6) P=0.56 Groups comparable at baseline? Yes.				Not reported. Virological outcomes <u>Viral clearance</u> Not reported.	
Dub�e, 2021 HYCOVID trial	<u>Type of study:</u> RCT; double-blind, placebo-controlled <u>Setting:</u> 48 hospitals in France and the Principality of Monaco; April 2 to May 21, 2020 Start: April 1, 2020 Suspended: May 26, 2020 Stopped: June 9, 2020 <u>Country:</u> France, Monaco <u>Source of funding:</u> <i>[farmaceut betrokken? Zoja, beschrijf kort de rol]</i> <u>Conflicts of interest:</u>	Mild-to-moderate COVID-19 patients; almost all hospitalized (99%), with (60%) or without supplemental oxygen (severely ill patients requiring oxygen therapy needed > 3L / min or ICU admission excluded) <u>Inclusion criteria:</u> • Men and non-pregnant women; aged ≥18 years • diagnosis of COVID-19 confirmed by positive SARS-CoV-2 RT-PCR on a nasopharyngeal swab within 2 days or chest-CT • ≥1 of the following risk factors for worsening: (i) need for supplemental oxygen to reach a peripheral capillary oxygen saturation of more than 94% (SpO2 >94%) or a ratio of oxygen partial pressure to fractional inspired oxygen less than or equal to 300 mmHg (PaO2/FiO2 ≤300 mmHg); (ii) • age ≥75 years; (iii) age 60-74 years and presence of ≥ 1 of following comorbidities: obesity (body mass index ≥30 kg/m2), arterial hypertension requiring treatment, or diabetes mellitus requiring treatment	Hydroxychloroquine + standard care Hydroxychloroquine (200 mg tablets, orally) at a dose of two tablets twice daily on the first day followed by one tablet twice daily for 8 days (total hydroxychloroquine dose of 4 g) plus standard care	Placebo + standard care Matching placebo at a dose of two tablets twice daily on the first day followed by one tablet twice daily for 8 days plus standard care	<u>Length of follow up:</u> 28 days days <u>Loss to follow-up:</u> I: 2/125 (1.6%) Reason: withdrew consent C: 1/25 (0.8%) Reason: withdrew consent Incomplete data: Clinical status data are missing at Day 14 and 28 for two patients in each group; not further described	Clinical outcomes <u>Mortality - day 28</u> I: 6 (4.8) C: 11 (8.9) RR 0.54 (0.21–1.42) Mortality other: day 14 I: 6 (4.8) C: 6 (4.9) RR 0.99 (0.33–2.99) <u>Duration of hospitalization</u> 'not reported' <u>Time to symptom resolution</u> Clinical evolution; WHO 9-point Ordinal Scale for COVID-19*; RR (95% CI); <i>definitions: absence of deterioration: stability or decrease of at least one point on the ordinal scale; clinical improvement: decrease of at least one point on the ordinal scale; recovery: score of 0, 1, or 2</i> Day 14 Absence of deterioration I: 112 (90.3) C: 111 (90.2)	<u>Definitions:</u> WHO Ordinal Scale for Clinical Improvement: <i>0: patient uninfected, no clinical or virological signs of infection; 1: patient at home, without limitation of activities; 2: patient at home, with limitation of activities; 3: patient hospitalized without oxygen therapy; 4: patient with oxygen therapy by mask or nasal prongs; 5: patient under non-invasive ventilation or high-flow oxygen; 6: patient under invasive mechanical ventilation; 7: patient under invasive mechanical ventilation and additional organ support, including vasopressors, renal replacement therapy, and extracorporeal membrane oxygenation; 8: death.</i> <u>Remarks:</u> -trial prematurely stopped <u>Authors conclusion:</u> In this underpowered trial involving mainly older patients with mild-to-moderate COVID-19, patients treated with hydroxychloroquine did not experience better clinical or virological outcomes than those receiving the placebo.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • requiring > 3 L/min of oxygen to reach an SpO2 of 94% • clinical condition necessitating admission to ICU • negative SARS-CoV-2 RT-PCR • short-term life-threatening comorbidity (life expectancy <3 months), • any condition contraindicating hydroxychloroquine treatment (known hypersensitivity or allergy, retinopathy, concomitant treatment associated with a risk of ventricular arrhythmias, use of medications that are contraindicated with hydroxychloroquine and cannot be replaced or stopped during the trial) • conditions associated with an increased risk of adverse event <p><u>N total at baseline:</u> Randomized: N = 250 Intervention: 125 Control: 125 In analysis: I: 123 C: 124</p> <p><u>Important characteristics:</u> Median age (IQR) – yr I: 76 (60-85) C: 78 (57-87) Male sex – no. (%) I: 65 (52.0) C: 56 (44.8)</p>				<p>RR 1.01 (0.93–1.09) Clinical improvement I: 84 (67.7) C: 81 (65.9) RR 1.01 (0.86–1.18) Recovery I: 71 (57.3) C: 68 (55.3) RR 1.03 (0.83–1.27) Day 28 Absence of deterioration I: 115 (92.7) C: 112 (91.1) RR 1.02 (0.95–1.10) Clinical improvement I: 98 (79.0) C: 93 (75.6) RR 1.03 (0.90–1.16) Recovery I: 91 (73.4) C: 84 (68.3) RR 1.06 (0.91–1.24)</p> <p><u>Respiratory support</u> <i>Use of intubation and mechanical ventilation</i> Day 14 I: 3 (2.4) C: 3 (2.4) RR 0.99 (0.20–4.82) Day 28 I: 3 (2.4) C: 4 (3.3) RR 0.74 (0.17–3.26)</p> <p>Safety <u>Adverse events</u> I: 124 C: 120 <i>Any adverse event - no. of patients (%)</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Median time (IQR) from onset of symptoms to inclusion – days I: 5 (3-9) C: 5 (3-8)</p> <p>Score on ordinal scale – no. (%)</p> <p>1. Ambulatory, no limitation of activity I: 1 (0.8) C: 1 (0.8)</p> <p>2. Ambulatory, limitation of activity I: 1 (0.8) C: 0 (0.0)</p> <p>3. Hospitalized, no oxygen therapy I: 46 (36.8) C: 50 (40.0)</p> <p>4. Hospitalized, oxygen therapy (≤ 3 L/min) I: 77 (61.6) C: 74 (59.2)</p> <p>Groups comparable at baseline.</p>				<p>I: 70 (56.5%) C: 61 (50.8)</p> <p><i>Adverse event leading to discontinuation of treatment - no. of patients (%)</i></p> <p>I: 4 (3.2) C: 2 (1.7)</p> <p>Of which: cardiac rhythm or conduction disorders: I: 4; C: 1</p> <p>Skin rash: I: 0; C: 1</p> <p><i>Serious adverse event - no. of patients (%)</i></p> <p>I: 3 (2.4) C: 4 (3.3)</p> <p>Of which: cardiac rhythm or conduction disorders: I: 3; C: 3</p> <p>Rash: I: 0; C: 1</p> <p>Virological outcomes</p> <p><u>Viral clearance</u></p> <p>Positive SARS-CoV-2 RT-PCR</p> <p>Day 5 I: 75/103 (72.8) C: 73/100 (73.0) RR 1.00 (0.84–1.18)</p> <p>Day 10 I: 52/91 (57.1) C: 47/83 (56.6) RR 1.01 (0.78–1.31)</p>	
Purwati, 2021	<p><u>Type of study:</u> RCT; double-blind</p> <p><u>Setting:</u> Multicenter; 4 sites in Indonesia; July and August 2020</p>	<p><u>Mild-to-moderate COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age > 18 years positive result on the COVID-19 PCR swab test 	<p><i>Only treatment groups that are in line with the PICO and can be directly compared to the control treatment were included.</i></p> <p><i>Group A:</i></p>	<p>Standard of care</p> <p>including administration of 500 mg azithromycin once a day</p>	<p><u>Length of follow up:</u> 7-14 days</p> <p><u>Loss to follow-up:</u> 0</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> not reported</p> <p><u>Duration of hospitalization</u> not reported</p> <p><u>Symptom resolution</u> not reported</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> Little to no details about study design and procedures</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> Indonesia</p> <p><u>Source of funding:</u> 'Indonesian Intelligence Agency (BIN) as the primary sponsor of this research and collaboration with the Indonesian National Army (TNI-AD).'</p> <p><u>Conflicts of interest:</u> 'The authors declare no conflicts of interest regarding this work.'</p>	<ul style="list-style-type: none"> presented mild, moderate, or severe symptoms informed consent <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> pregnant or breastfeeding mothers, individuals with severe liver disorders (indicated by increases in transaminases levels three times or more in excess of the normal range), impaired renal functions (indicated by decreases in creatinine clearance of less than 60 mL/minute) arrhythmia, and/or a compromised potassium/magnesium balance receiving conventional plasma therapy and/or anti-IL-6 therapy QT prolongation when QTc >60 ms, QTc >500 ms with a narrow QRS, or QTc 550 ms with wide QRS occurring during treatment resistance to one of the combinations of antibiotics studied, drug allergy events, and adverse events due to the administration of other drugs <p><u>N total at baseline:</u> Total randomized = 754 Randomized to relevant groups: N = 501 Intervention: Group A: 128 Group C: 123 Group D: 131</p>	<p>combination of 200/50 mg lopinavir/ritonavir twice a day and 500 mg azithromycin once a day.</p> <p><i>Group C:</i> 200 mg hydroxychloroquine twice a day and 500 mg azithromycin once a day</p> <p><i>Group D:</i> combination of 400/100 mg lopinavir/ritonavir twice a day and 500 mg azithromycin once a day.</p>			<p><u>Need for respiratory support</u> not reported</p> <p>Safety <u>Adverse events</u>, number of subjects Group A: 4 (dizziness, tachycardia, hearing loss, abdominal pain) Group C: 2 (tachycardia, otalgia) Group D: 6 (nausea, vomiting, dizziness, tachycardia, abdominal pain, diarrhea) Control: 4 (dizziness 2x, pruritus, tachycardia) Data from table; inconsistent with text of article</p> <p>Virological outcomes <u>Viral clearance</u> Copy number of virus Day 7 Group A: 0.0 (0.0–3,191.4) Group C: 0.0 (0.0–100.7) Group D: 0.0 (0.0–114.8) Control: 19.8 (0.0–1,445.6) <i>Also reported: day 1 and 3 + results for mild disease only</i></p> <p>Reported for day 1 an day 7: Median level of D-dimer; CRP level; IL-6 level; IL-10 level; Plasma level of TNF-α; Number of patients with leukocytosis (platelet count</p>	<p>The study findings suggest that the administration of lopinavir/ritonavir-doxycycline, lopinavir/ritonavir-azithromycin, and azithromycin-hydroxychloroquine as a dual drug combination produced a significantly rapid PCR conversion rate to negative in three-day treatment of mild to moderate COVID-19 cases. Further studies should involve observation of older patients with severe clinical symptoms in order to collate significant amounts of demographic data.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Control: 119</p> <p><u>Important characteristics:</u> Age, median (range), years: Group A: 37 (32-49) Group C: 36 (32-51) Group D: 37 (21-55) Control: 37 (23-55) Sex, n/N (%) male: Group A: 123 (96.1) Group C: 118 (97.5) Group D: 119 (91.5) Control: 113 (95.0) Disease severity Mild, n (%) Group A: 120 (93.8) Group C: 113 (93.4) Group D: 117 (90.0) Control: 115 (96.6) Moderate, n (%) Group A: 8 (6.3) Group C: 8 (6.6) Group D: 13 (10.0) Control: 4 (3.4)</p> <p>Groups comparable at baseline? Group D and control are younger; group D more moderate cases compared to control.</p>				<p>>12,000 per μL); Number of patients with thrombocytopenia (platelet count <150,000 per μL); Number of patients with lymphocytopenia (lymphocyte count <1,500 per μL); Number of patients with an increase of AST level; Number of patients with an increase of ALT level; Number of patients categorized according to serum creatinine level; level of AST; level of ALT; level of creatinine serum; BUN level.</p>	
Thakar, 2021	<p><u>Type of study:</u> RCT Exploratory RCT</p> <p><u>Setting:</u> a designated COVID-19 treatment facility (NCI-Jhajjar Campus) at the All India Institute of Medical Sciences (AIIMS), New Delhi</p>	<p>Patients with asymptomatic/mild COVID-19 [National Early Warning Score (NEWS) ≤ 4]</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> a COVID-19 RT-PCR test reported positive from a panel of government-approved laboratories asymptomatic or mildly symptomatic adults <p><u>Exclusion criteria:</u></p>	<p><u>Topical administration of Chloroquine (CQN) drops in the nose + standard symptomatic supportive care</u></p> <p>nasal instillation of 0.03 per cent CQN eye drops (Uv Lubi Unims 0.03% Drops, Manufactured by FDC Ltd, Mumbai). Six doses of 0.5 ml each were instilled daily for 10 days.</p>	<p><u>Standard symptomatic supportive care</u> (not further defined)</p>	<p><u>Length of follow up:</u> 10 days</p> <p><u>Loss to follow-up:</u> I: 0/30 (0%) C: 1/30 (0.03%) Reasons: 1 discontinued intervention</p>	<p>The modified intention-to-treat analysis was restricted to 49 patients.</p> <p>Clinical outcomes <u>Mortality</u> Not reported.</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Symptom resolution</u> Defined as clinical recovery.</p>	<p><u>Remarks:</u></p> <ul style="list-style-type: none"> The exploratory trial design did not mandate sample size calculation for efficacy. This being a new off-label intervention, ethical clearance was granted for 60 patients. Eleven patients were excluded due to enrolment error (2 – recovered; 9 – false-positive referral) The presentation of the results in the article was unclear. <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Study recruitment was from April 23 to May 6, 2020.</p> <p><u>Country:</u> India</p> <p><u>Source of funding:</u> -AllIMS Research Grant (Grant No. F.8-A-COVID-11/2020/RS) supported the study. -The authors declared no conflict of interest.</p>	<ul style="list-style-type: none"> recent intake of oral CQN or HCQ or any other specific treatment hypersensitivity to CQN/HCQ cardiovascular comorbidities pregnant or lactating ladies <p><u>N total at baseline:</u> N = 60 Intervention: 30 Control: 30</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 35.6 y (11.3) C: 34.2 y (9.4) Sex, n/N (%) male: I: 26/30 (0.9%) C: 21/30 (0.7%) Disease severity, n/N <i>Defined by National Early Warning Score (NEWS) at presentation</i> Score 1 I: 28/30 C: 28/30 Score 2 I: 1/30 C: 2/30 Score 3 I: 1/30 C: 0/30</p> <p>Groups comparable at baseline? Not reported.</p>	<p>The drops were self-administered by patients. A video demonstration educated patients on the method of drop instillation (head-hanging method). Doses were instilled at three hourly intervals in the day (0600-2100 h) with a nine hour break at night. Alternate nostrils were used for alternate doses.</p> <p>Plus all treatments and observations as for the control arm.</p>			<p>Noted as similar with 100 per cent asymptomatic by day seven in both arms.</p> <p><u>Need for respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u> No serious adverse events were reported. The nasal CQN arm had seven of 30 patients reporting minor local irritation from the drops, and one of these also reported additional nausea.</p> <p>Virological outcomes <u>Ct values</u> Virological outcomes also indicated similarly improving Ct values in both arms, and similar proportion of patients transitioning to non-infectivity by day 10 (controls - 19/25; nasal CQN - 15/24).</p> <p>Sequential Ct values plotted from days 0 to 10 indicated towards a general trend of improving Ct values (decreasing viral load) in both arms. Figure 2 compares the means of the Ct values on days 0, 3, 7 and 10 in the two arms indicating no differences, but a trend</p>	<p>This exploratory trial showed the safety profile of 0.03 per cent nasal CQN. No significant evidence of efficacy was demonstrated in patients with established infection. Favourable virus load trends were however noted when administered pre-infection but the findings were limited due to small sample.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						favouring the control arm (day 10, P=0.06).	
Chen, 2020a	<p><u>Type of study:</u> Open-label RCT</p> <p><u>Setting:</u> 11 public hospitals between April 1 and May 31.</p> <p><u>Country:</u> Taiwan (northern, central, and southern).</p> <p><u>Source of funding:</u> Research grant from the Hospital and Social Welfare Organizations Administration Commission, Ministry of Health and Welfare. Taiwan Biotech Co. Ltd.: donation of investigational products.</p> <p>The authors declare no conflicts of interests.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age 20–79 years; COVID-19 diagnosis (confirmed by pharyngeal real-time RT-PCR for SARS-CoV-2) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> severe illness (respiratory distress, oxygen supplementation, and evidence of infiltration according to chest roentgenography); documented history of hypersensitivity to quinine derivatives; retinal disease; hearing loss; severe neurological or mental illness; pancreatitis; lung disease; liver disease (alanine aminotransferase (ALT)/aspartate aminotransferase (AST) > 3× the normal upper limit); kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m² according 151 to MDRD or CKD-EPI); hematological disease; cardiac conduction abnormalities at electrocardiographic (ECG) screening with long QT syndrome or QTcF interval > 	<p><u>Hydroxychloroquine + standard of care (SOC):</u> HCQ 400 mg twice for 1 d and HCQ 200 mg twice daily for 6 days +SOC Enrollees were randomized within 4 days of diagnosis.</p>	<p><u>SOC</u></p> <p>Stratified by mild or moderate illnesses within 4 days of diagnosis.</p> <p>*mild clinical COVID-19 symptoms: supportive treatment</p> <p>*moderate clinical COVID19 symptoms: antimicrobial therapy</p> <p>(1) ceftriaxone 2 g daily for 7 days ± azithromycin 500 mg on day 1 and 250 mg on days 2–5; or (2) levofloxacin 750 mg daily for 5 d; or</p> <p>(3) levofloxacin 500 mg daily; or (4) moxifloxacin 400 mg daily for 7–14 days for subjects allergic</p>	<p><u>Follow-up</u> From randomization up to 14 days.</p> <p><u>Loss to follow-up</u> 2 in the HCQ group and 1 in the SOC group had withdrawn consents before the first dose was administered.</p>	<p><u>Time to negative rRT-PCR assessments from randomization to hospital day 14 (median)</u> I: 5 days (95% CI 1-9 days) C: 10 days (95% CI 2-12 days) p-value: 0.40</p> <p><u>Proportion of negative viral rRT-PCR on hospital day 14 (%)</u> I: 17/21 (81.0) C: 9/12 (75.0) p-value: 0.36</p> <p><u>Clinical recovery by day 14</u> I: 28.6% C: 41.7% p-value: 0.51</p> <p><u>Off-quarantined by day 14</u> I: 19.0% C: 16.7% p-value: not reported</p> <p><u>Mortality</u> No mortality reported</p> <p><u>Adverse events</u> No severe adverse events were reported</p>	<p><u>Remarks:</u> One (4.8%) in the HCQ group and two (16.7%) in the SOC group were concomitantly administered azithromycin.</p> <p><u>Authors conclusion:</u> HCQ failed the primary endpoint of shortening the viral clearance interval.</p> <p><i>A retrospective observational study was performed as well by the authors: review of medical registers (n=37). The retrospective study also demonstrated that HCQ conferred no therapeutic benefit to the COVID-19 cases investigated.</i></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>450 msec for males and > 470 msec for females according to Fridericia's correction at screening;</p> <ul style="list-style-type: none"> • known HIV infection; • active hepatitis B or C without concurrent treatment (positive for hepatitis B [HBsAg and HBeAg] or hepatitis C ribonucleic acid [RNA] titer > 800,000 IU/mL); • (m) G6PD; • psychiatric disorders and alcohol/ substance dependence/abuse that may jeopardize patient safety; • pregnant or breastfeeding woman. <p><u>N total at baseline:</u> N = 33 Intervention: 21 Control: 12</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 33.0 (12.0) C: 32.8 (8.3)</p> <p>Sex, n/N (%) male: I: 11/21 (52.4) C: 8/12 (66.7)</p> <p>Groups comparable at baseline? Yes</p>		to ceftriaxone or azithromycin or according to physician discretion. Oseltamivir 75 mg b.i.d. will be administered for 5 days to subjects presenting with concomitant influenza A or B infection.		<u>Sever prolongation</u> No severe prolongation was noted.	
Pan, 2020	<p><u>Type of study:</u> RCT (open-label, non-blinded)</p> <p><u>Setting & country:</u></p>	<p><u>N total at baseline:</u> N = 11,330</p> <p><i>Hydroxychloroquine arm</i> I: 947 C: 906</p>	<p>Hydroxychloroquine</p> <p>Oral; 4 tablets at hour 0, 4 tablets at hour 6, and, starting at hour 12, two tablets twice daily for</p>	Standard of care	<p><u>Length of follow up:</u> 28 days, or up to discharge</p> <p><u>Loss to follow-up:</u> I: 7/954 (0.7%)</p>	<p>Clinical outcomes</p> <p><u>All-cause in-hospital mortality,</u></p>	<p><u>Definitions/information:</u></p> <p><u>Taking trial drug midway through scheduled duration</u>, %, calculated only among patients who died or were</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>405 hospitals in 30 countries; WHO Solidarity Trial</p> <p><u>Source of funding:</u> Funded by the World Health Organization;</p> <p>ISRCTN Registry nr, ISRCTN83971151; ClinicalTrials.gov nr, NCT04315948.)</p>	<p><u>Important characteristics:</u> <u>Age, n/N (%):</u> I: <50y: 335/947(35.4%) 50-69y: 410/947(43.3%) ≥70y: 202/947 (21.3%) C: <50y: 317/906 (35.0%) 50-69y: 396/906 (43.7%) ≥70y: 193/906 (21.3%) <u>Sex, n/N (%) male:</u> I: 574/947 (60.6%) C: 535/906 (59.1%) <u>Respiratory support</u> I: No suppl. Oxygen at entry: 345/947(36.4%) Suppl. Oxygen at entry 517/947 (54.6%) Already receiving ventilation 85/947 (9.0%) C: No suppl. Oxygen at entry: 341/906 (37.6%) Suppl. Oxygen at entry 483/906 (53.3%) Already receiving ventilation 82/906 (9.2%) <u>Previous days in hospital</u> I: 0 days: 296/947 (32.2%) 1 day: 317/947 (33.5%) ≥2 days: 334/947 (35.3%) C: 0 days: 281/906 (31.0%) 1 day: 312/906 (34.4%) ≥2 days: 313/906 (34.5%)</p>	<p>10 days. Each tablet contained 200 mg of hydroxychloroquine sulfate (155 mg of hydroxychloroquine base per tablet; a little-used alternative involved 155 mg of chloroquine base per tablet). <i>Discontinued for futility on June 19, 2020</i></p> <p><u>Taking trial drug midway through scheduled duration*:</u> I: 95% C: 6%</p> <p><u>Use of non-study drug, n/N (%)s:</u> Corticosteroids I: 140 (14.8%) C: 140 (15.5%) Convalescent plasma I: 7 (0.7%) C: 3 (0.3%) Anti-IL-6 drug I: 21 (2.2%) C: 18 (2.0%) Non-trial interferon I: 2 (0.2%) C: 1 (0.1%) Non-trial antiviral I: 62 (6.6%) C: 54 (6.0%)</p>		<p>Reasons: no or unknown consent C: 3/909 (0.3%) Reasons: no or unknown consent</p>	<p><i>regardless of whether death occurred before or after day 28:</i> I: 104/947 (10.2%) C: 84/906 (8.9%) RR 1.18 (95% CI 0.90 to 1.56)</p> <p>HR=1.19 (0.89-1.59), Adjusted** HR=1.14 (0.89-1.46),</p> <p><u>All-cause in-hospital mortality, stratified by ventilation at randomization:</u> Ventilated: HR 1.26 (95% CI 0.76-2.10) Not ventilated: HR 1.16 (95% CI 0.82-1.65)</p> <p><u>Initiation of mechanical ventilation, in those not receiving ventilation at baseline:</u> I: 75/862 (8.7%) C: 66/824 (8.0%) RR 1.09 (95% CI 0.79 to 1.49)</p> <p><u>Composite death or initiation ventilation:</u> I: 150/947 (15.5%) C: 131/906 (14.3%) RR 1.10 (95% CI 0.88 to 1.36) Publication: RR 1.11 [0.87-1.42]</p> <p><u>Hospitalized, not discharged:</u> <i>Percentage of patients (rather than number of</i></p>	<p>discharged alive, % patients who were taking the trial drug midway through its scheduled duration (or midway through the time from entry to death or discharge, if this was shorter). <u>*Adjusted model all-cause mortality:</u> some overlap between the 4 control groups; an exploratory sensitivity analysis used multivariate Cox regression to fit all 4 treatment effects simultaneously; adjusted for several prognostic factors (age, sex, diabetes, bilateral lung lesions at entry (no, yes, not imaged at entry), and respiratory support at entry (no oxygen, oxygen but no ventilation, ventilation). <u>Authors conclusion:</u> These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>patients) ever reported as discharged who were still in the hospital:</p> <p>Day 7, % I: 64% C: 54%</p> <p>Day 14 I: 23% C: 20%</p> <p>Day 21 I: 11% C: 10%</p>	
Omrani, 2020	<p>Type of study: RCT (parallel)</p> <p>Setting: two units of Qatar's national healthcare system, Hamad Medical Corporation (HMC). The first was the Emergency Department (ED) at HMC's tertiary hospital, Doha's Hamad General Hospital (HGH). The second unit was a 3500-bed quarantine facility 20 miles north of Doha, at Umm Qarn</p> <p>Country: Qatar</p> <p>Source of funding: The study was supported by internal</p>	<p>SARS-CoV-2 PCR-positive males and females with mild or no symptoms.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Hospitalization; • Tachypnoea (respirations >29/minute); • Hypoxemia (pulse oximetry on room air <93%); • Treatment was also recommended for any patient with chest X-ray abnormality who had risk factors of older age (>60); • Immunocompromise; • Comorbidity (e.g. diabetes or hypertension) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Retinal or macular disease; • Psoriasis; • Hepatic or renal disease; • Porphyria; • Glucose-6-dehydrogenase (G6PD) deficiency; • QT-interval prolongation; • Hypersensitivity; • HC or AZ; • Pregnancy; 	<p>Intervention-1: Oral hydroxychloroquine plus orale azithromycin (500 mg day one, 250 mg daily on days two through five)</p> <p>Intervention-2: Oral hydroxychloroquine (600 mg daily for one week)</p>	Placebo	<p>Length of follow up: 21 days</p> <p>Loss to follow-up:</p> <ul style="list-style-type: none"> • 432 participants had all three symptom assessment follow-ups at day 7, 14 and 21. • 439 participants had symptom assessment at day 7. • 438 patients had symptom assessment at day 14 and 21. <p>Reasons for loss to follow-up</p> <ul style="list-style-type: none"> • Dropping out at participants request. • Hospitalization. • Transfer to military hospital <p>Unavailability for contact.</p>	<p>Clinical outcomes</p> <p>Mortality Not reported.</p> <p>Duration of hospitalization Not reported.</p> <p>Clinical improvement (/disease severity/disease progression) Not reported</p> <p>Need for respiratory support Not reported</p> <p>Safety Not reported</p> <p>Viral outcomes</p> <p><i>Virologic cure at day six, n/N (%) (95% CI)</i> I-1: 16/152 (1.05%) (95% CI= 6.1 to 16.5%) I-2: 19/149 (12.8%) (95% CI= 7.9 to 19.2%) C: 18/147 (12.2%) (95% CI= 7.4 to 18.7%) P=0.821</p>	<p>Definitions: -</p> <p>Remarks:</p> <p>Authors conclusion: The lessons of Q-PROTECT must be considered in light of the trial strengths and weaknesses, the medication risks and benefits, and the existing evidence base. Taking all of these factors into account, the investigators conclude that HC±AZ shows no sign of usefulness in the population studied, and that there is low likelihood of undiscovered drug benefits outweighing therapeutic risks.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>institutional funds of the Hamad Medical Corporation (government health service of the State of Qatar).</p> <p><u>Conflict of interest</u> The authors have no financial or personal relationships with other people or organizations that could represent a conflict of interest.</p>	<ul style="list-style-type: none"> Laboratory assessment revealed low levels of potassium or magnesium, or elevated creatine or transaminases. <p><u>N total at baseline:</u> N = 456 Intervention-1: 152 Intervention-2: 152 Control: 152</p> <p><u>Important characteristics:</u></p> <p>Age, median (IQR): I-1: 42 years (38-48) I-2: 40 years (31-47) C: 41 years (31-47)</p> <p>Sex, n/N (%) male: I-1: 150/152 (98.7%) I-2: 149/152 (98.0%) C: 150/152 (98.7%)</p> <p>Disease severity, median (IQR): Symptoms at enrolment, such as patient-reported fever and respiratory symptoms</p> <p>Patient-reported fever I-1: 46 (30.3%) I-2: 51 (33.6%) C: 52 (34.2%)</p> <p>Respiratory symptoms I-1: 37 (24.3%) I-2: 36 (23.7%) C: 34 (22.4%)</p> <p>Groups comparable at baseline? Not specifically reported.</p>				<p><i>Increase in cycle threshold from day one to day six, median (IQR) (95% CI)</i> I-1: 7.2 (3.9 to 11.5) (95% CI= 6.1 to 8.8) I-2: 7.5 (3.4 to 11.5) (95% CI= 5.7 to 8.8) C: 8.0 (4.1 to 11.7) (95% CI= 7.3 to 9.0) P=0.634</p> <p><i>Virologic cure at day 14, n/N (%) (95% CI)</i> I-1: 30/149 (20.1%) (95% CI= 14.0 to 27.5%) I-2: 42/146 (28.8%) (95% CI= 21.6 to 36.8%) C: 45/143 (31.5%) (95% CI= 24.0 to 39.8%) P=0.072</p>	
Self, 2020	<u>Type of study:</u> Double blind RCT	<u>Inclusion criteria:</u> • hospitalized COVID-19 patients for less than 48 hours	400 mg of hydroxychloroquine sulfate in pill form twice a	Matching placebo in the	<u>Length of follow up:</u> 28 days	Clinical outcomes <u>28 day mortality, n (%):</u>	<u>Remarks:</u> • -

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> Multicenter, April 2, 2020, and June 19, 2020, at 34 hospitals in the US within the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network</p> <p><u>Country:</u> United States of America</p> <p><u>Source of funding:</u> National Heart, Lung, and Blood Institute</p>	<ul style="list-style-type: none"> laboratory-confirmed SARS-CoV-2 infection symptoms of respiratory illness for less than 10 days <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> more than 1 dose of hydroxychloroquine or chloroquine in the prior 10 days QTc interval greater than 500 ms Prior receipt or planned administration of select medications that prolong the QTc interval Seizure disorder <p><u>N total at baseline:</u> N = 479 Intervention: 242 Control: 237</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 58 y (45-69) C: 57 y (43-68) Sex, n (%) male: I: 135 (55.8%) C: 132 (55.7%) COVID Outcomes Scale, mean (SD): <i>Defined by patient's clinical status (1-7), mild to severe.</i> 2: Hospitalized, receiving ECMO or invasive mechanical ventilation I: 13 (5.4) C: 19 (8.0) 3: Hospitalized, receiving noninvasive ventilation or nasal high-flow oxygen I: 28 (11.6) C: 27 (11.4)</p>	day for the first 2 doses and then 200 mg in pill form twice a day for the subsequent 8 doses, for a total of 10 doses over 5 days	same dosing frequency	<p><u>Loss to follow-up:</u> I: n/N (%) Reasons: C: n/N (%) Reasons:</p>	<p>I: 25 (10.4%) C: 25 (10.6%) Absolute difference: -0.2% (95% CI -5.7 to 5.3%); aOR: 1.07 (95% CI 0.54 to 2.09)</p> <p><u>Systematically collected safety events, n (%):</u> Cytopenia I: 92 (38) C: 87 (36.7)</p> <p>AST or ALT \geq2 times upper limit of normal I: 50 (20.7) C: 65 (27.4)</p> <p>Cardiac arrest treated with CPR I: 10 (4.1) C: 4 (1.7)</p> <p>Symptomatic hypoglycemia I: 10 (4.1) C: 8 (3.4)</p> <p>Ventricular tachyarrhythmia I: 5 (2.1) C: 6 (2.5)</p> <p>Seizure I: 1 (0.4) C: 0</p>	<p><u>Authors conclusion:</u> Among adults hospitalized with respiratory illness from COVID-19, treatment with hydroxychloroquine, compared with placebo, did not significantly improve clinical status at day 14. These findings do not support the use of hydroxychloroquine for treatment of COVID-19 among hospitalized adults.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>4: Hospitalized, receiving supplemental oxygen without positive pressure or high flow I: 116 (47.9) C: 108 (45.6)</p> <p>5: Hospitalized, not receiving supplemental oxygen I: 85 (35.1) C: 83 (35.0)</p> <p>Groups comparable at baseline? Yes</p>					
Lyngbakken, 2020	<p><u>Type of study:</u> single center, two-arm, open label, group-sequential, pragmatic randomized controlled trial</p> <p><u>Setting:</u></p> <p><u>Country:</u></p> <p><u>Source of funding:</u> The authors declare no competing interests.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients >18 years old; • SARS-CoV-2 positive patients. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Need of admission to intensive care unit on hospital admission; • History of psoriasis; • Reduced hearing/tinnitus; • Visual impairment; • Known adverse reaction to hydroxychloroquine sulfate; • Pregnancy • Prolonged corrected QT interval (>450 ms). <p><u>N total at baseline:</u> N = 53 Intervention: N = 27 Control: N = 26</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 56 (41 to 72)</p>	hydroxychloroquine sulfate (at a dose of 400 mg twice daily for 7 days) in addition to standard care.	Standard care alone.	30 days	<p><u>Rate of reduction in SARS-CoV-2 viral load</u> I: 0.24 (95% CI= 0.03 to 0.46) C: 0.14 (95% CI= -0.10 to 0.37)</p> <p>MD= 0.11 (95% CI= -0.21 to 0.43).</p> <p><u>Mortality</u> I: N = 1 (3.9%). C: N = 0 (0%)</p>	<p><u>Authors conclusion:</u> In conclusion, therapy with hydroxychloroquine did not impact SARS-CoV-2 viral kinetics in patients admitted to hospital with moderately severe COVID-19. Our results suggest no important antiviral effect of hydroxychloroquine in humans infected with SARS-CoV-2.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: 69 (51 to 74) P= not reported</p> <p>Sex, n/N (%) male: I: 19/27 (70.4%) C: 16/26 (61.5%)</p> <p>BMI in kg/m² (range): I: 25.6 (23.9 to 29.4) C: 27.6 (24.2 to 33.0)</p> <p>Groups comparable at baseline? Yes</p>					
Horby, 2020b	<p><u>Type of study:</u> Randomized, open label, controlled trial (RECOVERY trial)</p> <p>Setting: Multi-centre, 176 Hospitals</p> <p>Country: United Kingdom</p> <p>Source of funding: NIHR grant, NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, the NIHR Health Protection</p>	<p><u>Inclusion criteria:</u> Clinically suspected or laboratory confirmed COVID-19 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk by participation in the trial. Initially, recruitment was limited to patients ≥ 18 years, but this limit was removed.</p> <p><u>Exclusion criteria:</u> Patients with known prolonged electrocardiograph QTc interval. (Co-administration with medications that prolong the QT interval was not a contraindication but it was advised to check QT interval by performing an ECG).</p> <p><u>N total at baseline:</u> N = 4716 Intervention: 1561 Control: 3155</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 65.2 (15.2)</p>	<p>Hydroxychloroquine on top of usual care</p> <p>200mg tablet containing 155mg base equivalent. Patients received a loading dose of 4 tablets (800 mg) at zero and 6 hours, followed by 2 tablets (400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge (whichever occurred earlier).</p>	Usual care alone	<p>A online follow-up form was to be completed when participants were discharged, had died or at 28 days after randomization (whichever occurred earlier). Further analyses at 6 months.</p> <p>Follow-up information was complete for 4619 (98%) of the randomized patients.</p>	<p>28-day mortality (n/N/%) I: 421/1561(27.0) C: 790/3155 (25.0) Rate Ratio (95%CI): 1.09 (0.97 to 1.23) P=0.15</p> <p>Discharge within 28 days (n/N/%) I: 931/1561 (59.6) C:1983/3155 (62.9) Rate Ratio (95%CI): 0.90 (0.83 to 0.98) P= not reported</p> <p>Invasive mechanical ventilation or death (n/N/%)* I: 399/1300 (30.7) C: 705/2623 (26.9) Rate Ratio (95%CI): 1.14 (1.03 to 1.27) P= not reported</p> <p>Supraventricular tachycardia (n/N/%) I: 56/698 (7.6) C: 85/1357 (6.0) Rate Ratio (95%CI): not reported</p>	<p>Remarks: RECOVERY is a large, pragmatic, randomized, controlled platform trial designed to provide rapid and robust assessment of the impact of readily available potential treatments for COVID-19 on 28-day mortality. This paper published the preliminary results on hydroxychloroquine.</p> <p>From 12 May 2020, extra information was recorded on the occurrence of new major cardiac arrhythmia.</p> <p>Since preliminary data showed no beneficial effect of hydroxychloroquine, enrolment of participants was closed on 5 June and the preliminary result for the primary outcome was made public. Investigators were advised that any patients currently taking hydroxychloroquine as part of the study should discontinue the treatment.</p> <p><u>Authors conclusion:</u> The findings indicate that hydroxychloroquine is not an effective treatment for hospitalized patients with COVID-19 but do not address its use as</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Unit in Emerging and Zoonotic Infections, and NIHR Clinical Trials Unit Support Funding. Authors received funding from several parties.	C: 65.4 (15.4) P= not reported Sex, n/N (%) male: I: 960/1561 (61.5) C: 1974/3155 (62.6) P= not reported Groups comparable at baseline? Yes, groups were comparable at baseline.				P= not reported Ventricular tachycardia/fibrillation (n/%)** I: 3/698 (0.4) C: 5/1357 (0.4) Rate Ratio (95%CI): not reported P= not reported Atrioventricular block requiring intervention (n/%)** I: 1/698 (0.1) C: 1/1357 (0.1) Rate Ratio (95%CI): not reported P= not reported *Analyses exclude those on invasive mechanical ventilation at randomization **Data was available for 698 (I) versus 1357 (C) patients.	prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community.
Ulrich, 2020	<u>Type of study:</u> Multicenter, double-blind, randomized clinical trial <u>Setting:</u> NYU Langone Health (Tisch Hospital and Kimmel Pavilion, NYU Langone—Brooklyn Hospital, and NYU Winthrop Hospital), NYC	<u>Hospitalized patients with COVID-19</u> <u>Inclusion criteria:</u> <ul style="list-style-type: none"> At least one COVID-19 symptom (eg, fever, cough, dyspnea, nausea, diarrhea, myalgia, anosmia, dysgeusia); The subject's (or legally authorized representative's) written informed consent. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Subjects who met the primary end point at enrolment; 	Hydroxychloroquine sulfate 400 mg by mouth 2 times per day (day 1) and 200 mg by mouth 2 times per day (days 2-5). The 5-day course was based on in vitro projections to optimize HCQ tissue levels against SARS-CoV-2.	Placebo (calcium citrate 400 mg by mouth 2 times per day (day 1) and 200 mg by mouth 2 times per day (days 2-5). The 5-day course was based on in vitro projections to optimize HCQ tissue levels	<u>Length of follow up:</u> 30 days. <u>Loss to follow-up:</u> I: n/N (%) Reasons: C: n/N (%) Reasons:	Mortality (day 14), n/N (%) I: 3/67 (4.5%) C: 5/61 (8.2%) Total: 8/128 P=0.350 Mortality (day 30), n/N (%) I: 7/67 (10.4%) C: 6/61 (9.8%) Total: 13/128 (10.2) P=1.000 Duration of hospitalization (length of	<u>Definitions:</u> - <u>Remarks:</u> - <u>Authors conclusion:</u> Therapies against SARS-CoV-2 are urgently needed to improve COVID-19 morbidity and mortality. This double blind, placebo-controlled randomized trial did not suggest that HCQ is beneficial in preventing severe outcomes or improving clinical scores among non-ICU hospitalized patients with COVID19. Treatment with HCQ

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Health and Hospitals / Bellevue Hospital Center (BHC), and State University of New York (SUNY) Downstate Medical Center.</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> This work was supported by the New York University Grossman School of Medicine. R.J.U. is supported in part by the NYU CTSA grant (TL1 TR001445) from the National Center for Advancing Translational Sciences (NCATS) and the New York State Empire Clinical Research Investigator Program (ECRIP). M.J.M. and V.R. are supported by the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) grant (UM1 AI148574). J.A.D. is</p>	<ul style="list-style-type: none"> • Patients who had received any doses of HCQ or chloroquine (CQ) within 30 days; • Patients who were unable to take oral medications; • Patients who were allergic to HCQ or CQ; • Patients who had a baseline corrected QT (QTc) interval >500 ms; • Patients who were on concomitant therapy with antiarrhythmic medications (flecainide, amiodarone, digoxin, procainamide, propafenone, thioridazine, or pimozide); • Patients who had a history of cardiac arrest, retinal disease, or glucose-6-phosphate dehydrogenase deficiency. <p><u>N total at baseline:</u> N = 128 Intervention: 67 Control: 61</p> <p><u>Important characteristics:</u></p> <p>Age, mean (SD): I: 66.5 (16.4) years C: 65.8 (16.0) years P=0.804</p> <p>Sex, n/N (%) male: I: 45/67 (67.2%) C: 31/61 (50.8%) P=0.089</p> <p><u>Disease severity, median (IQR) Defined by COVID-19 severity score</u></p>		against SARS-CoV-2.		<p>stay – admission to discharge, mean (SD) I: 9.75 (10.3) C: 6.80 (5.92) Total: 8.34 (8.59) P=0.053</p> <p>Clinical improvement (COVID-severity score at day 14), n/N (%)</p> <p>1: death I: 3/67 (4.5%) C: 5/61 (8.2%) Total: 8/128 (6.2%)</p> <p>2: Ventilator or ECMO I: 2/67 (3.0%) C: 0/61 (0%) Total: 2/128 (1.6%)</p> <p>3: Hospitalized, on NIV or high-flow nasal I: 7/67 (10.4%) C: 2/61 (3.3%) Total: 9/128 (7.0%)</p> <p>4: Hospitalized, on supplemental oxygen I: 4/67 (6.0%) C: 1/61 (1.6%) Total: 5/128 (3.9%)</p> <p>5: Hospitalized, not on O2, ongoing medical care I: 2/67 (3.0%) C: 0/61 (0%) Total: 2/128 (1.6%)</p> <p>6: Hospitalized, not on O2, not requiring ongoing care I: 1/67 (1.5%) C: 2/61 (3.3%) Total: 3/128 (2.3%)</p>	was associated with a slight QTc interval prolongation, increased D-dimer, and a trend toward increased length of stay. However, our findings are limited due to a relatively small sample size, and larger randomized trials are needed.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>supported by National Institutes of Health Fogarty grants (D43 TW010046, D43 TW010562, and D43 TW011532). This research was supported in part by an NYU CTSA grant (UL1 TR001445) from the National Center for Advancing Translational Sciences, National Institutes of Health. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.</p> <p><u>Conflict of interest</u> The authors have no relevant financial disclosures. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.</p>	<p>3: Hospitalized, on non-invasive ventilation or high-flow nasal cannula I: 14/67 C: 7/61 Total: 21/128</p> <p>4: Hospitalized, on supplemental oxygen I: 26/67 (38.8%) C: 36 (59.0%) Total: 62/128</p> <p>5: Hospitalized, not on O2, requiring ongoing medical care I: 26/67 C: 17/61 Total: 43/128</p> <p>6: Hospitalized, not on O2, not requiring ongoing care I: 1/67 (1.5%) C: 1/61 (1.6%) Total: 2/128 (1.6%)</p> <p>P=0.777 <u>Symptom duration (days since symptom onset)</u> I: 6.50 (6.00) C: 7.00 (10.0) P=0.091</p> <p>Groups comparable at baseline.</p>				<p>7: Outpatient, no limitation on activities or home O2 I: 13/67 (19.4%) C: 18/61 (29.5%) Total: 31/128 (24.2%)</p> <p>8: Outpatient, no limitation on activities I: 28/67 (41.8%) C: 29/61 (47.5%) Total: 57 (44.5%)</p> <p>Unknown: I: 7/67 (10.4%) C: 4/61 (6.6%) Total: 11/128 (8.6%)</p> <p>Mechanical ventilation (day 14), n/N (%) I: 5/67 (7.5%) C: 4/61 (6.6%) Total: 9/128 (7/0%) P=1.000</p> <p>Mechanical ventilation (day 30), n/N (%) I: 5/67 (7.5%) C: 3/61 (4.9%) Total: 8/128(6.2%) P=0.778</p> <p>Viral outcomes <u>(fever-free days), mean (SD)</u> I: 6.40 (0.94) C: 6.31 (1.33) Total: 6.36 (1.13) P=0.631</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.					<u>O2-supplementation-free days, mean (SD)</u> I: 4.63 (2.44) C: 4.43 (2.40) Total: 4.53 (2.41) P=640	
Abd-Elsalam, 2020a	<p><u>Type of study:</u> A multicenter randomized controlled study</p> <p><u>Setting:</u> Tertiary referral centers</p> <p><u>Country:</u> Egypt</p> <p><u>Source of funding:</u> None.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Patients with SARS-CoV-2 infection (both genders). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Allergies/contraindication to HCQ; Pregnant and lactating females; Patients with cardiac problems. <p><u>N total at baseline:</u> N = 194 Intervention: 97 Control: 97</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 40.35y (18.65) C: 41.09y (20.07) P=0.80</p> <p>Sex, n/N (%) male: I: 56/97 male (57.7%) C: 58/97 male (59.8%) P=0.77</p>	Patients received HCQ 400 mg twice daily (in day 1) followed by 200 mg tablets twice daily added to the standard of care treatment adopted by the Egyptian Ministry of health for 15 days.	Patients received only the standard of care treatment adopted by the national Ministry of Health for 15 days.	All patients were followed up for 4 weeks.	<p><u>Disease severity (after 28 days), n (%)</u></p> <p><i>Recovered</i> I: n=52 (53.6%) C: n=33 (34.0%)</p> <p><i>Mild</i> I: n=23 (23.7%) C: n=39 (40.2%)</p> <p><i>Moderate</i> I: n=8 (8.2%) C: n=11 (11.3%)</p> <p><i>Severe</i> I: n=8 (8.2%) C: n=9 (9.2%)</p> <p><i>Death</i> I: n=6 (6.1%) C: 5 (5.1%)</p> <p><i>Need for intensive care unit</i> I: n=11 (11.3%) C: n=13 (13.4%)</p> <p><u>Duration to negative PCR; Mean (SD)</u> I: 17.01 (2.98)</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, our trial adds extra evidence from Egypt that HCQ may not be beneficial as a treatment for COVID-19.</p>

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						C: 17.64 (2.45) P= 0.11 <u>Duration to clinical improvement; Mean (SD)</u> I: 9.43 (1.87) C: 9.52 (2.94) P=0.80 Duration to hospital discharge; Mean (SD) I: 11.04 (2.71) C: 11.27 (2.19) P=0.52	
Brown, 2020	<u>Type of study:</u> RCT <u>Setting:</u> 13 Hospitals in Utah <u>Country:</u> USA <u>Source of funding:</u> Heart and Lung Research Foundation, Intermountain Research and Medical Foundation, and Office of the Associate Vice President for Research, University of Utah Health Sciences.	<u>Hospitalized COVID-19 patients with symptomatic laboratory-confirmed COVID-19, within 1-0 days of a positive test for COVID-19.</u> <u>Inclusion criteria:</u> Trial protocol met de exacte inclusie criteria kan ik niet vinden. <u>Exclusion criteria:</u> Ethical reasons (e.g., prisoners) or for safety reasons (e.g., known long QT, seizure disorder, renal or liver failure). <u>N total at baseline:</u> N = 85 Intervention: 42 Control: 43 <u>Important characteristics:</u> Age, median (IQR):	Hydroxychloroquine sulfate was administered orally as a loading dose of 400mg twice on the first day followed by 200mg twice daily for the following 4 days (total dose 2.4gm) or until discharge or death	Azithromycin was administered orally as a loading dose of 500mg on the first day, followed by 250mg daily for the next 4 days (total dose 1.5gm) or until discharge or death.	<u>Length of follow up:</u> 28 days <u>Loss to follow-up:</u> None	Clinical outcomes <i>Median posterior odds ratio (95% credible intervals) from proportional odds model</i> *An OR >1 favors azithromycin over hydroxychloroquine for this comparison. *An OR <1 favors azithromycin over hydroxychloroquine for this comparison. <u>28-day mortality</u> Too few events. <u>Day 7 COVID scale score</u> OR= 1.16 (0.68 to 1.96) <u>Day 14 COVID scale score</u> OR= 1.07 (0.63 to 1.83)	<u>Definitions:</u> - <u>Remarks:</u> - <u>Authors conclusion:</u> In summary, we find no suggestion of a large clinical benefit or harm associated with hydroxychloroquine as opposed to azithromycin among hospitalized patients with COVID-19, although AKI may be more common with hydroxychloroquine. Azithromycin may merit further investigation in focused trials, but should not be implemented in clinical care without additional evidence.

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		<p>I: 51y (42-60) C: 58y (43-68)</p> <p>Sex, n/N (%) female: I: 19/42 (44%) C: 14/43 (33%)</p> <p>[Disease severity], median (IQR):</p> <p>Mechanical ventilation I: N = 4 (9%) C: N = 5 (12%)</p> <p>Hospitalized, some oxygen (%) I: 24 (56%) C: N = 23 (55%)</p> <p>Hospitalized, no oxygen (%) I: N = 6 (14%) C: N = 6 (14%)</p> <p>Mechanical ventilation & other organ support I: N = 2 (5%) C: N = 2 (5%)</p>				<p><u>Day 28 COVID scale score</u> OR= 1.17 (0.68 to 2.00)</p> <p><u>Ventilator-free days at 28 days</u> OR= 0.85 (0.50 to 1.46)</p> <p><u>Hospital-free days at 28 days</u> OR= 0.91 (0.54 to 1.54)</p> <p><u>Days to a 1-point decrease in WHO COVID scale</u> OR= 1.02 (0.61 to 1.71)</p> <p><i>Median (IQR)</i></p> <p><u>ICU-free days at 28 days</u>: I: 18 (8 to 22) C: 19 (8.5 to 22)</p> <p><u>Ventilator-free days at 28 days</u> I: 18 (10.75 to 18) C: 18 (12-18)</p> <p><u>Days to a 1-point decrease in WHO COVID scale</u> I: 7 (3 to 13) C: 6 (2.5 to 10)</p> <p><i>Subgroup analysis (Median; Mean; Mode; 95% CI)</i></p> <p><u>Duration symptoms <10 days (N=52)</u> Median= 1.058</p>	

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						Mean= 1.105 Mode= 0.968 95% CI= 0.591 to 1.893 <u>Duration symptoms >10 days (N=33)</u> Median= 0.924 Mean= 0.973 Mode= 0.833 95% CI= 0.492 to 1.734 <u>Not in ICU at enrolment (N=48)</u> Median= 0.947 Mean= 0.992 Mode= 0.864 95% CI= 0.523 to 1.716 <u>In ICU at enrolment (N=37)</u> Median= 1.132 Mean= 1.187 Mode= 1.029 95% CI= 0.617 to 2.074	
Cavalcanti, 2020	<u>Type of study:</u> RCT <u>Setting:</u> Multicenter, 55 hospitals in Brazil <u>Country:</u> Brazil <u>Source of funding:</u> The trial was funded by the hospitals and research institutes participating in Coalition Covid-19	<u>Inclusion criteria:</u> Consecutive patients who were 18 years of age or older and who had been hospitalized with suspected or confirmed Covid-19 with 14 or fewer days since symptom onset. <u>Exclusion criteria:</u> Among the reasons for exclusion from the trial were the use of supplemental oxygen at a rate of more than 4 liters per minute as administered by a nasal cannula or at a level of at least 40% as administered by a Venturi mask; the use of	Hydroxychloroquine alone (HCQ) <i>Standard care plus hydroxychloroquine at a dose of 400 mg twice daily for 7 days. The use of macrolides was not allowed in the hydroxychloroquine-alone group.</i> Hydroxychloroquine + azithromycin (HCQ+AZI) Standard care plus hydroxychloroquine at a dose of 400 mg twice daily plus	Standard care The current standard care for Covid-19 was at the discretion of the treating physicians. The use of glucocorticoids, other immunomodulators, antibiotic agents, and antiviral agents was allowed. The administration	15 days	Clinical status at 15 days <i>Seven-level ordinal scale. Effect estimate (95% CI) HCQ+AZI vs control: 0.99 (0.57 to 1.73) HCQ vs control: 1.21 (0.69 to 2.11) HCQ+AZI vs HCQ: 0.82 (0.47 to 1.43)</i> <u>Clinical status at 7 days</u> <i>Six-level ordinal scale. Effect estimate (95% CI) HCQ+AZI vs control: 0.81 (0.54 to 1.22) HCQ vs control: 0.92 (0.61 to 1.38)</i>	<u>Remarks:</u> - Seven-level ordinal scale of primary outcome: score of 1 indicated not hospitalized with no limitations on activities; 2, not hospitalized but with limitations on activities; 3, hospitalized and not receiving supplemental oxygen; 4, hospitalized and receiving supplemental oxygen; 5, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or noninvasive ventilation; 6, hospitalized and receiving mechanical ventilation; and 7, death. - 24% tested negative on RT-PCR or test results were unavailable

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	Brazil. EMS Pharma provided additional funding and logistic support for the trial and also donated and supplied the trial drugs.	<p>supplemental oxygen administered by a high-flow nasal cannula or invasive or noninvasive ventilation; previous use of chloroquine, hydroxychloroquine, azithromycin, or any other macrolide for more than 24 hours before enrollment (and since the onset of symptoms); and a history of severe ventricular tachycardia or electrocardiographic findings with a corrected QT interval (QTc) of at least 480 msec.</p> <p><u>N total at baseline:</u> N = 665 Total / with positive RT-PCR I (HCQ): 221 / 159 I (HCQ+AZI): 217 / 172 Control: 227 / 173</p> <p><u>Important characteristics:</u> Age, mean (SD): I (HCQ): 51.3±14.5 I (HCQ+AZI): 49.6±14.2 C: 49.9±15.1 P=not reported</p> <p>Sex, n/N (%) male: I (HCQ): 142/221 (64%) I (HCQ+AZI): 123/217 (57%) C: 123/227 (54%) P=not reported</p> <p><u>Groups comparable at baseline?</u> Not reported, but likely because of randomisation</p>	azithromycin at a dose of 500 mg once a day for 7 days.	of hydroxychloroquine or chloroquine and macrolides were not allowed in the control group.		<p><i>HCQ+AZI vs HCQ: 0.89 (0.58 to 1.34)</i></p> <p><u>Use of high-flow nasal cannula or noninvasive ventilation (n (%))</u> <i>HCQ+AZI: 16 (9.3)</i> <i>HCQ: 17 (10.7)</i> <i>Control: 16 (9.2)</i></p> <p><u>Use of mechanical ventilation (n (%))</u> <i>HCQ+AZI: 19 (11.0)</i> <i>HCQ: 12 (7.5)</i> <i>Control: 12 (6.9)</i></p> <p><u>Duration of hospital stay (n (%))</u> <i>HCQ+AZI: 10.3±8.4</i> <i>HCQ: 9.6±6.5</i> <i>Control: 9.5±7.2</i> <i>Not significantly different.</i></p> <p><u>In-hospital death (n (%))</u> <i>HCQ+AZI: 5 (2.9)</i> <i>HCQ: 7 (4.4)</i> <i>Control: 6 (3.5)</i> <i>Not significantly different.</i></p> <p><u>Thromboembolic complications (n (%))</u> <i>HCQ+AZI: 2 (1.2)</i> <i>HCQ: 3 (1.9)</i> <i>Control: 2 (1.2)</i> <i>Not significantly different.</i></p> <p><u>Acute kidney injury (n (%))</u> <i>HCQ+AZI: 6 (3.5)</i> <i>HCQ: 4 (2.5)</i> <i>Control: 5 (2.9)</i> <i>Not significantly different.</i></p> <p><u>Number of days alive and</u></p>	<p>- analyses were performed among those with positive RT-PCR</p> <p>- despite intense efforts to maintain adherence to the assigned treatments, a lack of medications that were perceived as beneficial by clinicians and patients led to some protocol deviations.</p> <p>- the use of hydroxychloroquine plus azithromycin was widespread among patients hospitalized with Covid-19 in participating hospitals.</p> <p>The enrollment of patients with no previous use of these medications was challenging, so we decided to enroll patients provided that their previous use since the onset of symptoms was limited to 24 hours.</p> <p><u>Authors conclusion:</u></p> <p>- In this trial involving hospitalized patients with mild-to-moderate Covid-19, we did not find a significant difference in a 15-day ordinal clinical-status outcome among groups that received standard care, hydroxychloroquine alone, or hydroxychloroquine plus azithromycin. Patients who received hydroxychloroquine, either with azithromycin or alone, had more frequent events of QTc interval prolongation and elevation of liver-enzyme levels than patients who did not receive either agent.</p>

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						<p><u>free from respiratory support up to 15 days (mean (sd))</u> HCQ+AZI: 11.1±4.9 HCQ: 11.2±4.9 Control: 11.1±4.9 Not significantly different.</p> <p><u>Safety outcomes</u> More adverse events were reported in patients who received hydroxychloroquine plus azithromycin (39.3%) or hydroxychloroquine alone (33.7%) than in those who received azithromycin alone (18.0%) or none of the trial drugs (22.6%). Serious adverse events occurred in nine patients. Prolongation of the QTc interval was more common in patients receiving hydroxychloroquine plus azithromycin or hydroxychloroquine alone than in patients in the control group; however, fewer patients in the control group had serial electrocardiographic studies performed during follow-up than did patients in the other two groups. Elevation in liver-enzyme levels was more common in patients receiving hydroxychloroquine</p>	

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						plus azithromycin than in the control group.	
Mitjà, 2020	<p><u>Type of study:</u> open-label, randomized, controlled trial</p> <p><u>Setting:</u> Multicenter, 3 health administrative regions in Catalonia</p> <p><u>Country:</u> Spain</p> <p><u>Source of funding:</u> This work was mainly supported by the crowdfunding campaign JoEmCorono (https://www.yomcorono.com/) with the contribution of over 72,000 citizens and corporations. The study also received financial support from Laboratorios Rubió, Laboratorios Gebro Pharma, Zurich Seguros, SYNLAB Barcelona, and Generalitat de Catalunya. Laboratorios Rubió also contributed to</p>	<p><u>Inclusion criteria:</u> Adult patients aged 18 years or more were eligible if they had mild symptoms of Covid-19 (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like-illness) for less than five days before enrollment, were non-hospitalized, and had a positive PCR test for SARS-CoV-2 in the baseline nasopharyngeal swab.</p> <p><u>Exclusion criteria:</u> Patients were excluded if they had moderate-to-severe Covid-19 disease (e.g., required hospitalization), any condition that might preclude following the study procedures safely (e.g., mental disability), known allergy or hypersensitivity to study drugs, known retinal and severe liver or renal diseases, history of cardiac arrhythmia, known QT prolongation or other diseases that could be exacerbated by study drugs (e.g., psoriasis), active treatment with medications that are contraindicated with study drugs, or known HIV infection. Females who were pregnant (verbally declared or positive pregnancy test) or breastfeeding were also excluded</p> <p><u>N total at baseline:</u> N = 293 Intervention: 136 Control: 157</p>	<p>Hydroxychloroquine</p> <p>HCQ - Dolquine®, 800 mg on day 1, followed by 400 mg once daily for six days)</p>	<p>Usual care</p> <p>No treatment aside from usual care</p>	28 days	<p><u>Reduction of viral RNA load in nasopharyngeal swabs at days 3, and 7</u> The mean differences in viral load from baseline to day 3 were -1.41 and -1.41 Log10 copies/mL in the control and intervention arm, respectively (difference [d] 0.01 [95% CI -0.28; 0.29]) The comparative analysis of the reduction of the viral load followed a similar trend at day 7: -3.37 and -3.44 in the control and intervention arm, respectively (d -0.07 [-0.44; 0.29]).</p> <p><i>Secondary outcomes</i> Clinical progression Risk of hospitalization was similar in the control arm (7.1%, 11/157) and the intervention arm (5.9%, 8/136; RR 0.75 [95% CI 0.32; 1.77]). No patients required mechanical ventilation or died during the study period.</p> <p><u>Time to complete resolution of symptoms within 28 days</u> <i>Median time from randomization to the resolution of Covid-19 symptoms was not significantly different in the control arm (12.0 days,</i></p>	<p><u>Remarks:</u> - Initially, the protocol included the use of HCQ and cobicistat-boosted darunavir (DRVc) combined treatment, but it was adapted to HCQ alone after the recommendation of the pharmaceutical company not to use DRVc for the treatment of Covid-19 due to lack of activity in-vitro and the negative results in human clinical trials of closely related HIV protease inhibitors.</p> <p><u>Authors conclusion:</u> - Compared with usual care, early treatment with HCQ failed to reduce the RNA viral load in nasopharyngeal swabs after 3 and 7 days of treatment and shorten the time to complete resolution of symptoms in adults with PCR-confirmed mild Covid-19. - Our results indicate no impact on viral burden up to 7 days nor symptoms resolution or hospitalization rate up to 28 days following diagnosis. The added value of our study is the randomized-controlled design and the use of the agreed minimal outcome set for Covid-19 clinical trials, including RT-PCR to conclusively determine the viral burden. Our findings provide the scientific community and policymakers with essential insights on the inefficacy of HCQ as a therapeutic candidate for SARS-CoV-2, at least in similar settings and conditions to ours.</p>

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	the study with the required doses of hydroxychloroquine (Dolquine®).	<p><u>Important characteristics:</u> Age, mean (SD): I: 41.6 (12.4) C: 41.7 (12.6) P=not reported</p> <p>Sex, n/N (%) male: I: 98/136 (72.1%) C: 103/157 (65.6%) P=not reported</p> <p><i>Groups comparable at baseline?</i> Yes</p>				<p><i>IQR 6–21) and the intervention arm (10.0, IQR 4–18; log-rank-test for survival analysis p = 0.38)</i></p> <p><u>Safety outcomes</u> In the safety population 16/184 (8.7%) patients in the control group and 121/169 (72.0%) in the intervention group experienced at least one AE during the 28 days of follow-up (Table 3). The most frequent treatment-related AEs among participants given HCQ were gastrointestinal (e.g., diarrhea, nausea, and abdominal pain) and nervous system disorders (e.g., drowsiness, headache, and metallic taste). Twenty SAE were reported, 12 in the control arm and 8 in the intervention arm, none of them related to HCQ.</p>	
Skipper, 2020	<p><u>Type of study:</u> Randomized, double-blind, placebo-controlled trial</p> <p><u>Setting:</u> Internet-based trial across the United States and Canada (40 states and 3 provinces).</p> <p><u>Country:</u> USA and Canada</p>	<p><u>Inclusion criteria:</u> We enrolled nonhospitalized adults who were required to have 4 or fewer days of symptoms and either PCR-confirmed SARS-CoV-2 infection or compatible symptoms after a high-risk exposure to a person with PCR-confirmed COVID-19 within the past 14 days.</p> <p><u>Exclusion criteria:</u> Participants were excluded if they were younger than 18 years,</p>	<p>Hydroxychloroquine</p> <p>800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) once daily for 4 more days (5 days in total).</p>	<p>Placebo</p> <p>Placebo tablets of folic acid, 400 mcg, were prescribed as an identical regimen for the control group. In Canada, the placebo tablets were lactose.</p>	14 days	<p><u>Change in symptom severity score over 14 days</u> on a 10-point VAS I: -2.6 points C: -2.33 points (absolute difference, -0.27 points [95% CI, -0.61 to 0.07 points]; P = 0.117)</p> <p>Hospitalisation or death With hydroxychloroquine, 4 hospitalizations and 1 nonhospitalized death occurred (n = 5 events).</p>	<p><u>Remarks:</u> -participants with no data were excluded from analyses (5.3%) -also probable COVID-19 patients were included. Only 58% of participants received SARS-CoV-2 testing because of severe U.S. testing shortages. -primary outcome was changes after interim analyses</p> <p><u>Authors conclusion:</u> - Hydroxychloroquine</p>

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	<p><u>Source of funding:</u> By Steve Kirsch, Jan and David Baszucki, the Minnesota Chinese Chamber of Commerce, the Alliance of Minnesota Chinese Organizations, and the University of Minnesota Foundation. Authors were supported by several funds. Apotex Canada and Rising Pharmaceuticals in the United States provided a donation of some of the hydroxychloroquine tablets used.</p>	<p>were hospitalized, received certain medications, or met other safety exclusion criteria.</p> <p><u>N total at baseline:</u> N = 423 Intervention: 212 Control: 211</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 41 (33–49) C: 39 (31–50) P=not reported</p> <p>Sex, n/N (%) male: I: 89/212 (42%) C: 96/211 (45%) P=not reported</p> <p>Groups comparable at baseline? Yes</p>				<p>With placebo, 10 hospitalizations and 1 hospitalized death occurred (n = 10 events); of these hospitalizations, 2 were not COVID-19–related (nonstudy medicine overdose and syncope). The incidence of hospitalization or death did not differ between groups (P = 0.29).</p> <p><u>Mediation adherence</u> 77% (157 of 203) of participants receiving hydroxychloroquine reported complete adherence to the regimen, compared with 86% (166 of 194) receiving placebo</p> <p><u>Adverse events</u> Adverse effects were more common in those receiving hydroxychloroquine than placebo through the 5-day regimen (43% [92 of 212] vs. 22% [46 of 211]; P < 0.001).</p>	<p>did not substantially reduce symptom severity or prevalence over time in nonhospitalized persons with early COVID-19. This trial may not inform whether an effect would be observed in populations at higher risk for severe COVID-19. Further randomized controlled clinical trials are needed in early COVID-19.</p> <p>- Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19.</p>
Tang, 2020	<p><u>Type of study:</u> multicentre, randomised, parallel, open label trial</p> <p><u>Setting:</u> 16 government designated covid-19 treatment centres in three</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥18 years • RT-PCR confirmed ongoing SARS-CoV-2 infection in upper or lower respiratory tract • willingness to participate, consent not to be enrolled in other clinical trials during the study period <p>Not mandatory: pneumonia on chest CT</p>	<p>Standard care + hydroxychloroquine (HCQ)</p> <p>HCQ: start within 24 hours after randomisation, Day 1-3: loading dose 1200 mg daily for three days</p>	Standard care	<p><u>Follow-up duration:</u> 28 days</p> <p><u>Loss to follow-up:</u> none</p>	<p><u>Viral clearance</u> Probability SARS-CoV-2 <u>negative conversion at 28 days:</u> I: 85.4% (95% CI 73.8 - 93.8) C: 81.3% (95% CI 71.2 - 89.6) Mean diff: 4.1% (95% CI - 10.3% to 18.5%).</p>	<p><u>Remarks:</u></p> <ul style="list-style-type: none"> • This was a RCT, open-labelled. • Data regarding viral clearance and alleviation of symptoms were analysed according to intention-to-treat protocol. • Almost all patients had mild to moderate disease (only 2/150 severe)

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	<p>provinces (Hubei, Henan, and Anhui); 11 to 29 February 2020</p> <p><u>Country:</u> China</p> <p><u>Source of funding:</u> Multiple funding. Described in detail; see manuscript</p>	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Severe conditions (e.g. malignancies, heart, liver, or kidney disease or poorly controlled metabolic diseases unsuitability for oral administration pregnancy or lactation allergy to HCQ cognitive impairments or poor mental status, disabling cooperation severe hepatic and renal impairment or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis. <p><u>N total at baseline:</u> 150 Intervention: 75 Control: 75</p> <p><u>Important characteristics:</u> Age, mean±SD: I: 48.0 ± 14.1 C: 44.1 ± 15.0 Sex, n/N (%) male: I: 42/75 (56%) C: 40/75 (53%) Days from disease onset to randomisation, mean±SD: I: 16.0±9.9 C: 17.1±11.1</p> <p>Groups comparable at baseline. Also described: exposure history, treatment before randomisation, vital signs, comorbidities, laboratory parameters</p>	<p>From day 4 on: maintenance dose 800 mg daily</p> <p>Treatment duration: 2 weeks in mild to moderate disease, 3 weeks in severe disease</p> <p>In case of adverse events related to HCQ as adjusted by investigators, the dose of HCQ was adjusted.</p>			<p><u>Median time to negative conversion, days:</u> I: 8 (95% CI 5 – 10) C: 7 (95% CI 75 – 8) HR: 0.85, (95% CI 0.58 to 1.23) P=0.34</p> <p><u>Alleviation of symptoms Probability alleviation day 28 days</u> I: 59.9%, (95% CI 45.0 - 75.3) C: 66.6% (95% CI 39.5 - 90.9) Diff -6.6% (95% CI -41.3 - 28.0)</p> <p><u>Time to alleviation, days, Median:</u> I: 19 C: 21 HR 1.01, 0.59 to 1.74 P=0.97</p> <p><u>Safety</u> (based on actual exposure) <u>Duration HXQ treatment, days, median (range):</u> I: 14 (1-22) C: n.a.</p> <p><u>Adverse events, n/N (%):</u> I: 21/70 (30%) C: 7/80 (9%)</p> <p><u>Serious adverse events, n/N (%):</u> I: 2 /70 (3%) (1xupper respiratory tract infection, 1x disease progression C: 0</p>	<ul style="list-style-type: none"> Longer follow-up period (supplem. Data) shows results consistent with reported results <p><u>Authors conclusion:</u> Administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospital with mainly persistent mild to moderate covid-19. Adverse events were higher in hydroxychloroquine recipients than in non-recipients.</p>
Borba, 2020	<u>Type of study:</u> Randomized, double-blinded,	<u>Inclusion criteria:</u> • age > 18 years	<u>High dosage</u> CQ (600mg CQ (4x150mg tablets, twice daily for 10	<u>Low dosage</u> CQ (450mg CQ (3x150mg	<u>Length of follow-up:</u> 13 days	<u>Safety outcomes:</u> No differences in hematological or renal	<u>Comments:</u> Preliminary results, follow-up until day 28 is ongoing with a larger sample size

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>phase IIb clinical trial</p> <p><u>Setting:</u> Hospitalized COVID-19 patients were randomized in the clinical trial between March 23 and April 5 2020 at Hospital e Pronto-Socorro Delphina Rinaldi Abdel Aziz</p> <p><u>Country:</u> Manaus, Western Brazilian Amazon</p> <p><u>Source of funding:</u> This study was funded by the Government of the Amazonas State, Farmanguinhos (Fiocruz), SUFRAMA, CAPES, FAPEAM, and federal funds granted by a coalition of Brazilian senators.</p>	<ul style="list-style-type: none"> respiratory rate >24 rpm and/or heart rate higher than 125 bpm (in the absence of fever) and/or peripheral oxygen saturation <90% in ambient air and/or shock (defined as mean arterial pressure <65 mmHg, with the need for vasopressors medicine or oliguria or a lower level of consciousness) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> age < 18 years <p><u>N total at baseline:</u> N = 81 Intervention (I): 41 (high dosage CQ arm) Control (C): 40 (low dosage treatment)</p> <p><u>Important characteristics:</u> Intervention group Mean age: 54.7 ± 13.7 Male gender: 31/41(75.6%)</p> <p>Control group Mean age: 47.4 ± 13.3 Male gender: 10/40 (75%)</p> <p><u>Groups comparable at baseline?</u> High dosage group is slightly older. History of heart disease was more frequent among patients receiving the higher CQ dosage (p=0.05)</p>	<p>days, total dose 12g) CQ 150mg tablets (Farmanguinhos, Fiocruz, Brazil).</p>	<p>tablets + 1 placebo) twice daily on day 0, 3x150mg tablets +1 placebo tablet followed by 4 placebo tablets from D1 to D4, and then 4 placebo tablets twice daily from D5-D9, total dose 2.7g)</p> <p>Placebo tablets (Farmanguinhos, Fiocruz, Brazil).</p>	<p><u>Loss-to-follow-up:</u> Not reported</p>	<p>toxicity was seen between the groups.</p> <p><u>Death at D13</u> High dosage:16/41 (39%) Low dosage: 6/40 (15%)</p>	<p>Most patients were confirmed COVID-19 by RT-PCR posteriori (62/81, 76.5%). The non-confirmed patients presented compatible clinical and epidemiological COVID-19 presentation and were analysed together</p> <p><u>Author's conclusion:</u> Preliminary findings suggest that the higher CQ dosage (10-day regimen) should not be recommended for COVID-19 treatment because of its potential safety hazards.</p>
4. Immunoglobulin							
4.1. Hyperimmunoglobulin							
Pollizzo (2022)	<u>Type of study:</u>	<u>Hospitalised patients with COVID-19 who had been symptomatic</u>	hIVIG	Placebo	<u>Length of follow-up:</u> 28 days.	Clinical outcomes	<u>Definitions:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Randomised, double-blind, placebo-controlled trial.</p> <p><u>Setting:</u> 63 hospital sites.</p> <p><u>Country:</u> Argentina, Denmark, Germany, Greece, Indonesia, Israel, Japan, Nigeria, Spain, the UK, and the USA.</p> <p><u>Source of funding:</u> The study was funded by the US National Institutes of Health. Except for named members of the writing and study group, the funder had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit.</p> <p><u>Conflicts of interest:</u> Transparently reported.</p>	<p><u>for up to 12 days and did not have acute end-organ failure.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adults aged 18 years and older; Hospitalised with documented SARS-CoV-2 infection and symptoms attributable to COVID-19 for 12 days or less. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Previous passive immunotherapies; End-organ failure (including vasopressor therapy, new renal replacement therapy, and mechanical ventilation); Known IgA deficiency with anti-IgA antibodies; Certain thrombotic conditions and prothrombotic disorders. <p><u>N total at baseline:</u> N = 579 Intervention: N = 295 Control: N = 284</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 58 (48 to 70) years C: 60 (50 to 70) years</p> <p>Sex, n/N (%) male: I: 149/295 (51%) C: 180/284 (63%)</p> <p>Disease severity not reported.</p> <p>Groups comparable at baseline? Yes.</p>	<p>Infusion of hVIG was to commence at a rate of 0.5 mg/kg per min for approximately 30 min. If tolerated, the rate of infusion could be doubled after intervals of not less than 30 min up to a maximum of 4 mg/kg per min.</p> <p>+ Standard of care</p>	<p>Infusion of placebo was to commence at a rate of 0.5 mg/kg per min for approximately 30 min. If tolerated, the rate of infusion could be doubled after intervals of not less than 30 min up to a maximum of 4 mg/kg per min.</p> <p>Standard of care background therapy included up to 10 days of study-provided remdesivir unless contraindicated. Other aspects of standard care including corticosteroids, prophylactic anti-coagulation, supplemental oxygen, and other end-organ support, as clinically indicated.</p>	<p><u>Loss-to-follow-up:</u> Not reported.</p> <p><u>Incomplete outcome data:</u> Not reported.</p>	<p><u>Mortality: number of deaths up to day 28, n/N (%)</u> I: 5/295 (1.7%) C: 5/284 (1.8%) OR 1.01 (95% CI 0.29 to 3.60) P=0.98</p> <p><u>Mortality: number of deaths up to day 28, n/N (%)</u> I: 18/295 (6.1%) C: 22/284 (7.7%) HR 0.80 (95% CI 0.42 to 1.51) P=0.49</p> <p><u>Duration of hospitalization: number of patients discharged from hospital or reached most favourable ordinal scale category (category 1), n/N (%)</u> I: 268/295 (90.8%) C: 252/284 (88.7%) RRR 1.07 (95% CI 0.92 to 1.26) P=0.37</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support: Ordinal outcome at day 7+</u> Summary OR 1.06 (95% CI 0.77 to 1.45) P=0.72</p>	<p>†Ordinal outcome is based on a seven-category ordinal scale: 1=can independently undertake usual activities with minimal or no symptoms; 2=no supplemental oxygen, symptomatic and unable to undertake usual activities; 3=supplemental oxygen <4 L/min); 4=supplemental oxygen ≥4 L/min or symptoms/signs of extra-pulmonary conditions; 5=non-invasive ventilation, high-flow oxygen, or symptoms and signs of acute stroke (National Institute of Health Stroke Scale >14) 6=invasive ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy; 7=death</p> <p>The summary statistic cited is a proportional OR based on use of multiple imputation</p> <p>OR = odds ratio RRR = recovery rate ratio HR= hazard ratio</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> When administered with standard of care including remdesivir, SARS-CoV-2 hVIG did not demonstrate</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>Respiratory support:</u> <u>number of patients reaching one of the two most favourable ordinal scale categories (categories 1 and 2), n/N (%)</u> I: 178/295 (60.3%) C: 160/284 (56.3%) RRR 1.11 (95% CI 0.91 to 1.35) P=0.30</p> <p>Safety <u>Serious adverse events at day 7, n/N (%)</u> I: 8/295 (2.7%) C: 6/284 (2.1%) OR 1.32 (95% CI 0.45 to 3.92) P=0.61</p> <p><u>Serious adverse events at day 28, n/N (%)</u> I: 16/295 (5.4%) C: 20/284 (7.0%) OR 0.72 (95% CI 0.37 to 1.40) P=0.33</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	efficacy among patients hospitalised with COVID-19 without end-organ failure. The safety of hIVIG might vary by the presence of endogenous neutralising antibodies at entry.
Ali, 2021	<p><u>Type of study:</u> RCT; single-blinded</p> <p><u>Setting:</u> Single-center; enrolment from June 19, 2020 to February 3, 2021</p> <p><u>Country:</u></p>	<p>Hospitalized severely or critically ill COVID-19 patients with ARDS.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Hospitalized • severely (hospitalized, requiring any supplemental oxygen) or critically (hospitalized, requiring noninvasive ventilation, high- 	<p>Intravenous immunoglobulin (IVIG) + standard of care</p> <p>4 intervention arms:</p> <p>I: 0.15 g/Kg with SOC</p> <p>II: 0.2 g/Kg with SOC,</p>	<p>Standard of care</p> <p>“SOC according to the national clinical management guideline for COVID-19 Infection which</p>	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: 0/10 II: 0/10 III: 0/10 IV: 0/10 C: 0/10</p>	<p>Clinical outcomes <u>Mortality (28-30 day)</u> I-total: 10/40 (25%) C: 6/10 (60%) RR 0.417 (95% CI 0.199 to 0.871) <u>Subgroups – RR compared to control</u> I: RR 0.333 (95% CI 0.087 to 1.272)</p>	<p><u>Definitions:</u> <u>Clinical status:</u> “Patients’ clinical status was assessed on seven-category ordinal scale and was recorded on the specific observation days. The ordinal scale had following seven categories: 1, not hospitalized and no limitations of activities; 2, not hospitalized, with limitation of activities, home oxygen</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Karachi, Pakistan</p> <p><u>Source of funding:</u> "The work is supported by Higher Education Commission (HEC), Pakistan (Ref no. 20-RRG-134/RGM/R&D/HEC/2020)."</p> <p><u>Conflicts of interest:</u> "Muneeba Ahsan Sayeed, Farah Saleem, Sheikh Muhammad Muhaymin, Sadaf Khan, Shobha Luxmi, Habiba Arain, Abdul Samad Khan, Hamid Mehmood, Abdur Rasheed, Ashraf Jahangeer, SaifUllah Baig, Saeed Quraishy declare they have no competing interests. Shaukat Ali, Syed Muneeb Uddin, Elisha Shalim, Fatima Anjum, Ayesha Ali, Mir Rashid Ali, Iqra Ahmed, Tehreem Mushtaq, Faisal Shahab, Suneel Kumar, Mujtaba Khan, were part of C-IVIG production</p>	<p>flow oxygen devices or invasive ventilation) ill</p> <ul style="list-style-type: none"> Acute Respiratory Distress Syndrome (ARDS): i.e. dyspnea, respiratory rate ≥ 30/min, blood oxygen saturation $\leq 90\%$, PaO₂/FiO₂ < 300, and lung infiltrates $> 50\%$ on chest X-ray <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> history of IgA deficiency autoimmune disorder thromboembolic disorder allergic reaction to immunoglobulin treatment pregnant females patients requiring two or more inotropic agents to maintain blood pressure acute or chronic kidney injury/failure <p><u>N total at baseline:</u> N = 50 Intervention: 40 (10 in every arm) Control: 10</p> <p><u>Important characteristics:</u> Age, mean \pm SD: I: 47.06\pm8.75 II: 67.4 \pm 9.17 III: 54.14\pm14.46 IV: 55.3 \pm 13.9 C: 59.1 \pm 12.06</p> <p>Sex, n/N (%) male: I: 7 (70%) II: 10 (100%) III: 5 (50%) IV: 6 (60%)</p> <p>Days from onset of symptoms, Mean \pm S.D</p>	<p>III: 0.25 g/Kg with SOC</p> <p>IV: 0.3 g/Kg with SOC.</p> <p>"Plasma donors with variable titers contributed to the pool, however a lower limit of 10 cut-off index (COI) was established by measurement through electrochemiluminescence immunoassay analyzer (ECLIA). The variable titer of convalescent plasma donors led to the variable titer of pooled plasma, and subsequently variable anti-SARS-CoV-2 antibody level of up to 104\pm30 COI measured through ECLIA [7]]. Patients infused with C-IVIG followed a pre-infusion protocol and were given methylprednisolone (40-mg) I.V. and adequate hydration was ensured. The infusion protocol is explained in detail in additional methods in supplementary appendix."</p>	<p>includes airway support, antiviral medications, anticoagulant, steroid, hemodynamic support and antibiotics when required. SOC included Remdesivir (200 mg loading then 100 mg once daily for 5 days), Enoxaparin and corticosteroids, dexamethasone (6 mg once daily) or Methylprednisolone (0.5–1 mg/kg twice daily) initiated at the time of hospitalization till resolution of ARDS"</p>		<p>II: RR 0.5 (95% CI 0.171 to 1.463) III: RR 0.167 (95% CI 0.024 to 1.145) IV: RR 0.667 (95% CI 0.268 to 1.660) "Severe COVID-19 patients showed a significant reduction in mortality (P = 0.002) when compared to critical COVID-19 patients, with mortality in 10 out of 23 (43.5%) critical patients and none among the 17 severe patients (data not shown)."</p> <p>Days to death, median (IQR) unless stated otherwise I: 5.5 (range 4-7) II: 16 (range 8-25) III: 26 = frequency (median/IQR not available) IV: 10 (5-18) C: 9 (5.5-19)</p> <p><u>Duration of hospitalization</u> Days to discharge from hospital, median (IQR) I: 5.5(4.25-11.75) II: 10(5-15) III: 6(4.5-11) IV: 7.5(5.5-9) C: 8(8-8.75)</p> <p><u>Time to symptom resolution</u> Days to improvement in ordinal scale* by 3 categories I: 5(4-11)</p>	<p>requirement, or both; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring any supplemental oxygen; 5, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 6, hospitalized, receiving invasive mechanical ventilation; and 7, death."</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Relatively small study Not all outcomes reported (the same) to all study arms (e.g. media+ IQR, median+range or frequency reported of different study arms for same outcome measure) Announced outcomes differ from specifics in study register Some concerns regarding risk of bias <p><u>Authors conclusion:</u> The study reports use of hyperimmune intravenous immunoglobulin prepared from convalescent plasma in treating severe and critical COVID-19 patients. Single dose of C-IVIG in combination with standard of care was found both safe and efficacious while increasing the chance of survival and reducing the risk of disease progression.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	team at Dow University of Health Sciences."	<p>I: 10 ± 2.90 II: 8 ± 2.05 III: 7 ± 4 IV: 8.5 ± 2.9 C: 8 ± 3.08</p> <p>Clinical status*, n (%)</p> <p>4. Hospitalized, requiring any supplemental oxygen (severe)</p> <p>I: 5(50) II: 5(50) III: 4(40) IV: 3(30) C: 5 (50)</p> <p>5. Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices</p> <p>I: 4 (40) II: 5 (50) III: 6 (60) IV: 7 (70) C: 5 (50)</p> <p>6. Hospitalized, receiving invasive mechanical ventilation</p> <p>I: 1(10) II: 0 III: 0 IV: 0 C: 0</p> <p>Groups comparable at baseline?.</p>				<p>II: 9(5-14) III: 4(2.5-6) IV: 4(2.75-6) C: 7.5(3.25-8)</p> <p>Horowitz index score; PaO2/FiO2 ratio to assess severity of ARDS, median (IQR)</p> <p>I-total: 359 (127 - 400) P=0.009 C: 105 (73.5 - 319.5)</p> <p>Sub group scores</p> <p>I: 393 (124.75 - 441.5) II: 359 (156 - 400) III: 0.54 (361.5) – unclear whether info is missing IV: not reported</p> <p><u>Respiratory support</u></p> <p>Clinical status* at day 7, n/10 (%)</p> <p>Score 3</p> <p>I: 1 (10) II: 0 III: 3 (30) IV: 0 C: 2 (20)</p> <p>Score 4</p> <p>I: 1 (10) II: 2 (40) III: 1 (10) IV: 3 (30) C: 2 (20)</p> <p>Score 5</p> <p>I: 1 (10) II: 5 (30) III: 0 IV: 2 (20) C: 3 (30)</p> <p>Score 6</p> <p>I: 0 II: 0</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>III: 1 (10) IV: 1 (10) C: 0 <i>Also reported, n/10 (%) for scores 1, 2, 3 and 7.</i></p> <p>Days to invasive ventilation, median (IQR) I: N/A II: 7(2.25-8.75) III: 8 = frequency, no other info available IV: 5(2.25-8.5) C: 8(2-8.5)</p> <p>Safety <u>Adverse events</u> Number (%) patients who had adverse event during treatment I: 7/10 (70) II: 8/10 (80) III: 5/10 (50) IV: 8/10 (80) C: 7/10 (70)</p> <p>Virological outcomes <u>Viral clearance</u> Days to negative SARS-CoV-2 PCR, median (IQR) I: 8 (15-11.5) II: 11.5 (7.25-20.25) III: 23 (13.5-34.5) IV: 5.5 (2.75-7.75) C: 15 (4.2-49)</p> <p><i>Also reported: change in C-reactive protein (CRP) levels, radiological changes in patient's X-ray, change in Ferritin, and Lactate Dehydrogenase (LDH) level</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Supplement: routine vitals measurement during hospital stay, and assessing laboratory parameters like Liver Function Test (LFT), Procalcitonin, Sodium, Potassium, Chloride and Bicarbonate levels during hospital stay from day of enrollment till 28th day after enrollment	
4.2. Intravenous immunoglobulin							
Mazeraud, 2021 (ICAR trial)	<p><u>Type of study:</u> multicentre, double-blind, placebo-controlled phase 3 trial</p> <p><u>Setting:</u> ICU-based, between April 3 and October 20, 2020</p> <p><u>Country:</u> 43 centres in France</p> <p><u>Source of funding:</u> This study was supported by Groupe Hospitalier Universitaire Paris Psychiatrie et Neurosciences as the sponsor. This study was funded by a grant from the French ministry of Health and Laboratoire Français du</p>	<p>patients in ICU with COVID-19-associated moderate or severe acute respiratory distress syndrome requiring invasive mechanical ventilation</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • critically ill patients with COVID-19, confirmed by a positive PCR test • admitted to intensive care unit • requiring invasive mechanical ventilation for moderate-to-severe ARDS (according to the Berlin Definition criteria) • enrolled in the study within 72 h after starting invasive mechanical ventilation <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • acute renal failure at admission • pregnancy • immunoglobulin A deficit • allergy to IVIG • participation in another intervention trial <p><u>N total at baseline:</u> Randomized: N = 146</p>	intravenous immunoglobulins (CLAYRIG [†] in a total dose of 2 g/kg, divided into 4 perfusions of 0.5/kg each given over at least 8 h over 4 days)	placebo	<p><u>Length of follow-up:</u> 90 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> I: 2/69 (2.9%) <i>Reasons</i></p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 1)</i> • <i>lost to follow-up (n = 1)</i> <p>C: 1/77 (1.3%) <i>Reason</i> <i>lost to follow-up (n = 1)</i></p>	<p>The primary outcome was the number of ventilator-free days at day 28, defined as the number of days between the last extubation day and day 28. Prespecified subgroup analyses (according to time to randomisation, age, and BMI) were also performed.</p> <p>Clinical outcomes</p> <p><u>Mortality</u></p> <p><u>Mortality at day 28</u> I: 24/69 (35%) C: 20/77 (26%) OR 1.52 (95%CI: 0.75-3.09)</p> <p><u>Mortality at day 90</u> I: 28/69 (41%) C: 31/77 (40%) OR 1.01 (95%CI: 0.52-1.97)</p> <p><u>Duration of hospitalisation</u></p> <p><u>Time to ICU discharge</u> Days, median (IQR) I: 21 (15.0-27.0) C: 21 (13.0-29.0)</p>	<p><u>Definitions:</u></p> <p>* Acute renal failure was defined as plasma creatinine > 354 µmol/L, an increase in plasma creatinine baseline concentration by 3 times or more, a diuresis < 0.3 mL/kg over the last 24 h, or anuria over the last 12 h.</p> <p>† CLAYRIG is a saccharose and maltose free IVIG.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In patients with COVID-19 who received invasive mechanical ventilation for moderate-to-severe acute respiratory syndrome, IVIG did not improve clinical outcomes at day 28 and tended to be associated with an increased frequency of serious adverse events, although not significant. The effect of IVIGs on earlier disease stages of COVID-19 should be assessed in future trials.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>fractionnement et des Biotechnologies supplied the intravenous immunoglobulins for free. Neither the funder of the study nor the organisation providing the study drug had a role in study design, data collection, data analysis, data interpretation, or writing of the report. The study sponsor (Groupe Hospitalier Universitaire Paris Psychiatrie et Neurosciences, Paris, France) participated in the trial, collected the data, and did the analysis.</p> <p><u>Conflicts of interest:</u> The authors declare no competing interests.</p>	<p>Intervention: N = 69 Control: N = 77</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 65.1 y (12.2) C: 66.5 y (9.3)</p> <p>Sex, n/N (%) male: I: 49/69 (71%) C: 54/77 (70%)</p> <p>Charlson Comorbidity score, median (IQR): I: 3 (1-4) C: 3 (2-4)</p> <p>Performance status ≤ 1: I: 45/69 (65%) C: 90/77 (78%)</p> <p>COVID-19 treatment before and 2 days after randomisation: <u>Corticosteroid</u> I: 49/69 (71%) C: 55/77 (71%)</p> <p><u>Tocilizumab</u> I: 5/69 (7%) C: 7/77 (9%)</p> <p><u>Antibiotics</u> I: 56/69 (81%) C: 65/77 (84%)</p> <p>Patients in the intervention group were less often 65 years or older (55% vs. 64%) and less often had a performance status ≤ 1 (65% vs. 78%).</p>				<p>Hodges-Lehman median difference 1.0 (95%CI: -6.0-7.0) $p = 0.74$</p> <p><u>Time to hospital discharge</u> Days, median (IQR) I: 34 (29.0-46.0) C: 39 (27.0-49.0) Hodges-Lehman median difference -2.0 (95%CI: -11.0-8.0) $p = 0.84$</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> <u>Patients receiving mechanical ventilation at day 28</u> I: 15/69 (22%) C: 22/77 (29%) OR 1.44 (95%CI: 0.67-3.07)</p> <p><u>Time to last extubation</u> Days, median (IQR) I: 12.5 (8.0-18.0) C: 9.5 (7.0-18.0) Hodges-Lehman median difference 1.0 (95%CI: -3.0-4.0) $p = 0.38$</p> <p><u>Other</u> <u>Number of ventilation-free days at day 28 (primary outcome)</u> Median (IQR) I: 0.0 (0.0-8.0) C: 0.0(0.0-6.0)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Hodges-Lehman median difference 0.0 (95%CI: 0.0-0.0) p = 0.21</p> <p>Mean I: 6.7 (95%CI: 4.6-8.8) C: 7.0 (95%CI: 4.9-9.2) Hodges-Lehman median difference 0.5 (95%CI: -3.5-2.5)</p> <p><u>Lung injury score at day 28</u> Median (IQR) I: 2.8 (2.4-3.1) C: 2.7(2.2-3.1) Hodges-Lehman median difference 0.0 (95%CI: -0.5-0.5) p = 0.60</p> <p><u>Sequential organ failure assessment score at day 28</u> Median (IQR) I: 7 (3-10) C: 6 (4-10) Hodges-Lehman median difference 1 (95%CI: -3-2) p = 0.65</p> <p><u>Clinical ordinal score at day 28</u> Median (IQR) I: 3 (1.0-4.0) C: 3 (1.0-5.0) Hodges-Lehman median difference 0 (95%CI: -1.0-0.0) p = 0.47</p> <p><u>Clinical ordinal score at day 90</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Median (IQR) I: 1 (1.0-1.0) C: 1 (1.0-1.0) Hodges-Lehman median difference 0.0 (95%CI: 0.0-0.0) p = 0.56</p> <p>Safety <u>Any adverse events</u> I: 152 C: 154</p> <p><u>Patients with at least one adverse event</u> I: 51/68 (75%) C: 54/76 (71%)</p> <p><u>Any serious adverse events</u> I: 78 C: 47</p> <p><u>Patients with at least one adverse event</u> I: 22/68 (32%) C: 15/76 (20%)</p> <p><u>Ventilator-associated pneumonia</u> I: 28/68 (41%) C: 29/76 (38%)</p> <p><u>Catheter-related infection</u> I: 10/68 (15%) C: 8/76 (11%)</p> <p><u>Other infection</u> I: 1/68 (1%) C: 3/76 (4%)</p> <p><u>Septic shock</u> I: 7/68 (10%) C: 5/76 (7%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>Acute kidney injury</u> I: 15/68 (22%) C: 16/76 (21%)</p> <p><u>Renal replacement therapy</u> I: 4/68 (6%) C: 5/76 (7%)</p> <p><u>Deep vein thrombosis or pulmonary embolism</u> I: 10/68 (15%) C: 3/76 (4%)</p> <p><u>Other</u> I: 46/68 (68%) C: 30/76 (39%)</p> <p>Virological outcomes Not reported</p>	
Raman, 2021	<p><u>Type of study:</u> Open-label, multicenter, parallel group, randomized, safety and efficacy phase II study.</p> <p><u>Setting:</u> Four centers across four Indian cities, between July 2020 and September 2020.</p> <p><u>Country:</u> India.</p> <p><u>Source of funding:</u> Virchow Biotech Private Limited, Hyderabad, extended financial</p>	<p><u>Hospitalized COVID-19 patients with moderate disease</u></p> <p><u>Inclusion criteria:</u> - Male or female aged 18 years or older with RT-PCR confirmed COVID-19 illness; - Patients with moderate pneumonia defined as: body temperature 38 degrees or more or PaO₂/FiO₂ 100-300 mmHg or respiratory rate >24/min and oxygen saturation 90-93% on room air or lung involvement confirmed with chest X-ray.</p> <p><u>Exclusion criteria:</u> - Viral pneumonia with other viruses besides COVID-19; - IgA deficiency or history of anaphylaxis to immunoglobulin therapy;</p>	intravenous immunoglobulin (IVIG) therapy + standard of care	<p>Standard of care alone.</p> <p>Standard of care consisted of azithromycin, lopinavir/ritonavir; piperacillin + tazobactam; acetaminophen and pantocid.</p>	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: N=3 discontinued C: N=1 discontinued</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> I: 0/47 (0%) C: 1/49 (2%)</p> <p><u>Duration of hospitalization, mean (SD)</u> I: 7.72 (2.69) days C: 17.50 (5.01) days P=0.0001</p> <p><u>Number of days in intensive care unit, mean (SD)</u> I: 4.0 (1.4) C: 5.0 (3.0) P=0.69</p> <p><u>Time to symptom resolution</u> <u>Number of days for normalization of body temp <37 degrees celcius, mean (SD)</u></p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> - After hospital admission, patients daily received immunoglobulin 0.4 g/kg body weight for 5 days. - Standard of care consisted of Azithromycin; Lopinavir/ritonavir; Piperacillin + Tazobactam; Acetaminophen and Pantocid. - Patients with comorbid diseases such as diabetes and/or hypertension were given appropriate treatment.</p> <p><u>Author's conclusion:</u> In summary, initiation of IVIG as adjuvant treatment for COVID-19 patients with moderate pneumonia in combination with standard care of treatment, can reduce the use of mechanical ventilation, shorten the hospital length of stay, promote the</p>

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	<p>support to conduct this study.</p> <p><u>Conflicts of interest:</u> Two of the Thummala C Raghuram and Vishaly T Aravinda are full-time employees of Virchow Biotech, India. The other six authors do not have any commercial interest relevant to the manuscript. Data presented in this manuscript was not presented at any meeting.</p>	<p>- severe pneumonia were defined as: respiratory rate ≥ 30 times/min or oxygen saturation $\leq 90\%$ in resting state or PaO₂/FiO₂ ≤ 100 mmHg or respiratory failure requiring mechanical ventilation or ICU monitoring with signs of other organ failure; - either immunoglobulin or hydroxychloroquine treatment; - pregnant or lactating.</p> <p><u>N total at baseline:</u> N = 100 Intervention: N = 50 Control: N = 50</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 48.4 (11.6) C: 49.0 (13.5) P=0.82 Sex, n/N (%) male: I: 14/50 (28%) male C: 19/50 (38%) male Diabetes Mellitus N (%) I: 13 (26%) C: 14 (28%) P=0.82 Hypertension N (%) I: 18 (36%) C: 13 (26%) P=0.28 Obesity N (%) I: 8 (16%) C: 8 (16%) P=1.0 Disease severity: not reported Oxygen Saturation (%) I: 95.1 \pm 3.6 C: 95.1 \pm 3.1</p>				<p>I: 2.18 (1.87) C: 5.45 (4.39) P=0.005 <i>Number of days for cessation of cough, mean (SD)</i> I: 3.52 (1.16) C: 6.67 (2.29) P=0.0001</p> <p><u>Respiratory support</u> <i>Number of days on mechanical ventilation, mean (SD)</i> I: 2.42 (0.9) C: 4.47 (2.7) P=0.01 <i>Number of days for normalization of oxygen, mean (SD)</i> I: 2.45 (1.63) C: 4.75 (3.0) P=0.03 <i>Number of days for normal respiratory rate, mean (SD)</i> I: 2.44 (1.81) C: 5.45 (4.27) P=0.06</p> <p>Safety <u>Adverse events</u> I: N=17 (from 15 patients) C: N=20 (from 12 patients)</p> <p>N=1 death N=1 tachycardia N=1 rashes Other adverse events in the study: dyspnea, swelling at infusion site, headache, and diarrhoea (no exact numbers reported).</p>	<p>early recovery of patients, and improve the effective treatment of patients to achieve significant clinical efficacy. The limitations of the present study include open-label design and small sample size. Besides, follow-up of patients was not done after their hospital discharge.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		P=0.97 Groups comparable at baseline? Yes.				Virological outcomes <u>Viral clearance</u> Proportion of patients with negative RT-PCR during the study period, day 14, 28, end of study Announced, but not reported.	
Gharebaghi, 2020	<u>Type of study:</u> randomized placebo-controlled double-blind clinical trial. <u>Setting:</u> Department of Cardiology, Urmia University of Medical Sciences, Urmia, Iran Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran <u>Country:</u> Iran	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> Being over 18 years of age; Possessing a PCR-confirmed COVID-19 diagnosis; Involvement of > than 30% of both lungs (ground-glass opacity) in high-resolution computed tomography (HRCT) (confirmed by two radiologists); O2 saturation (satO2) of < 90%; A lack of adequate response to initial treatment including at least both one antiviral and one chloroquine-class drug. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Age of less than 18 years; Pregnancy; 	Intravenous immunoglobulin. The IVIg group received IVIg (human) flebogamma 5% DIF GRIFOLS, in addition to their prior initial treatment (the initial treatment methods continued in the treatment group during the trial). Treatment group patients received four vials of 5 gm5 IVIg daily for three consecutive days.	Placebo control. The control group continued to receive the same treatments as were introduced initially, in addition to a placebo.	Not reported	<u>Mortality yes/no (median; IQR)</u> I: 14 (70) / 15 (38.4) C: 6 (30) / 24 (61.5) Unad. OR= 0.27 (95% CI= 0.08 to 0.85) P=0.025 <u>Multivariable regression analysis result for prediction of mortality of patients with severe COVID-19</u> <u>Adjusted OR (95% CI)</u> IVIg (Treatment group): Adjus. OR= 0.003 (95% CI= 0.001 to 0.815)P=0.042 Age: Adjus. OR= 1.485 (95% CI= 1.011 to 2.181) P=0.044	<u>Remarks:</u> - <u>Authors conclusion:</u> The results of our study suggest that the administration of IVIg in patients with severe COVID-19 infection who did not respond to initial treatments could improve clinical outcomes and thus reduce mortality rates. Regarding high price of IVIg, we suggest that it should be considered in patients with > 30% involvement of lungs in lung CT scan, whom their dyspnea do not improve with standard treatment, those with persistent satO2 under 90%, and those who develop aggravation of lung involvement in serial lung CT scans, especially in younger adults.

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	<p><u>Source of funding:</u> None declared.</p>	<ul style="list-style-type: none"> Coagulation disorders; History of hypersensitivity to IVIg; Advanced heart failure; Pulmonary fibrosis/history of lung surgery; Presence of either sarcoidosis or tuberculosis. <p><u>N total at baseline:</u> N = 59 Intervention: N = 30 Control: N = 29</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 55.5 (45 to 60) C: 56 (47 to 66) P=0375</p> <p>Sex, n/N (%) male: I: 21/30 (70%) C: 20/29 (68.9%)</p> <p>Groups comparable at baseline?</p>				<p>Systolic BP: Adjus. OR= 1.078 (95% CI= 0.924 to 1.258) P=0.336</p> <p>Diastolic BP: Adjus. OR= 0.543 (95% CI= 0.303 to 0.972) P=0.040</p> <p>O2 saturation: Adjus. OR= 0.841 (95% CI= 0.621 to 1.138) P=0.262</p> <p>PLT: Adjus. OR= 1.000 (95% CI= 0.999 to 1.000) P=0.132</p> <p>LDH: Adjus. OR= 1.023 (95% CI= 1.000 to 1.046) P= 0.048</p> <p>BUN: Adjus. OR= 1.136 (95% CI= 0.990 to 1.304) P=0.069</p> <p>Creatinine: Adjus. OR= 0.018 (95% CI= 0.001 to 6.085) P=0.177</p> <p>PaO2: Adjus. OR= 0.834 (95% CI= 0.593 to 1.173) P=0.298</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Tabarsi, 2020	<p><u>Type of study:</u> RCT</p> <p><u>Setting:</u> Dr. Masih Daneshvari Hospital, a university affiliated and selected referral center for COVID-19 patients.</p> <p><u>Country:</u> Tehran, Iran</p> <p><u>Source of funding:</u> Not reported.</p> <p><u>Declaration of competing interest</u> The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.</p>	<p>Severely ill patients between 18 and 65 years old with COVID-19, confirmed based on the reports of Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or bilateral pulmonary infiltration in computed tomography (CT) scan of the chest were included in the study.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients aged between 18-65 • Diagnosed with COVID-19 confirmed based on the reports of RT-PCR or bilateral pulmonary infiltration in computed topography. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients who denied signing the consent form; • Patients with allergy reaction while injecting IVIg with severe extravasation and anaphylactic shock; • Midly ill patients; • Patients recovering and improving upon Hydroxychloroquine, lopinavir/ritonavir, and supportive therapy; • Pregnancy or breastfeeding. <p><u>N total at baseline:</u> N = 84 Intervention: N = 52 Control: N = 32</p> <p><u>Important characteristics:</u> Age, mean (SD): I: .54.29 y (12.85) C: 52.47 y (14.99)</p>	<p>Intratect® (Biotest), 400 mg/Kg daily for three doses, if they met necessary criteria for receiving the drug</p> <p>All patients in de intervention group were premedicated with 500 mg Acetaminophen, 100 mg Hydrocortisone, and 25 mg Diphenhydramine 30 min before the injection.</p> <p>*Patients in both groups received oxygen and fluid support, lopinavir/ritonavir (200/50 mg, Hetero labs), two tablets a day, and hydroxychloroquine (Tehran-Daru) 200 mg two times daily</p>	<p>Patients in the control group did not receive IVIg treatment</p> <p>*Patients in both groups received oxygen and fluid support, lopinavir/ritonavir (200/50 mg, Hetero labs), two tablets a day, and hydroxychloroquine (Tehran-Daru) 200 mg two times daily</p>	<p><u>Length of follow up:</u> 1-22 days</p> <p><u>Loss to follow-up:</u> None.</p>	<p>Clinical outcomes</p> <p><u>Mortality (expired→), n/N</u> I: 24/52 C: 14/32 P=0.830</p> <p><u>Duration of hospital stay, median (IQR)</u> I: 8.5 (6 to 12) days C: 5.5 (4 to 8) days P=0.003</p> <p><u>Length of ICU stay, median (IQR)</u> I: 5 (3 to 7) days C: 4 (2 to 7) days P=0.720</p> <p><u>Need for mechanical ventilation, n/N, wihin 22 days</u> I: 21/52 C: 10/32 P=0.390</p> <p><u>Nasal or face mask oxygen therapy n/N, within 22 days</u> I: 23/52 C: 15/32 P=0.630</p> <p><u>Need for admission to ICU, n/N, within 22 days</u> I: 39/52 C: 27/32 P=0.300</p> <p><u>More than 50% improvements in chest CT scan, n/N, within 22 days</u> I: 7/52</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> The obtained data did not support the beneficial effects of using IVIg in combination with hydroxychloroquine and lopinavir/ritonavir for SARS-Cov-2 patients, as the mortality rate, radiographic changes, and the need for mechanical ventilation did not show noticeable improvement. However, the length of the ICU and hospital stay might be shorter upon early IVIg initiation.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Sex, n/N (%) male: I: 40/52 (76.92%) C: 25/32 (78.12%)</p> <p>[Disease severity], mean (SD): Not reported.</p> <p>Hypertension, n/N (%) I: 11/52 (21.15%) CL 6/32 (18.75%) P=0.790</p> <p>Ischemic heart disease, n/N (%) I: 3/52 (5.76%) C: 2/32 (6.25%) P=1.000</p> <p>Chronic obstructive pulmonary disease, n/N (%) I: 1/52 (1.92%) C: 0/32 (0%) P=1.000</p> <p>Malignancy, n/N (%) I: 0/52 (0%) C: 1/32 (3.12%) P=0.380</p> <p>Diabetes n/N (%) I: 10/52 (19.23%) C: 8/32 (25%) P=0.530</p> <p>Chronic kidney disease, n/N (%) I: 3/52 (5.76%) C: 1/32 (3.12%) P=1.000</p> <p>Rheumatoid arthritis, n/N (%) I: 1/52 (1.92%) C: 0/32 (0%) P=1.000</p>				<p>C: 2/32 P=1.000</p> <p><u>Time from admission to administration (days) in the intervention group</u> Frequency: 52 days Minimum: 1 day Maximum: 22 days Mean (SD): 3.84 (3.35)</p> <p>*Study also reported the comparison of the lab tests between the two groups. Results are not reported in the evidence table.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline/ Yes → There were no significant differences between the two groups in terms of patients' age, gender, and past medical history.					
4.3. Normal immunoglobulin							
NA	NA	NA	NA	NA	NA	NA	NA
5. Convalescent plasma							
Sullivan, 2022	<p><u>Type of study:</u> Multicenter, double-blind, randomized, controlled trial</p> <p><u>Setting:</u> 23 trial sites in the US, between June 3, 2020, through October 1, 2021</p> <p><u>Country:</u> US</p> <p><u>Source of funding:</u> Funded by the Department of Defense and others. The trial sponsors did not contribute to the trial design, to the collection, analysis, and interpretation of data, or to the decision to submit the manuscript for publication.</p> <p><u>Conflicts of interest:</u> Transparently and extensively reported.</p>	<p>Outpatients ≥ 18 y with symptomatic COVID-19, regardless of their risk factors for disease progression or vaccination status</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • symptomatic COVID-19 • pregnant women as well as those who had received a COVID-19 vaccine before or during follow-up and those who had received glucocorticoids were eligible. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • previous COVID-19-related hospitalization or planned hospitalization within 24 h after enrollment • previous reactions to blood-product transfusions • inability to adhere to the protocol • receipt of monoclonal antibodies before enrollment. <p><u>N total at baseline:</u> Randomized: N = 1225 Intervention: N = 610 Control: N = 615</p>	<p>Convalescent plasma</p> <p>Administered in a single dose at a volume of approximately 250 ml.</p>	<p>Control plasma</p> <p>Administered in a single dose at a volume of approximately 250 ml.</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u></p> <p>Intervention: 77/610 (13%)</p> <p>Reasons:</p> <ul style="list-style-type: none"> • did not receive allocated intervention (n = 18) • lost to follow-up (n = 50) • decided to withdraw from trial (n = 9) <p>Control: 89/615 (14%)</p> <p>Reasons:</p> <ul style="list-style-type: none"> • did not receive allocated intervention (n = 26) • lost to follow-up (n = 52) • decided to withdraw from trial (n = 7) • withdrew because of physician decision (n = 1) died (n = 3) 	<p>Clinical outcomes</p> <p><u>Mortality</u> <u>Death before day 28:</u> I: 0/592 (0%) C: 3/589 (0.5%)</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Invasive respiratory support</u> Not reported.</p> <p><u>Non-invasive respiratory support</u> Not reported.</p> <p><u>Other COVID-19-related hospitalization</u> I: 17/592 (3%) C: 37/589 (6%) p = 0.0005</p> <p><u>Hospitalization unrelated to COVID-19</u> I: 4/592 (0.7%) C: 3/589 (0.5%)</p>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • COVID-19-related hospitalization within 28 days after transfusion. <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • no prespecified secondary outcomes are reported <p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In participants with COVID-19, most of whom were unvaccinated, the administration of convalescent plasma within 9 days after the onset of symptoms reduced the risk of disease progression leading to hospitalization.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Modified ITT population: Intervention: N = 592 Control: N = 589</p> <p><u>Important characteristics:</u> Age, median (IQR): I: .42 y (32-54) C: 44 y (43-55)</p> <p>Sex, n/N (%) female: I: 323/592 (54.6%) C: 352/589 (59.8%)</p> <p>There were no obvious imbalances between the trial groups with respect to baseline characteristics.</p>				<p><u>Mechanical ventilation, ICU hospitalization, or both due to COVID-19</u> I: 3/592 (0.5%) C: 4/589 (0.7%)</p> <p><u>Non-ICU hospitalization due to COVID-19, with supplemental oxygen</u> I: 12/592 (2%) C: 26/589 (4%)</p> <p><u>Non-ICU hospitalization due to Covid-19, without supplemental oxygen</u> I: 2/592 (0.3%) C: 4/589 (0.7%)</p> <p><u>A stay of >24 hr for observation in an emergency department, field hospital, or other health care unit or receipt of oxygen for >24 hr outside of hospital</u> I: 0/592 (0%) C: 0/589 (0%)</p> <p><u>Expected time free of hospitalization</u> Days I: 27.26 C: 26.27 Difference: 0.99±0.28 p = 0.004</p> <p><u>Probability of remaining free of hospitalization</u> I: 97% C: 93% Risk difference (%points): 4±1 p = 0.006</p>	

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						<p>Safety A total of 16 grade 3 or 4 adverse events (7 in the convalescent-plasma group and 9 in the control plasma group) occurred in participants who were not hospitalized.</p> <p>Virological outcomes Not reported.</p>	
Song, 2022	<p>Type of study: Randomized, open-label, multicenter, controlled clinical</p> <p>Setting: Hospitalized, between June 02, 2020 and November 18, 2020</p> <p>Country: 7 sites across Brazil</p> <p>Source of funding: Brazilian Ministry of Science, Technology and Innovation, Funding de Amparo à Pesquisa do Estado de Sao Paulo</p> <p>Conflicts of interest: Authors declare no competing interests.</p>	<p>Outpatients with mild-to-moderate COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≤18 years • RT-PCR-confirmed COVID-19 infection in any clinical sample • <10 days after onset of symptoms at screening • Intubated patients were considered eligible within 48 h of orotracheal intubation • Presence of COVID-19 pneumonia with a typical, indeterminate, or atypical compatible chest CT-scan and at least one of the following criteria: <ul style="list-style-type: none"> - need for >3 L of O2 in catheter/mask or >25% in the Venturi mask to maintain O2 saturation >92%; - or presence of respiratory distress syndrome with PaO2/FiO2 <300 mmHg <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Already enrolled in another clinical trial evaluating antiviral or immunobiological 	<p>Intervention I: Low-volume convalescent plasma in a volume of 200ml (150-300ml) + Standard care</p> <p>Intervention II: High-volume convalescent plasma in a volume of 400ml (300-600ml) + Standard care</p>	<p>Standard of care</p> <p>SoC included: Oxygen supplementation, corticosteroids, anticoagulation, and/or antibiotics, according to the clinical judgement of attending physician</p>	<p>Length of follow-up: 28 days</p> <p>Incomplete outcome data & loss-to-follow-up: Intervention (LV): N=3/43 (7%) Reason: did not receive plasma (n=3)</p> <p>43 included in analysis of primary outcome</p> <p>Intervention (HV): N=3/44 (6.8%) Reason: received low-volume plasma (n=3)</p> <p>44 included in analysis of primary outcome</p> <p>Control: N=1/42 (2.3%) Reason: received low-volume plasma (n=1)</p> <p>42 included in analysis of primary outcome</p>	<p>Clinical outcomes Mortality: 28-day overall survival, % (CI): I (LV): 69.9% (56.9-85.7) I (HV): 79.9% (67.7-92.2) C: 83.7% (72.5-96.6))</p> <p>LV vs. C: -13.8% (-38.7-11.2) HV vs. C: -4.6% (-25.7-16.4)</p> <p>Duration of hospitalization Length of hospital stay, days I (LV): 16.0 (8-20) I (HV): 13 (9-20) C: 13.5 (10.7-21.2)</p> <p>LV vs. C: -0.5 (-4.2-5.3) HV vs. C: -2.0 (-2.3-6.3)</p> <p>Time to symptom resolution Multistate model representation of the mean times in the different WHO scale states in each randomized group in presented in figure 3.</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Time to clinical improvement at day 28 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Incidence of acute adverse events, as defined by the International Society of Blood Transfusion/International Haemovigilance Network • Evaluation according to an ordinal scale of 10 categories in D7, D14 and D28, duration of mechanical ventilation, length of hospital stay in survivors up to 28 days and time from the beginning of treatment to death (in the control group, this time will be determined at 24 hours after randomization). • Detection of SARS-CoV-2 in nasopharyngeal swab (and tracheal secretion if intubated patient) on days 0, 1, 3, 7, 14 and 28 after transfusion in groups B and C, and 24 hours after randomization in the group A (control). • Specific IgS, IgM and IgA titers for SARS-CoV-2 on days 0 (before transfusion), 1, 3, 5, 7, 14 and 28 after transfusion in groups B and C,

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		<p>therapy for the treatment of COVID-19.</p> <ul style="list-style-type: none"> • IgA deficiency • Presence of a clinical condition that does not allow infusion of 400 ml of volume at clinical discretion • Pregnancy or breastfeeding • Receipt of immunoglobulin in the last 30 days • Presence of significant risk of death within the next 48 hours at clinical discretion. <p><u>N total at baseline:</u> N = 129 Intervention I (low-volume): N=42 Intervention II (high-volume): N=43 Control: N=44</p> <p><u>Important characteristics:</u> Age, median (IQR): I (LV): 62.8 y (50.6-70.2) I (HV): 55.0 y (45.1-69.1) C: 62.0 y (47.8-69.8)</p> <p>Sex, n/N (%) male: I (LV): 25/43 (58.1%) I (HV): 30/44 (68.2%) C: 33/42 (78.6%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline? There was a higher proportion of seropositive (igG) patients in the control group (80%), this could favor plasma groups (LV=58%, HV=66%).</p>				<p><u>Invasive respiratory support</u> Not reported</p> <p><u>Non-invasive respiratory support</u> Not reported</p> <p>Safety <u>Serious adverse events</u> Not reported</p> <p>Virological outcomes <u>Viral clearance</u> Undetectable SARS-CoV-2 PCR I (LV): 12/25 (48%) I (HV): 10/27 (37%) C: 6/24 (25%) LV vs.C: 23.0 (-4.0-47.2) HV vs. C: 12.0 (-13.9 - -36.1)</p> <p>Neutralizing antibodies titers I (LV): 1:120 (1:20-1:640) I (HV) 1:160 (1:20-1:640) C: 1:160 (1:30-1:1920)</p> <p>LV vs. C: -1:330 (-1:2432 – 1:1772) HV vs C: -1:256 (-1:2388 – 1:1875)</p>	<p>and 24 hours after transfusion randomization in group A (control).</p> <ul style="list-style-type: none"> • Detection of neutralizing antibodies on days 0 (before transfusion), 1, 14 and 28 after transfusion in groups B and C, and 24 hours after randomization in group A (control). <p><u>Definitions:</u> -</p> <p><u>Remarks:</u> Supplementary Tables are not available.</p> <p>Limitations of the study include the fact that each center may have had different standard of care treatment protocols, although the use of corticosteroids, proven effective as support therapy, was used by all centers.</p> <p><u>Authors conclusion:</u> The administration of either low or high volume of convalescent plasma in patients with severe COVID-19 had no impact on clinical improvement with up to 10 days of symptoms onset. There was also no significant impact on secondary outcomes (duration of mechanical ventilation, length of hospital stays, time to SARS-CoV- 2 negativity in nasopharyngeal swab, time to antibodies titers).</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
De Santis, 2022	<p>Type of study: Open-label multicentre randomized controlled trial</p> <p>Setting: hospital-based, between April - November 2020</p> <p>Country: 5 hospitals (4 in the state of São Paulo, 1 in Campo Grande). Brazil</p> <p>Source of funding: This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (grant no. 20/05367-3).</p> <p>Conflicts of interest: Not reported</p>	<p>Hospitalized COVID-19 patients</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Diagnosis of COVID-19 based on RT-PCR results • Respiratory distress • Begin within 10 days of initial symptoms • Age 18-80 years <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • History of previous severe allergy to plasma transfusion • Severe congestive heart failure • Terminal renal failure • Hepatic cirrhosis • Any severe illness expected to confer a short life expectancy • Participation in any other clinical trial • Immunosuppression <p>N total at baseline: N = 110 Intervention: 37 Control: 73</p> <p>Important characteristics:</p> <p>Age, mean (SD): I: 56.1 y (15.2) C: 59.3 y (12.4)</p> <p>Sex, n/N (%) male: I: 23/36 (63.9%) C: 44/71 (64.8%)</p> <p>Disease severity, median (range): <i>Defined by Simplified Acute Physiology Score 3 at admission to ICU</i> I: 56 (37-94)</p>	<p>Convalescent plasma</p> <p>The total transfusion dose of CCP per patient was 1,800 mL (minimum dose 1,200 mL), divided into 3 daily doses of 600 mL for 3 days. The 600 mL volumes were divided into 2 subunits of 300 mL or 200 and 400 mL</p> <p>+</p> <p>Standard treatment</p>	<p>Standard treatment</p> <p>Not defined.</p>	<p>Length of follow-up: 60 days</p> <p>Loss-to-follow-up or incomplete data: I: 1/37 (2.7%) <i>Reason</i></p> <ul style="list-style-type: none"> • <i>did not receive CCP transfusion</i> <p>C: 2/73 (2.7%) <i>Reasons</i></p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 1)</i> • <i>did not have pneumonia (n = 1)</i> <p>No loss-to-follow up</p>	<p>Clinical outcomes</p> <p>Mortality at hospitalization day 30 I: 8/36 (22.2%) C: 18/71 (25.4%) P=0.81</p> <p>Mortality at hospitalization day 60 I: 11/36 (30.6%) C: 25/71 (35.2%) P=0.67</p> <p>Duration of hospitalization not reported</p> <p>Hospital-free days at hospitalization day 30, median (range) I: 3 (0-24) C:0 (0-28) P=0.27</p> <p>Hospital-free days at hospitalization day 30, median (range) I: 30.5 (0-53) C:21 (0-58) P=0.27</p> <p>Time to symptom resolution not reported</p> <p>Invasive respiratory support not reported</p> <p>Non-invasive respiratory support not reported</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Death rate at days 30 and 60 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Ventilator-free days • Hospital-free days on days 30 and 60 after randomization • Adverse reactions to plasma transfusion <p>Definitions: Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0.</p> <p>Remarks: -</p> <p>Authors conclusion: In this randomized clinical trial, transfusion of high-dose CCP did not reduce death rates, hospitalization durations, or number of days receiving mechanical ventilation for patients with very severe COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		C: 68 (39-100) Groups comparable at baseline.				<p><u>Ventilator-free days at hospitalization day 30, median (range)</u> I: 12.5 (0-30) <i>n</i>=35 C: 12.0 (0-60) <i>n</i>=70 P=0.82</p> <p><u>Ventilator-free days at hospitalization day 30, median (range)</u> I: 42.5 (0-60) <i>n</i>=33 C: 39.0 (0-60) <i>n</i>=67 P=0.80</p> <p>Safety <u>Serious adverse events</u> No serious adverse reactions attributable to CCP transfusion were observed during study follow-up.</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p> <p>Also reported Scatter plots of inflammatory biomarker levels (CRP, IL-6)</p>	
Aleman, 2022	<p><u>Type of study:</u> Multicenter, double-blind, randomised, placebo-controlled trial</p> <p><u>Setting:</u> 4 health-care centers, between November 10, 2020 and July 28, 2021</p>	<p>Outpatients ≥ 50 y with the onset of mild-to-moderate COVID-19 symptoms ≤ 7 days before randomisation</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 50 y • non-hospitalised • mild-to-moderate COVID-19* • confirmed SARS-CoV-2 infection, with a positive PCR or validated antigen rapid test result received no more than 5 days before randomisation 	<p>Convalescent plasma + standard medical treatment</p> <p>Participants received one intravenous infusion of 250-300 mL of ABO-compatible high-titre methylene blue-treated convalescent plasma. For participants with a bodyweight of less than 45 kg, dosing was bodyweight adjusted to 5 mL/kg.</p>	<p>Placebo + standard medical treatment</p> <p>Participants received one intravenous infusion of 250 mL of sterile 0.9% saline solution. For participants with a</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: 6/188 (3%) Reasons: • did not receive allocated intervention (<i>n</i> = 4) • lost to follow-up (<i>n</i> = 2)</p>	<p>Clinical outcomes <u>Mortality</u> <u>Death rate</u> I: 0/188 (0%) C: 1/188 (1%) RR 0.20 (95%CI: 0.01-4.14)</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u></p>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • hospitalisation within 28 days from baseline • mean change in viral load in nasopharyngeal swabs from baseline to day 7 <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • time to complete symptom resolution • change in the 10-point WHO Clinical Progression Scale score within the 60 days following infusion • change from baseline in inflammatory markers on day 7

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> Spain</p> <p><u>Source of funding:</u> Grifols, Crowdfunding campaign YoMeCorono. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.</p> <p><u>Conflicts of interest:</u> The authors declare no competing interests.</p>	<ul style="list-style-type: none"> • symptom onset no more than 7 days before randomisation <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • severe COVID-19 • required hospitalisation for any cause • history of a previous SARS-CoV-2 infection • received one or two doses of a COVID-19 vaccine • contraindications to the investigational product • increased thrombotic risk • history of clinically significantly abnormal liver function or chronic kidney disease stage 4 or worse • patients who were pregnant, breastfeeding, or planning a pregnancy during the study period <p><u>N total at baseline:</u> N = 376 Intervention: N = 188 Control: N = 188</p> <p><u>Important characteristics:</u> Age, median (IQR): I: .56 y (52-62) C: 56 y (53-63)</p> <p>Sex, n/N (%) male: I: 105/188 (56%) C: 98/188 (52%)</p> <p>Disease severity: <i>Mild</i> I: 183/188 (97%) C: 183/188 (97%)</p> <p><i>Moderate</i></p>	Standard medical treatment is not further specified.	<p>bodyweight of less than 45 kg, dosing was bodyweight adjusted to 5 mL/kg.</p> <p>Standard medical treatment is not further specified.</p>	<p>Control: 3/188 (2%) Reasons: did not receive allocated intervention (n = 3)</p>	<p><u>Time to complete symptom resolution</u> Days, median (IQR) I: 12.00 (6.00-21.25) C: 12.00 (6.00-22.00) p = 0.76</p> <p><u>Invasive respiratory support</u> Not reported.</p> <p><u>Non-invasive respiratory support</u> Not reported.</p> <p><u>Other</u> <u>Hospitalisation within 28 days from baseline</u> I: 22/188 (12%) C: 21/188 (11%) RR 1.05 (95%CI: 0.78-1.41)</p> <p><u>Change in the 10-point WHO Clinical Progression Scale score within the 60 days following infusion</u> No difference between the groups.</p> <p><u>Change from baseline in inflammatory markers on day 7</u> No significant differences in D-dimer, Ferritin, lymphocyte count, CRP and prealbumin, but a minor difference in IL-6 with no clinical significance.</p> <p>Safety Serious adverse events</p>	<ul style="list-style-type: none"> • mean change in viral load in nasopharyngeal swabs from baseline to day 28 • death rate • rate of adverse events <p><u>Definitions:</u> * Mild and moderate COVID-19 were defined according to international guidelines: patients with fever, cough, sore throat, malaise, headache, and muscle pain were considered to have mild COVID-19, whereas evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen 94% or more on room air was considered moderate COVID-19.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Methylene blue-treated convalescent plasma did not prevent progression from mild to severe illness and did not reduce viral load in outpatients with COVID-19. Therefore, formal recommendations to support the use of convalescent plasma in outpatients with COVID-19 cannot be concluded.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 5/188 (3%) C: 5/188 (3%)</p> <p>Groups comparable at baseline.</p>				<p><u>Severe adverse events grade 3-4</u> I: 27/188 (14%) C: 21/188 (11%)</p> <p>One participant with mild COVID-19 signs and symptoms developed a thromboembolic event 7 days after convalescent plasma infusion, which was reported as a serious adverse event possibly related to COVID-19 or to the experimental intervention.</p> <p><u>Adverse events</u> <u>Treatment-related adverse events</u> I: 24/188 (13%) C: 8/188 (4%) RR 3.00 (95%CI: 1.38-6.51)</p> <p><u>Virological outcomes</u> <u>Viral clearance</u> Not reported.</p> <p><u>Other</u> <u>Change in viral load from baseline from baseline to day 7</u> log₁₀ copies per mL, mean (SD; N) I: -2.41 (1.32; 174) C: -2.32 (1.43; 174) Crude difference -0.10 (95%CI: -0.35 to 0.15)</p> <p><u>Change in viral load from baseline from baseline to day 28</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						log ₁₀ copies per mL, mean (SD; N) I: -3.86 (1.56; 180) C: -4.00 (1.45; 172) Crude difference 0.12 (95%CI: -0.17 to 0.40)	
Ray, 2022	<p>Type of study: A single center open label phase 2 randomised control trial</p> <p>Setting: hospital-based, between May 31, 2020, and October 12, 2020</p> <p>Country: 1 hospital, Kolkata, India</p> <p>Source of funding: Government funding agency</p> <p>Conflicts of interest: The authors declare no competing interests.</p>	<p>Hospitalized COVID-19 patients with mild or moderate ARDS</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Aged <18 y SARS-CoV-2 infection confirmed by RT-PCR severe COVID-19 as indicated by mild (PaO₂/FiO₂ 200-300) or moderate ARDS (PaO₂/FiO₂ 100-200) not requiring mechanical ventilation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> pregnant women admitted late after 10 days of initial presentation <p>N total at baseline: Randomized: N = 80</p> <p>Intervention: N = 40 Control: N = 40</p> <p>Important characteristics: Age, median (IQR): Not reported*</p> <p>Sex, n/N (%) male: I: 30/40 (75%) C: 27/40 (67.5%)</p> <p>Groups comparable at baseline? Demographic characteristics of the patients between</p>	<p>Convalescent plasma: 200 ml ABO-matched CP on two successive days</p> <p>+ Standard of care</p> <p>11 patients in the CPT arm received Remdesivir</p>	<p>Standard of care as per guidelines of Indian Council of Medical Research</p> <p>One patient in the SOC arm received Tocilizumab,</p> <p>13 patients in the SOC arm and</p>	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up or incomplete data: Not reported</p>	<p>Clinical outcomes</p> <p>Mortality I:10/40 (25%) C:14/40 (35%)¹</p> <p>MH HR: 0.67 (95% CI: 0.30 – 1.505) p=0.34</p> <p>Duration of hospitalisation Not reported</p> <p>Time to symptom resolution †</p> <p>Respiratory support</p> <p>Safety Adverse events No adverse events were reported.</p> <p>Virological outcomes Virological clearance</p> <ul style="list-style-type: none"> <p><i>Also reported: plotted total hospital stay (no statistics were performed), plotted S/F ratio (no statistics were performed), SPO₂/FiO₂ kinetics of individual patients during hospitalization</i></p>	<p>Definitions: -</p> <p>Remarks: *Age was not reported</p> <p>¹ numbers were obtained from the supplemental table 4</p> <p>†Time taken for recovery from ARDS in all patients could not be determined accurately for all patients due to emergent operational limitations in access to computed tomography facility and arterial blood gas analysis for follow-up.</p> <p>Instead, recovery from COVID-19 disease was assessed in terms of time taken for discharge from the hospital, although it was not pre-specified in the trial protocol.</p> <ul style="list-style-type: none"> Comparison of time taken for the patients in the two arms to register negative RT-PCR for SARS-CoV-2 could not be done due to statutory suspension of clinical use of repeat RT-PCR among hospitalized patients <p>Authors conclusion: In severe COVID-19 patients with mild or moderate ARDS no significant clinical benefit was registered in this clinical trial with convalescent plasma therapy in terms of prespecified outcomes.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		two parallel arms were not significantly different.					
Bajpai, 2022	<p><u>Type of study:</u> A phase 3, randomized, multicenter, open-label trial (COPLA-II trial)</p> <p><u>Setting:</u> Hospitalized patients, enrolled from June 14, 2020 to December 15, 2020</p> <p><u>Country:</u> 2 centers, India</p> <p><u>Source of funding:</u> Not reported</p> <p><u>Conflicts of interest:</u> None to declare</p>	<p>Hospitalized patients with severe COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ≤18 years • Severe COVID-19 according to WHO definition¹ <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with a history of allergy to plasma • Pregnancy • Multiorgan failure • HIV • Viral hepatitis • Cirrhosis • Renal impairment on dialysis and Renal replacement therapy (RRT) • Cancer • Uncontrolled hypertension • Diabetes • Arrhythmias • Unstable angina and haemodynamically unstable patients requiring vasopressors • Expected life expectancy less than 24 hours <p><u>N total at baseline:</u> N = 400 Intervention: N=200 Control: N=200</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 54.7 y (9.5) C: 56.3 y (12.6)</p>	<p>Convalescent plasma: two doses of 250 mL on consecutive days</p> <p>+</p> <p>Standard of care</p>	<p>standard of care</p> <p>The standard of care was based on the detailed guidelines for COVID-19 management laid down by the Ministry of Health and Family Welfare, India.</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> No incomplete outcome data and lost-to-follow up</p>	<p>Clinical outcomes</p> <p><u>Mortality till 7 days, n/N (%)</u> I: 25/200 (12.5%) C: 21/200 (10.5%)</p> <p><u>Mortality till 28 days, n/N (%)</u> I: 42/200 (21%) C: 37/200 (18.5%)</p> <p>*percentages are self-calculated, the authors calculated the percentages by taking the 'rows' instead of 'columns'</p> <p><u>Duration of hospitalization, median (IQR)</u> I: 12 (9-16) C: 13 (9-18) P=0.98</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Invasive respiratory support</u> <u>Patients on machinal ventilation till 7 days, n/N (%)</u> I: 2/200 (1%) C: 3/200 (1.5%) P=0.68</p> <p><u>Non-invasive respiratory support</u></p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Time to clinical improvement <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Proportion of patients in each treatment group based on the ordinal scale at 48 h, 7, 14 and 28 days • Duration of O₂ therapy • ICU stay • Hospital stay • Proportion on mechanical ventilation at day 7 • Mortality at day 7 and 28 • Adverse events • Presence of antibodies to SARS-CoV-2 in serum after plasma administration on baseline, 28 h, 7 and 28 days • Changes in cytokine levels • Acute phase reactant till 28 days <p><u>Definitions:</u> ¹The WHO Interim Guidance defined severe COVID-19 as following any of the two criteria out of five including ventilated patient within 24 hours, respiratory rate ≥30 beats/min, oxygen saturation in the resting state level less than 90% in resting state, Partial pressure of oxygen/ Fractional inspired oxygen ratio (PaO₂)/(FiO₂) ≤300 mm Hg, and lung infiltrates ≥50% within 24–48 hours</p> <p>time to clinical improvement was defined as a reduction in ordinal scale by two points or live discharge, whichever was earlier up</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Sex, n/N (%) male: I: 143/200 (71.5%) C: 126/200 (63%)</p> <p>Disease severity Defined with Sequential Organ Failure Assessment, mean (SD) I: 2.68 (1.12) C: 2.54 (0.99)</p> <p>Groups comparable at baseline? Yes</p>				<p><u>Duration of oxygen therapy (days), median (IQR)</u> I: 8 (6-12) C: 10 (6-12)</p> <p>Safety <u>Serious adverse events</u> Not reported</p> <p>Virological outcomes <u>Viral clearance</u> Neutralising antibodies (%) at 14 days I: 78/78 (100%) C: 83/85 (97.6%) P=0.173</p>	<p>to 28 days.</p> <p>Percentages presented in the article are incorrect.</p> <p>Adverse events are presented in the methods, but not in the results.</p> <p><u>Remarks:</u> The primary and key secondary endpoints were also evaluated in pre-specified subgroups of patients who required oxygen therapy via either HFNC or low flow nasal cannula at baseline or patients having a baseline imputed PaO₂/FIO₂ ≤ 100 or 101–200 at baseline, and in all randomized patients.</p> <p>Due to declining rates of COVID-19 hospitalizations and utilization of standard of care medications prohibited by regulatory guidance, the trial was stopped early.</p> <p><u>Authors conclusion:</u> Convalescent plasma with adequate antibody titres should be transfused in COVID-19 patients along with SMT in the initial 3 days of hospitalisation for better clinical outcomes.</p>
Baldéon, 2022	<p><u>Type of study:</u> Random double blinded, placebo-controlled</p> <p><u>Setting:</u> Hospital-based, between May 2020 to January 2021</p>	<p>Hospitalized patients with recently diagnosed COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • COVID-19 diagnoses based on positive RT-PCR test, clinical diagnosis or lung imaging test • patients with impairment of previously normal lung function 	<p>Convalescent plasma 5 ml/kg body weight for one occasion</p> <p>+ standard care based on Ecuadorian COVID-19 treatment guidelines for hospital practice</p>	<p>Non-convalescent plasma 5 ml/kg body weight for one occasion</p> <p>+ standard care based on Ecuadorian</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> none</p>	<p>Clinical outcomes Mortality n/N (%) I: 7/63 (11.1%) C: 12/95 (12.6%) RR = 1.003, 95% CI (0.3938, 2.555) P= 0.372</p>	<p><u>Remarks:</u> Considering the results of the intermediate statistical analyses that could not evidence an important advantage in the use of CP over the NCP in the survival rate of participating patients, the ethics committee and the research team advised to suspend the trial. Consequently, the</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> 3 centers Quito, Ecuador</p> <p><u>Source of funding:</u> The was funded by the initiative Salvar Vidas Ecuador (SalvarVidasEC).</p> <p><u>Conflicts of interest:</u> None to declare.</p>	<p>defined with a SaO₂ <90% at 0.5FiO₂ and/or with an increased O₂ need in the previous 24 h upon admission</p> <ul style="list-style-type: none"> patients with a score of 5-6 on te NEWS2 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> pregnant or lactating women diagnosis of cancer, HIV, superimposed systemic infections, liver failure, renal failure, chronic obstructive pulmonary disease, pulmonary fibrosis, and restrictive pulmonary pathologies receiving immunosuppressant participating in any other clinical trial patients with history of blood/derivate transfusion <p><u>N total at baseline:</u> Randomized: N = 158</p> <p>Intervention: N = 63 Control A: N = 95</p> <p><u>Important characteristics:</u> Age, mean ± SD I: 56.3 ± 12.7 C: 55.0 ± 13.3</p> <p>Sex, n/N (%) male: I: 42/63 (66.7%) C: 65/95 (68.4%)</p> <p>Haemoglobin concentrations were statistically higher in the placebo group (15.5 ± 1.9 compared to 14.7 ± 1.7 in the intervention group)</p>		<p>COVID-19 treatment guidelines for hospital practice</p>		<p><u>Duration of hospitalisation</u> Days mean ± SD I: 11.9 ± 7.6 C: 12.7 ± 8.6 P= 0.531</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> Not reported</p> <p><u>Safety</u> Not reported</p> <p><u>Virological outcomes</u> Not reported</p>	<p>study was halted with 79% (158/200) of the calculated sample.</p> <p><u>Authors conclusion:</u> Present results showed that administration of CP with antibodies against SARS-CoV-2 to COVID-19 patients with moderate infection did not affect their survival rate compared with infected patients treated with NCP. However, early treatment of COVID-19 patients with CP tended to decrease the LOH while the delay in CP treatment was associated with a longer hospital stay. In addition, delay in CP treatment negatively affected the recovery of the respiratory rate.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Bar, 2021 (PennCCP2 trial)	<p>Type of study: open-label RCT</p> <p>Setting: hospital-based, between May 18, 2020 and January 8, 2021</p> <p>Country: 2 tertiary referral centres in the USA</p> <p>Source of funding: University of Pennsylvania.</p> <p>Conflicts of interest: One author reports consultancy fees from Pfizer. One author reports consultancy fees from Viiv, Gilead, and Janssen. One author reports consultancy fees from Gilead and Merck. One author SEH reports consultancy fees from Sanofi Pasteur, Lumen, Novavax, and Merck. One reports consultancy fees from Merck, Gilead, Janssen, and Viiv.</p>	<p>hospitalized patients with COVID-19 pneumonia</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age ≥ 18 y • RT-PCR-confirmed SARS-CoV-2 infection • hospitalized • radiographic documentation of pneumonia • abnormal respiratory status* <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • contraindication to transfusion • participating in other clinical trials of investigational COVID-19 therapy • clinical suspicion that the etiology of acute illness was primarily due to a condition other than COVID-19 • ABO-compatible CCP was unavailable <p>N total at baseline: Randomized: N = 80</p> <p>Intervention: N = 41 Control: N = 39</p> <p>Important characteristics:</p> <p>Age: < 45 y I: 10 (25.0) C: 2 (5.1)</p> <p>45-60 y I: 6 (15.0) C: 15 (38.5)</p> <p>61-74 y I: 14 (35.0) C: 12 (30.8)</p>	convalescent plasma (CCP; 2 units of locally sourced plasma) + standard care	standard care	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up or incomplete data: I: 1/41 (2.4%) <i>Reasons</i></p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 1)</i> <p>C: 0/39 (0%)</p>	<p>Clinical outcomes</p> <p>Mortality Mortality at day 14 I: 1/40 (2.5%) C: 2/39 (5.1%) OR 0.479 (95%CI: 0.008-9.558)</p> <p>Mortality at day 28 I: 2/40 (5.0%) C: 10/39 (25.6%) OR 0.156 (95%CI: 0.015-0.814)</p> <p>Duration of hospitalisation Not reported</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support Mechanical ventilation or ECMO I: 5/40 (12.8%) C: 10/39 (25.6%) OR 0.419 (95%CI: 0.1-1.531)</p> <p>Days with mechanical ventilation or ECMO Median (IQR) I: 0 (0-0) C: 0 (0-0.5) p = 0.085</p> <p>Days with any O₂ support Median (IQR) I: 7 (2-10.25) C: 8 (4-18.5) p = 0.169</p>	<p>Definitions: * Abnormal respiratory status was defined as defined as S_aO₂ < 93%, or requiring supplemental O₂, or tachypnea with a respiratory rate ≥ 30 h.</p> <p>Remarks: -</p> <p>Authors conclusion: Two units of locally sourced CCP administered early in hospitalization to majority seronegative participants conferred a significant benefit in clinical severity score and 28-day mortality. Results suggest CCP may benefit select populations, especially those with comorbidities who are treated early.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>75+ y I: 10 (25.0) C: 10 (25.6)</p> <p>Sex, n/N (%) male: I: 21/40 (52.5%) C: 15/39 (38.5%)</p> <p>Patients in the intervention group were more often younger than 45 years old (25.0% vs. 5.1%) and male (52.5% vs. 38.5%). Also, patients in the intervention more often had blood type 0 (62.5% vs. 46.2%) and less often blood type B (5.0% vs. 15.4%).</p>				<p>Other</p> <p><u>Clinical severity score (primary outcome)</u> Median (IQR) I: 7 (2.75-12.5) C: 10 (5.5-30) p = 0.03</p> <p><u>WHO ordinal score at day 14</u> Median (IQR) I: 2 (1-4) C: 2 (1.5-6.5) OR 0.481 (95%CI: 0.212-1.072)</p> <p><u>WHO ordinal score at day 28</u> Median (IQR) I: 1 (1-2) C: 2 (1-7.5) OR 0.562 (95%CI: 0.243-1.288)</p> <p>Safety</p> <p><u>Participants with ≥ 1 serious adverse events</u> I: 12/40 (30.0%) C: 15/42 (38.5%) OR 0.689 (95%CI: 0.242-1.929)</p> <p><u>Maximum grade adverse event per subject</u> Median (IQR) I: 1 (0-3) C: 3 (0-4.5) OR 0.507 (95%CI: 0.221-1.148)</p> <p><u>Number of adverse events per subject</u> Median (IQR)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I: 0.5 (0-2.25) C: 1 (0-7) p = 0.151 <u>Maximum grade serious adverse event per subject</u> Median (IQR) I: 0 (0-3) C: 0 (0-4.5) OR 0.553 (95%CI: 0.218-1.375) <u>Number of serious adverse events per subject</u> Median (IQR) I: 0 (0-1) C: 0 (0-1) p = 0.737 Virological outcomes Not reported	
Ortigoza, 2021	<p><u>Type of study:</u> RCT randomized, double-blind, placebo-controlled trial</p> <p><u>Setting:</u> 21 US hospitals from April 17, 2020, to March 15, 2021</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> CONTAIN COVID-19 was supported in part by philanthropic funds to New York</p>	<p>hospitalized adults with COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients ≥18 years of age • Hospitalized for COVID-19 respiratory symptoms • Hospitalized for less than 72 hours OR within day 3 to 7 from first signs of illness • Laboratory confirmed COVID-19 • On supplemental oxygen, non-invasive ventilation or high-flow oxygen (clinical status 3 or 4) • N.B. It is assumed patients may be on other randomized controlled trials of pharmaceuticals for COVID-19 and patients who meet eligibility criteria will 	<p>Convalescent Plasma</p> <p>One unit of CCP (approximately 250 mL) was infused within 24 hours of randomization at a rate of less than or equal to 500 mL/h.</p>	<p>Placebo</p> <p>250 mL of normal saline</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up:</u> Intervention: 5/468 (1.1%) Reasons (not clearly described)</p> <p>Control: 10/473 (2.1%) Reasons (not clearly described)</p>	<p>Clinical outcomes <u>primary (WHO scores on day 14) outcome</u> cOR of 0.94 (95% CrI, 0.75-1.18; P[cOR<1] = 72% and P[cOR<0.8] = 8%)</p> <p><u>secondary (WHO scores on day 28) outcome</u> cOR 0.92 (95% CrI, 0.74-1.16; P[cOR<1] = 76% and P[cOR<0.8] = 10%)</p> <p><u>Mortality (Day 28)</u> I: 59/462 (12.8%) C: 71/462 (15.4%) OR (0.86; 95% CrI, 0.60-1.25; P[OR<1] = 78% and P[OR<0.8] = 34%)</p> <p><u>Duration of hospitalization</u> not reported</p>	<p><u>Definitions:</u> 11-point WHO Ordinal Scale: 0: Not hospitalized, no RNA detected 1: Not hospitalized, RNA detected 2: Not hospitalized, symptomatic, independent 3: Not hospitalized, symptomatic, assistance required 4: Hospitalized, without oxygen 5: Hospitalized, oxygen by mask or nasal prongs 6: Hospitalized, oxygen by NIV or HFNC 7: Hospitalized, MV, PO2/FIO2 ≥150 8: Hospitalized, MV, PO2/FIO2 <150 or vasopressors 9: Hospitalized, MV, PO2/FIO2 <150 or vasopressors, dialysis, or ECMO 10: Death</p> <p><u>Remarks:</u> ---</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>University and Montefiore Medical Center/Albert Einstein College of Medicine</p> <p><i>*Other sources of the funding are available in the article.</i></p> <p><u>Conflicts of interest:</u> Dr Philley reported receiving personal fees from INSMED as an advisory board member, consultant, researcher...</p> <p><i>*Conflict of interest for all authors are described in the article.</i></p>	<p>not be excluded on this basis.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Receipt of pooled immunoglobulin in past 30 days • Contraindication to transfusion or history of prior reactions to transfusion blood products • Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) • Volume overload secondary to congestive heart failure or renal failure • considered unlikely to survive past 72 hours based on investigator assessment • receipt of a COVID-19 vaccine <p><u>N total at baseline:</u> N = 941 Intervention: 468 Control:473</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 62 y (51-72) C: 64 y (54-74)</p> <p>Sex, n/N (%) male: I: 284/468 (60.7%) C: 272/473 (57.5%)</p> <p>Groups comparable at baseline? Yes</p>				<p><u>Time to symptom resolution</u> not reported</p> <p><u>Respiratory support</u> not reported</p> <p>Safety <u>Adverse events</u> Any adverse events (excluding transfusion reactions) I: 44 (9.4%) C: 39 (8.2%) (P = .57)</p> <p><u>transfusion reactions</u> I: 8 (1.7%) C: 2 (0.4%) (P = .06)</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p> <p>Subgroup analyses are also available for primary and secondary outcomes in supplementary file.</p>	<p><u>Authors conclusion:</u> In this trial, CCP did not meet the prespecified primary and secondary outcomes for CCP efficacy. However, high-titer CCP may have benefited participants early in the pandemic when remdesivir and corticosteroids were not in use.</p>
Holm, 2021	<u>Type of study:</u> open-label, multicentre	hospitalized patients with a need for supplemental oxygen treatment	Usual care + 200-250 mL of convalescence plasma IV during 30 min on three consecutive days.	Usual care alone (not defined)	<u>Length of follow-up:</u> 28 days	Clinical outcomes <u>Number of days in need of oxygen</u> Days, median (IQR)	<u>Remarks:</u> The study was prematurely terminated which resulted in a small sample size. The intended

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>randomized clinical trial</p> <p><u>Setting:</u> hospital-based, Two clinical sites, June 2020 - January 2021</p> <p><u>Country:</u> Sweden</p> <p><u>Source of funding:</u> This study was funded by the Skåne Region.</p> <p><u>Conflicts of interest:</u> The authors declare no competing interest.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • confirmed SARS-CoV-2 infection (positive on RT-PCR) no later than 4 days prior inclusion • Oxygen saturation >93% <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • habitual oxygen saturation <94% • severe immunosuppression <p><u>N total at baseline:</u> Randomized: N = 31</p> <p>Intervention: N = 17 Control: N = 14</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 80 y (60-86) C: 65 y (43-84)</p> <p>Sex, n/N (%) male: I: 11/17 (65%) C: 8/14 (57%)</p> <p>Groups were comparable at baseline.</p>			<p><u>Loss-to-follow-up or incomplete data:</u> One patient withdrew informed consent and for one patient plasma was not available</p>	<p>I: 11 (6-15) C: 7 (5-9) P=0.43</p> <p><u>Length of stay</u> Days, median (IQR) I: 13 (7-16) C: 8 (6-10) P=0.21</p> <p><u>Progression to high flow nasal cannula</u> I: 4/17 (25%) C: 4/14 (31%) OR 0.75 (95%CI: 0.18-1.88), p=0.87</p> <p><u>Progression to ventilator treatment</u> I: 1/17 (7%) C: 4/14 (0%) OR 0 (95%CI: 0-7.41), p=0.45</p> <p><u>Death</u> I: 2/12 (12%) C: 3/14 (21%) OR 0.49 (95%CI: 0.08-2.79), p=0.64</p>	<p>sample size of 100 patients is also small compared to other CCP studies in this context.</p> <p><u>Authors conclusion:</u> In this randomized controlled study of CCP treatment versus SOC, there was no significant difference between the groups in any primary or secondary outcome. We were thus unable to reject the null hypothesis. The results should be interpreted with caution due to the small sample size increasing the risk of a type 2 error.</p>
Menichetti, 2021	<p><u>Type of study:</u> open-label, multicentre randomized clinical trial (TSUNAMI trial)</p> <p><u>Setting:</u> hospital-based, 27 clinical sites between July 15</p>	<p>hospitalized patients with moderate-to-severe COVID-19 pneumonia</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • confirmed SARS-CoV-2 infection (positive on RT-PCR) • Radiologically confirmed pneumonia within more than 10 days from onset of symptoms 	<p>Intravenous high-titer convalescent plasma (CP) (≥1:160, by microneutralization test), 200 mL given from 1 to a maximum of 3 infusions.</p> <p>+ usual care</p>	<p>Usual care alone</p> <p>Remdesivir (intravenous [IV], 200mg on the first day and 100mg once daily from day 2 to day 5),</p>	<p><u>Length of follow-up:</u> 30 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Four patients withdrew informed consent and were not included in the intention-to-treat population.</p>	<p><u>Clinical outcomes</u> <u>Worsening of respiratory failure or death</u> I: 59/231 (25.5%) C: 67/239 (28%) OR 0.88 (95%CI: 0.59-1.33), p=0.54</p> <p><u>Mortality at day 30</u> I: 14/231 (6.1%) C: 19/241 (7.9%)</p>	<p><u>Definitions:</u> Worsening of respiratory failure was defined as PaO₂/FiO₂ ratio <150mmHg</p> <p>Virological cure was defined as two consecutive nasopharyngeal swabs resulting negative</p> <p><u>Remarks:</u> * Three patients in the control group withdrew consent after randomization</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>and December 8, 2020</p> <p><u>Country:</u> Italy</p> <p><u>Source of funding:</u> This study was sponsored by the Italian National Institute of Health, Istituto Superiore di Sanità (ISS) and the Italian Medicines Agency, Agenzia Italiana del Farmaco (AIFA). The sponsors had no role.</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported.</p>	<p>• PaO₂/FiO₂ ratio between 200 and 350mmHg at baseline.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Pregnant and lactating women • Patients with known hypersensitivity to blood products • Recipients of immunoglobulin <30 days • Patients with conditions precluding infusion of blood products • Participating in any other clinical trials • Patients requiring non- and invasive mechanical ventilations • Patients receiving treatment with IL-1, IL-6 or Janus kinase inhibitors <p><u>N total at baseline:</u> Randomized: N = 487 Modified ITT population: N = 473*</p> <p>Intervention: N = 232 Control: N = 241</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 65 y (55-74) C: 63 y (54-74)</p> <p>Sex, n/N (%) male: I: 150/232 (64.7%) C: 154/241 (63.9%)</p> <p>Coexisting conditions</p> <p><u>Hypertension</u> I: 82/232 (35.3%) C: 97/241 (40.3%)</p>		<p>glucocorticoids (IV dexamethasone 6mg daily or equivalent), and low-molecular-weight heparin (subcutaneous enoxaparin, 40-60mg daily or intermediate/high dose in selected cases), according to the AIFA recommendations</p>		<p>OR 0.75 (95%CI: 0.37-1.54), p=0.43</p> <p><u>Mechanical ventilation or death</u> I: 25/230 (10.9%) C: 25/240 (10.4%) OR 1.05 (95%CI: 0.58-1.88), p=0.87</p> <p><u>Virological cure</u> I: 14/199 (7.0%) C: 13/209 (6.2%) P=0.93</p> <p><u>Time from hospitalization to discharge, in days</u> Median [IQR] I: 12 [7-23] C: 13 [7-25] P=0.73</p>	<p>and two patients did not receive treatment (medical decision and patient refusal). In the intervention group, one patient withdrew consent after randomization and eight patients did not receive treatment (lack of compatible plasma (n=4), medical decision (n=1), patient refusal (n=3).</p> <p><u>Authors conclusion:</u> In patients with moderate to severe COVID-19 pneumonia, high-titer anti-SARS-CoV-2 CP did not reduce the progression to severe respiratory failure or death within 30 days.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Type 2 diabetes</i> I: 46/232 (19.8%) C: 45/241 (18.7%)</p> <p>Groups were comparable at baseline.</p>					
Estcourt, 2021	<p>Type of study: International, multicenter, open-label randomized controlled trial.</p> <p>Setting: 129 sites.</p> <p>Country: Australia, Canada, UK, US</p> <p>Source of funding: The funders/ sponsors had no role in the design and conduct of the trial; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Several of the authors are employees of the sponsoring organizations</p>	<p>Hospitalized critically ill adults with COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection • A potentially eligible patient who met any of the following criteria were excluded from participation in REMAP-CAP trial: <ol style="list-style-type: none"> 1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment 2. Patient is expected to be discharged from hospital today or tomorrow 3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven 	<p>Convalescent plasma</p> <p>High-titer, ABO compatible convalescent plasma (total volume approximately 550mL ± 150mL) within 48 hours of randomization. The first unit was given on the first day of the study. If the patient had no serious adverse reaction to the transfusion the second unit of convalescent plasma was administered with a minimum of 12 hours between transfusions, which was to allow appropriate assessment of adverse reactions to the initial transfusion. Both transfusions were to be given within 48 hours from randomization</p>	<p>No convalescent plasma</p> <p>Patients assigned to this intervention did not receive any preparation of immunoglobulin intended to neutralize SARS-CoV-2 (convalescent plasma, hyperimmune globulin or monoclonal antibodies) during the index hospitalization. All other aspects of care that were not specified within the platform (for example if enrolled in another domain) were according to local practice determined by</p>	<p>Length of follow-up: Up to 90 days.</p> <p>Loss-to-follow-up: 13 patients withdrew consent.</p> <p>Incomplete outcome data: Eight patients had missing data for the primary outcome.</p>	<p>Clinical outcomes</p> <p>Organ support-free days (day 21) severe state, median (IQR) I: 0 (-1 to 16) C: 3 (-1 to 16) Adj. OR – mean (SD) 0.97 (0.08) Adj. OR – median (95% CI) 0.97 (0.83 to 1.15)</p> <p>Organ support-free days (day 21) moderate state, median (IQR) I: 22 (21.25 to 22) C: 14 (-1 to 22) Adj. OR – mean (SD) 2.68 (5.19) Adj. OR – median (95% CI) 1.58 (0.82 to 5.95)</p> <p>In-hospital deaths moderate state, n/N (%) I: 401/1075 (37.3%) C: 347/904 (38.4%)</p> <p>In-hospital deaths severe state, n/N (%) I: 5/42 (11.9%) C: 7/24 (24.2%) Adj OR – mean (SD) (0.11) Adj. OR – median (95% CI) 1.04 (0.85 to 1.27)</p>	<p>Definitions: Severely or critically ill: patients admitted to an intensive care unit (ICU) and receiving respiratory (invasive or noninvasive mechanical ventilation, including high-flow nasal cannula with a flow rate ≥30 L per minute and fractional inspired oxygen concentration ≥40%) or cardiovascular (infusion of vasopressor or inotropes) organ support.</p> <p>Moderate state: Not being admitted to an ICU, or admitted to an ICU but not receiving organ failure support.</p> <p>Remarks: -</p> <p>Authors conclusion: Among critically ill adults with confirmed COVID-19, treatment with 2 units of high-titer, ABO-compatible convalescent plasma had a low likelihood of providing improvement in the number of organ support-free days.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>(Monash University, Utrecht Medical Center, St Michael's Hospital, and the Global Coalition for Adaptive Research); however, beyond the declared author contributions, the sponsors had no additional role.</p> <p><u>Conflicts of interest:</u> See the description in the original study.</p>	<p>pandemic infection 4. Previous participation in this REMAP within the last 90 days.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • COVID-19 infection was confirmed by microbiological testing; • Patients were excluded from the Immunoglobulin Domain if they had any of the following: <ol style="list-style-type: none"> 1. More than 48 hours had elapsed since intensive care unit (ICU) admission 2. Patient had already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during the hospital admission 3. More than 14 days had elapsed since hospital admission 4. The treating clinician believed that participation in the domain would not be in the best interests of the patient 5. Known hypersensitivity/allerg 		the treating clinician.		<p><u>In-hospital survival</u> Adj OR – mean (SD) 1.02 (0.10) Adj. OR – median (95% CI) 1.02 (0.83 to 1.24)</p> <p><u>28-day survival (time to event)</u> I: Adj. HR – mean (SD) 1.05 (0.08) I: Adj. HR – median (95% CI) 1.05 (0.91 to 1.20) C: Adj. HR – mean (SD) 1 C: Adj. HR – median (95% CI) 1</p> <p><u>90-day survival (time to event)</u> I: Adj. HR – mean (SD) 1.05 (0.07) I: Adj. HR – median (95% CI) 1.05 (0.92 to 1.19) C: Adj. HR – mean (SD) 1 C: Adj. HR – median (95% CI) 1</p> <p><u>Organ support-free days in survivors, median (IQR)</u> I: 14 (3 to 18) C: 14 (7 to 18)</p> <p><u>Respiratory support-free days</u> I: median (IQR) 0 (-1 to 15) I: Adj. OR – mean (SD) 0.95 (0.08) I: Adj. OR – median (95% CI) 0.95 (0.81 to 1.11) C: median (IQR) 2 (-1 to 16) C: Adj. OR – mean (SD) 1 C: Adj. OR – median (95% CI) 1</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>y to plasma and plasma products.</p> <p>6. Known previous history of transfusion-related acute lung injury</p> <p>7. Known objection to receiving plasma products</p> <p><u>N total at baseline:</u> N = 1987 Intervention: 1078 Control: 909</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 61 y (52-69) C: 61 y (52-70)</p> <p>Sex, n/N (%) male: I: 727/1078 (67.4%) C: 618/909 (68.0%)</p> <p>Disease severity, mean (SD): Not reported.</p> <p>Groups comparable at baseline? Yes.</p>				<p><u>Cardiovascular support-free days</u> I: median (IQR) 14 (-1 to 21) I: Adj. OR – mean (SD) 0.96 (0.08) I: Adj. OR – median (95% CI) 0.95 (0.80 to 1.13) C: median (IQR) 14.5 (-1 to 21) C: Adj. OR – mean (SD) 1 C: Adj. OR – median (95% CI) 1</p> <p><u>Length of ICU stay</u> I: Adj. HR – mean (SD) 0.96 (0.05) I: Adj. HR – median (95 CI) 0.95 (0.86 to 1.06) C: Adj. HR – mean (SD) 1 C: Adj. HR – median (95% CI) 1</p> <p>Safety <u>Patients with ≥1 serious adverse event, n/N (%)</u> I: 32/1075 (3.0%) C: 12/905 (1.3%) I: Adj. absolute effect – median (95% CI) 1.4 (0.2 to 4.2) C: Adj. absolute effect – median (95% CI) -</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Bégin, 2021	<u>Type of study:</u> multicenter, international, open-label,	<p>hospitalized patients with COVID-19 receiving O₂ within 12 days of respiratory symptom onset</p> <p><u>Inclusion criteria:</u></p>	convalescent plasma (1 or 2 units of apheresis plasma amounting to approx. 500 ml from 1 or 2 donors)	standard care	<u>Length of follow-up:</u> 30 days; patients who were in hospital beyond day 30 were	<p>Clinical outcomes Mortality <u>In-hospital death by day 90</u> I: 156/625 (25.0%) C: 69/313 (22.0%)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>randomized controlled trial</p> <p><u>Setting:</u> hospital-based, between May 14 2020 and January 29 2021</p> <p><u>Country:</u> 72 hospital sites in Canada, the US and Brazil</p> <p><u>Source of funding:</u> Funding for the study was provided by Canadian Institutes of Health Research COVID-19 May 2020 Rapid Research Funding Opportunity; Ontario COVID-19 Rapid Research Fund; Toronto COVID-19 Action Initiative 2020; Fondation du CHU Ste-Justine; Ministère de l'Économie et de l'Innovation du Québec; Fonds de Recherche du Québec; University Health Network Emergent Access Innovation Fund; University Health Academic Health Science Centre Alternative</p>	<ul style="list-style-type: none"> age ≥ 16 y (Canada) or ≥ 18 y (US, Brazil) admitted to hospital ward with confirmed COVID-19 required supplemental O₂ 500 ml of ABO-compatible COVID-19 convalescent plasma was available <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> >12 days from the onset of respiratory symptoms imminent or current intubation contraindication to plasma transfusion plan for no active treatment <p><u>N total at baseline:</u> Randomized: N = 940 ITT population: N = 921</p> <p>Intervention: = 614 Control: N = 307</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 67.7 y (16.0) C: 67.1 y (14.8)</p> <p>Sex, n/N (%) male: I: 369/625 (59.0%) C: 185/313 (59.1%)</p> <p>Groups were comparable at baseline.</p>			<p>followed until discharge up to day 90</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention: N = 11 (1.8%) <i>Reason</i></p> <ul style="list-style-type: none"> lost to follow-up after discharge (n = 11) <p>Control: N = 6 (1.9%) <i>Reason</i> lost to follow-up after discharge (n = 6)</p>	<p>RR 1.13 (95%CI: 0.88-1.45)</p> <p><u>Time to in-hospital death by day 90</u> HR 1.02 (95%CI: 0.76-1.35)</p> <p><u>Death by day 30</u> I: 141/614 (23.0%) C: 63/307 (20.5%) RR 1.12 (95%CI: 0.86-1.46)</p> <p><u>Duration of hospitalisation</u> <u>Length of stay in critical care and hospitably day 30</u> Days, mean (SD) I: 4.3 (7.9%) C: 3.7 (7.1%) mean difference 0.7 (-0.3-1.7)</p> <p><u>Length of stay in hospital by day 90</u> HR 0.91 (95%CI: 0.80-1.04)</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> <u>Ventilator-free days by day 30</u> Days, mean (SD) I: 23.4 (10.4) C: 24.0 (10.5) mean difference -0.6 (95%CI: -2.1-0.7)</p> <p><u>Other</u> <u>Intubation or death by day 30 (primary outcome)</u> I: 199/614 (32.4%) C: 86/307 (28.0%)</p>	<p>This trial was stopped at the planned interim analysis because the conditional power estimate was 1.6% (below the stopping criterion of 20%).</p> <p><u>Authors conclusion:</u> The CONCOR-1 trial did not demonstrate a difference in the frequency of intubation or death at 30 d with convalescent plasma or standard of care in hospitalized patients with COVID-19 respiratory illness. The antibody content had a significant effect-modifying role for the effect of convalescent plasma on the primary outcome. The lack of benefit and the potential concern of harm caution against the unrestricted use of convalescent plasma for hospitalized patients with COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Funding Plan; Saskatchewan Ministry of Health; University of Alberta Hospital Foundation; Alberta Health Services COVID-19 Foundation Competition; Sunnybrook Health Sciences Centre Foundation; Fondation du CHUM; Ottawa Hospital Academic Medical Organization; Ottawa Hospital Foundation COVID-19 Research Fund; Sinai Health System Foundation; and McMaster University. These organizations and institutions did not have any role in the writing of the manuscript or the decision to submit it for publication.</p> <p><u>Conflicts of interest:</u> None to declare.</p>					<p>RR 1.16 (95%CI: 0.94-1.43)</p> <p><u>Time to intubation or in-hospital death by day 30</u> HR 1.14 (95%CI: 0.89-1.47)</p> <p><u>Need for extracorporeal membrane oxygenation</u> Not reported</p> <p><u>Need for renal replacement therapy by day 30</u> I: 10/614 (1.6) C: 6/307 (2.0) RR 0.83 (95%CI: 0.31-2.27)</p> <p>Safety <u>Convalescent plasma-associated adverse events</u> 35/614 (5.7%)</p> <p><u>Occurrence of ≥ 3 grade adverse events by day 30</u> I: 260/614 (42.3%) C: 109/307 (35.5%) RR 1.19 (95%CI: 1.00-1.42)</p> <p>Virological outcomes Not reported</p>	
Avendaño-Solá, 2021	<p><u>Type of study:</u> multicenter, open-label, randomized controlled trial</p> <p><u>Setting:</u></p>	<p>hospitalized patients with COVID-19 pneumonia</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age ≥ 18 y 	convalescent plasma (single unit of 250-300 ml) and standard care	standard care alone	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention:</p>	<p>Pre-specified subgroup analyses of the primary endpoint were planned according to the level of neutralizing antibodies in the administered plasma,</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> The trial was temporarily stopped on July 10, 2020, after the first interim</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>hospital-based, between April 4 2020 and February 5 2021</p> <p><u>Country:</u> 72 hospitals in Spain</p> <p><u>Source of funding:</u> The funder of the study (Government of Spain, Instituto de Salud Carlos III) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.</p> <p><u>Conflicts of interest:</u> None to declare.</p>	<ul style="list-style-type: none"> laboratory-confirmed SARS-CoV-2 infection requiring hospitalization for COVID-19 without mechanical ventilation or high flow O₂ devices, and at least 1 of the following: <ul style="list-style-type: none"> radiographic evidence of pulmonary infiltrates by imaging clinical assessment and S_pO₂ ≤ 94% on room air that requires supplemental O₂ ≤ 7 days between onset of symptoms and treatment administration day <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> requiring mechanical ventilation or high flow O₂ devices at screening > 7 days since onset of symptoms participation in any other clinical trial of an experimental treatment for COVID-19 in the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatments any incompatibility or allergy to the administration of human plasma stage 4 chronic kidney disease or requiring dialysis (eGFR < 30) <p><u>N total at baseline:</u> Randomized: N = 350 ITT population: N = 350</p> <p>Intervention: N = 179</p>			<p>N = 4 (2.2%)</p> <p><u>Reasons</u></p> <ul style="list-style-type: none"> withdrew consent (n = 2) lost to follow-up after discharge (n = 2) <p>Control: N = 8 (4.7%)</p> <p><u>Reason</u> withdrew consent (n = 8)</p>	<p>duration of symptoms at randomization, positivity of antibodies at patient baseline and period of patient recruitment according to the different waves of pandemics.</p> <p>Clinical outcomes</p> <p><u>Mortality</u></p> <p><u>Mortality at day 14</u> I: 6/179 (3.4%) C: 10/171 (5.9%) RR 0.58 (95%CI: 0.22-1.56)</p> <p><u>Mortality at day 28</u> I: 7/179 (3.9%) C: 14/171 (8.2%) RR 0.49 (95%CI: 0.20-1.17)</p> <p><u>Overall survival</u> HR 0.46 (95%CI: 0.19-1.14)</p> <p><u>Duration of hospitalisation</u> <u>Duration of hospital stay</u> Not reported</p> <p><u>Time to discharge</u> Days, median (IQR) I: 9 (8-11) C: 9 (8-10)</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> <u>Number of days alive and free from mechanical ventilation</u> no significant difference</p>	<p>analysis, due to a drastic fall in recruitment (end of first wave in Spain), although prespecified futility or efficacy stop criteria had not been reached. Nevertheless, the trial recruitment was resumed shortly after, with the surge of the second wave, and the trial was finally completed as planned.</p> <p><u>Authors conclusion:</u> CP showed a significant benefit in preventing progression to non-invasive ventilation or high-flow oxygen, invasive mechanical ventilation or ECMO, or death at 28 days. The effect on the predefined primary endpoint at 14 days and the effect on overall survival were not statistically significant.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Control: N = 171</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 62.7 y (15.7) C: 63.4 y (14.89)</p> <p>Sex, n/N (%) male: I: 118/179 (65.9%) C: 111/171 (64.9%)</p> <p>Groups were comparable at baseline.</p>				<p>Other <u>Non-invasive ventilation or high flow O₂, invasive mechanical ventilation or ECMA, or death at day 14 (primary outcome)</u> I: 21/179 (11.7%) C: 28/171 (16.4%) RR 0.94 (95%CI: 0.87-1.03)</p> <p><u>Non-invasive ventilation or high flow O₂, invasive mechanical ventilation or ECMA, or death at day 28</u> I: 15/179 (8.4%) C: 29/171 (17.0%) RR 0.91 (95%CI: 0.84-0.99)</p> <p><u>Time to first clinical deterioration</u> No significant difference</p> <p><u>Number of rehospitalizations</u> I: 6/179 (3.4%) C: 7/171 (5.1%)</p> <p>Safety <u>Serious or grade 3-4 adverse events</u> I: 15/179 (8.4%) C: 16/172 (9.3%)</p> <p><u>Convalescent plasma infusion-related adverse events</u> 20/179 (11.1%)</p> <p>Virological outcomes Not reported</p>	
Körper, 2021	<u>Type of study:</u>	<u>Hospitalized patients with COVID-19</u>	standard treatment and 3 units of CCP.	Standard treatment alone.	<u>Length of follow-up:</u> 60 days	Clinical outcomes <u>Overall survival</u>	<u>Definitions:</u> Standard treatment: Patients in both groups received other anti-viral

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Multicenter, open-label randomized controlled trial.</p> <p><u>Setting:</u> 13 hospitals.</p> <p><u>Country:</u> Germany</p> <p><u>Source of funding:</u> Bundesministerium für Gesundheit (German Federal Health): ZMV11-2520COR802</p> <p>The entire study was funded by the German Federal 54 Ministry of Health. The Ministry had no role in analyzing 55 the data, writing the manuscript or deciding to submit it for 56 publication.</p> <p><u>Conflicts of interest:</u> The other authors have declared that no conflict of interest exists.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • SARS-CoV-2 infection confirmed by PCR; • Age between 18-75 years; • Severe disease defined by at least one of the following: <ul style="list-style-type: none"> • Respiratory rate >29 breaths/minute under ambient air; • Requirement of any type of respiratory support (defined as supplemental oxygen or non-invasive ventilation or invasive ventilation or ECMO); • Needs treatment on ICU; • Written informed consent by patient or representative. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Accompanying diseases other than COVID-19 with an expected survival time of less than 12 months; • Previous treatment with any SARS-CoV-2 convalescent plasma; • The opinion of the clinical team; • Progression to death is imminent and inevitable within the next 48 hours, irrespective of the provision of treatment; • Interval >72 hours since start of mechanical ventilation; • Not considered eligible for extracorporeal oxygenation support; • Chronic obstructive lung disease (COPD) stage 4; 	<p>patients randomized to CCP received all three planned CCP transfusions with a median total volume of 846 ml.</p>		<p><u>Loss-to-follow-up:</u> None.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p><i>Probability of overall survival at day 60</i> I: 77.9% (95% CI 63.6 to 87.1) C: 68.1% (95% CI 53.5 to 79.1%)</p> <p><u>Duration of hospitalization</u> <i>Median time to discharge from hospital, median (IQR)</i> I: 31 days (16 to not reported) C: 51 days (20 to not reported) P=0.24</p> <p><i>Median time to discharge from ICU, median (IQR)</i> I: 29 days (9 to not reported) C: 42 days (12 to not reported) P=0.39</p> <p><u>Time to symptom resolution</u> <i>Median time to clinical improvement by >1 points on the ordinal severity scale, median (IQR)</i> I: 26 days (15 to not reported) C: 66 days (13 to not reported) P=0.27</p> <p><u>Respiratory support</u> <i>Requiring ventilation support or ICU treatment and no tachypnea, i.e. respiratory rate <30/minute</i></p>	<p>treatment and/or supportive treatment according to 406 institutional standard procedures.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, among hospitalized adult patients with severe COVID-19, CCP added to standard therapy compared to standard therapy alone did not result in a statistically significant improvement of the primary outcome, i.e. survival free of ventilation support on day 21 and the key secondary outcome time to clinical improvement. Frequency and severity of adverse events did not differ between treatment groups. The consistent trend for a benefit across all primary and secondary outcomes among patients who have received a higher amount of neutralizing antibodies provides a signal that better outcomes can be achieved by high dose CCP treatment combining both very high titers of neutralizing antibodies with high CCP volumes. This should be addressed in further studies which focus on highly selected CCP with very high SARS-CoV-2 antibody titers.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Lung fibrosis with usual interstitial pneumonia pattern in CT and severe emphysema; • Chronic heart failure NYHA >2 and/or pre-existing reduction of left ventricular ejection fraction to <31%; • Shock of any type requiring >0.4 ug/kg/min noradrenaline or requiring more than two types of vasopressor medication for more than 8 hours; • Liver cirrhosis Child C; • Liver failure: bilirubin >5x upper limit of normal (ULN) and elevation of ALT/AST (at least one >10 x ULN); • Any history of adverse reactions to plasma proteins; • Known deficiency of immunoglobulin A; • Pregnancy; • Breastfeeding woman; • Volume overload until sufficiently treated; • Participation in another clinical trial with an investigational medicinal product. <p><u>N total at baseline:</u> N = 105 Intervention: N=53 Control: N=52 → N=7 cross-over to convalescent plasma & n=45 no crossover.</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 59 y (53-65) C: 62 y (55-66) P=0.24</p> <p>Sex, n/N (%) male:</p>				<p>I: 43.4% C: 32.7% P=0.32</p> <p><i>Requiring supplemental oxygen, non-invasive or invasive ventilation on day 35, %</i> I: 18.4% C: 28.0%)</p> <p>Safety <u>Adverse events</u> <i>At least one adverse event, (%)</i> 81.0% experienced at least one adverse event. Neither the frequency of AEs nor the worst AE grade did significantly differ between the groups (p=0.62 and P=0.18).</p> <p><u>Serious adverse events, (%)</u> I: 41.5% C: 48.1%.</p> <p>Virological outcomes <u>Viral clearance</u> <i>Median time to first negative SARS-CoV-2 PCR from nasopharyngeal swab, median (IQR)</i> I: 7 days (4 to 17) C: 8 days (5 to 21)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 42/53 (79.3%) C: 35/52 (67.3%)</p> <p>Disease severity, percentage of patients receiving supplemental oxygen or non-invasive ventilation (score 4 and 5 on the ordinal severity scale) or invasive ventilation (score 6 and 7) was 59.1% and 34.3% respectively.</p> <p>Groups comparable at baseline? Yes → Overall, the CCP group and the control group were similar in terms of demographic characteristics and disease severity as assessed by the distribution on the ordinal severity scale, the type of ventilation support and the laboratory results at baseline, except ferritin levels at baseline and the interval from hospitalization to randomization</p>					
Devos, 2021	<p>Type of study: Prospective, randomized open-label, multicenter clinical trial.</p> <p>Setting: 22 Belgian centres, and coordinated by the University Hospitals Leuven.</p> <p>Country: Belgium</p> <p>Source of funding:</p>	<p>Hospitalized COVID-19 patients</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Adults aged 18 years and older; • Hospitalized patients with laboratory or radiological confirmed COVID-19 were screened for eligibility. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Patients receiving mechanical ventilation and/or endotracheal intubation; • Pregnancy; • Lactation; • A documented previous grade 3 allergic reaction to plasma transfusions; 	<p>Convalescent plasma plus standard of care</p> <p>Two units of convalescent plasma (approximately 200-250 mL) were administered within 12 hours after randomization, with a second administration of two units 24-36 hours after the first administration.</p>	Standard of care	<p>Length of follow-up: 30 days</p> <p>Loss-to-follow-up: All patients in the intervention group and the control group were included in the full analysis set.</p> <p>For the per protocol analysis, n=26 patients were excluded because they received less than 4 units of convalescent plasma. In the control group, n=2 patients were</p>	<p>Clinical outcomes</p> <p>All-cause mortality at 15 days, kaplan-meier (95% CI) I: 3.1 (95% CI 1.7 to 5.8) C: 4.9 (95% CI 2.5 to 9.6) HR 0.61 (95% CI 0.24 to 1.54)</p> <p>All-cause mortality at 30 days, kaplan-meier (95% CI) I: 9.1 (95% CI 6.3 to 12.9) C: 8.7 (95% CI 5.3 to 14.3) HR 0.99 (95% CI 0.52 to 1.88)</p> <p>Duration of hospitalization</p>	<p>Definitions: The study protocol did not specify the standard of care therapy.</p> <p>Remarks: -</p> <p>Authors conclusion: In summary, transfusion of a high volume of 4 units of convalescent plasma with high neutralising antibody-titres early in hospitalised COVID-19 patients could not change the natural course of antibody titres and did not result in a significant improvement of the clinical status, nor did the intervention reduce mortality.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>The Belgian Health Care Knowledge Centre (KCE).</p> <p><u>Conflicts of interest:</u> All authors report support for the present manuscript from Belgian Healthcare Knowledge Center (KCE). Quentin Van Thillo reports grants from FWO – Vlaanderen Basic Research 2019-2021 outside the submitted work. Geert Meyfroidt reports FWO – Vlaanderen Senior Clinical Researcher Grant outside the submitted work.</p>	<ul style="list-style-type: none"> Treatment with rituximab or another anti-CD20 monoclonal antibody during the past year. <p><u>N total at baseline:</u> N = 489 Intervention: N=326 Control: N=163</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 62 y (14) C: 62 y (14) P=0.772</p> <p>Sex, n/N (%) male: I: 219/320 (68.4%) C: 113/163 (69.3%)</p> <p>Disease severity Not reported.</p> <p>Groups comparable at baseline? Yes → “Both groups were well matched.”</p>			excluded because they received convalescent plasma within 30 days.	<p><i>Hospital discharge at 30 days, incidence estimated using Cumulative Incidence Function accounting for competing risk (%) (95% CI)</i> I: 80.5% (95% CI 75.7 to 84.4) C: 79.8 (95% CI 72.8 to 85.2) Subdistribution HR 1.06 (95% CI 0.87 to 1.30)</p> <p><i>ICU admission at 30 days, incidence estimated using Cumulative Incidence Function accounting for competing risk (%) (95% CI)</i> I: 36.0 (95% CI 30.8 to 41.3) C: 34.4 (95% CI 27.2 to 41.7) Subdistribution HR 1.00 (95% CI 0.74 to 1.34)</p> <p><i>ICU life discharge, incidence estimated using Cumulative Incidence Function accounting for competing risk (%) (95% CI)</i> I: 78.3 (95% CI 69.5 to 84.8) C: 82.1 (95% CI 69.0 to 90.1) Subdistribution HR 0.95 (95% CI 0.66 to 1.35)</p> <p><u>Time to symptom resolution</u> <i>Sustained improvement or discharge within 30 days, incidence estimated using Cumulative Incidence</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Function accounting for competing risk (%) (95% CI)</i> I: 82.6% (95% CI 77.9 to 86.3) C: 84.7 (95% CI 78.1 to 89.4) Subdistribution HR 0.98 (95% CI 0.81 to 1.20)</p> <p><u>Respiratory support</u> <i>Supplemental oxygen at 30 days, incidence estimated using Cumulative Incidence Function accounting for competing risk (%) (95% CI)</i> I: 89.5% (95% CI 85.5 to 92.4) C: 89.0% (95% CI 83.0 to 92.9) Subdistribution HR 1.01 (95% CI 0.86 to 1.29)</p> <p><i>Mechanical ventilation at 30 days, incidence estimated using Cumulative Incidence Function accounting for competing risk (%) (95% CI)</i></p> <p><u>Incidence</u> I: 15.0 (95% CI 11.3 to 19.2) C: 13.5 (95% CI 8.8 to 19.2) Subdistribution HR 1.08 (95% CI 0.65 to 1.80)</p> <p>Safety <u>Adverse events</u> <i>Any venous thromboembolisms, n/N (%)</i> I: 1/320 (0.3%) C: 1/163 (0.6%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Deep vein thrombosis, n/N (%)</i> I: 0/320 (0%) C: 0/163 (0%)</p> <p><i>Pulmonary embolism, n/N (%)</i> I: 1/320 (0.3%) C: 1/163 (0.6%)</p> <p><u>Serious adverse events</u> <i>Number of subjects with serious adverse events, n/N (%)</i> I: 66/320 (20.6%) C: 34/163 (20.9%)</p> <p><i>Number of serious adverse events, N</i> I: 78 C: 40</p> <p>For the full list of adverse events, check the supplementary materials of the study</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Korley, 2021	<p><u>Type of study:</u> phase 3, multicentre, randomized, placebo-controlled, single-blind trial (C3PO clinical trial)</p> <p><u>Setting:</u> 48 hospital emergency departments in 21</p>	<p>patients with SARS-CoV-2 infection as confirmed by nucleic acid assay, with an onset of symptoms within 7 days before enrolment</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 50 y • One or more risk factors for disease progression: <ul style="list-style-type: none"> • hypertension; • diabetes; 	one unit of ABO compatible Covid-19 convalescent plasma	Placebo (250 ml of normal saline) coloured with a parenteral multivitamin concentrate to resemble plasma	<p><u>Length of follow-up:</u> 30 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention : N = 14(5.5%) <i>Reasons</i></p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 2)</i> • <i>unavailable data before day 30 (n=7)</i> 	<p>Clinical outcomes <u>Mortality within 30 days</u> I: 5/257 (1.9%) C: 1/254 (0.4%) risk difference, -1.6 95% CI (-4.2 to 0.50)</p> <p><u>Duration of hospitalisation</u> <u>Discharge by day 14</u> Not reported</p>	<p><u>Definitions:</u></p> <p>COVID Outpatient Ordinal Outcomes Scale</p> <p>1 = patient requires care in the hospital</p> <p>2 = patient requires care in the ED or urgent care</p> <p>3 = patient at home with symptoms rated as moderate (defined as fever, shortness of breath, abdominal pain)</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>States; August 2020 - February 2021</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> supported (including funding and material support in the form of plasma and testing supplies) by the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke of the National Institutes of Health and by the Biomedical Advanced Research and Development Authority and the Operation Warp Speed interagency program.</p> <p><u>Conflicts of interest:</u> Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.</p>	<ul style="list-style-type: none"> coronary artery disease; chronic lung disease; chronic kidney disease; immunosuppression; sickle cell disease, obesity (body mass index [BMI]>30) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> age < 18 y prisoners or wards of the state inability to complete follow up assessments history of adverse reactions from blood-product trans received any blood product within the past 120 daysfusion not eligible to receive up to 250 ml of fluid received another investigational treatment <p><u>N total at baseline:</u> Randomized: N = 511 I: N = 257 C: N = 254</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 54 y (42–62) C: 54 y (40-62)</p> <p>Sex, n/N (%) male: I: 122/257 (47.5%) C: 115/254 (45.3%)</p> <p>Groups were comparable at baseline.</p>			<ul style="list-style-type: none"> Died (n=5) <p>Control: N = 6 (2.4%)</p> <p><i>Reasons</i></p> <ul style="list-style-type: none"> withdrew consent (n = 2) unavailable data before day 30 (n=3) Died (n=1) 	<p><u>Hospital-free days within 30 days</u> Mean: I: 28.3 C: 28.6 mean difference, 0.3; 95% CI (-0.4 to 1.1)</p> <p><u>Time to symptom resolution</u> <u>Days to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> Not reported</p> <p><u>Other</u> <u>Worsening of symptoms based on the 5-category outpatient scale within the 15 days after randomization</u> I: 107/257(41.6%) C: 116/254 (45.7%) HR 0.90; 95% CI, 0.69 to 1.17</p> <p><u>Safety</u> <u>Serious adverse events</u> I1: 3/257 (1.2%) C: 0/254 (0%)</p> <p><u>Virological outcomes</u> <u>Viral load</u> Not reported</p>	<p>4 = patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness of breath) 5 = patient in their usual state of health</p> <p><u>Remarks:</u> ClinicalTrials.gov number, NCT04355767</p> <p><u>Authors conclusion:</u> The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Kirenga, 2021	<p>Type of study: Open-label, randomized clinical trial.</p> <p>Setting: Mulago National Referral Hospital Treatment Unit</p> <p>Country: Uganda.</p> <p>Source of funding: This trial was funded by the Government of Uganda through the Makerere University Research and Innovations Fund.</p> <p>Conflicts of interest: None declared.</p>	<p>Patients with <u>documented SARS-CoV-2-positive RT-PCR.</u></p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Patients with documented SARS-CoV-2-positive RT-PCR. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Patients with a prior diagnosis of IgA deficiency; Patients who were unable to participate in follow-up procedures. <p>N total at baseline: N = 136 Intervention: N = 69 Control: N = 67</p> <p>Important characteristics: Age, median (IQR): I: 48 y (35 to 64) C: 53 y (44 to 61)</p> <p>Sex, n/N (%) male: I: 48/69 (69.6%) C: 49/67 (73.1%)</p> <p>Disease severity, mean (SD): Not reported.</p> <p>Groups comparable at baseline? Yes.</p>	<p>Convalescent plasma (CCP) plus standard of care (CCP + SOC)</p> <p>The lower limit of anti-SARS-CoV-2 IgG antibody titres for plasma units was 27.5 AU/mL, which was equivalent to 2.2µg/mL. CCP was administered over look 2–3hours at a rate of 1.4–2mL/ min and a second aliquot transfused at the same rate 3hours after completion of the first one.</p>	<p>Standard of care (SOC)</p> <p>Standard of care was according to the Uganda COVID-19 case management guidelines.</p>	<p>Length of follow-up: Day 28.</p> <p>Loss-to-follow-up: Intervention: N=8 (9.0%) Reasons: withdrew before transfusion (N=6), plasma stock out (N=1), died before transfusion (N=1)</p> <p>Control: N=6 (9.0%) Reasons: withdrew (wanted plasma)</p> <p>Incomplete outcome data: None.</p>	<p>Clinical outcomes Mortality (28-30 day) I: 10/69 (14.5%) C: 8/67 (11.9%) RR 1.21 (95% CI 0.51 to 2.89) P=0.661</p> <p>Duration of hospitalization Not reported.</p> <p>Time to symptom resolution, median, (IQR) I: 7 (5 to 7) days C: 7 (5 to 10) days P=0.450</p> <p>Time to symptom resolution among symptomatic patients, median (IQR) I: 2 (1 to 4) days C: 2 (1 to 4) days P=0.772</p> <p>Respiratory support Progression to severe/critical disease (oxygen saturation <93% or needing oxygen), n/N (%) I: 9/41 (22%) C: 7/29 (24.1%) RR 0.91 (95% CI 0.38 to 2.16) P=0.830</p> <p>Safety Adverse events I: N = 15 C: N=14</p> <p>Virological outcomes</p>	<p>Definitions: -</p> <p>Remarks: -</p> <p>Authors conclusion: In conclusion CCP therapy did not result in beneficial virological or clinical improvements in this trial. Further trials are needed to determine subgroups of patients who may benefit from COVID-19 CCP in Africa.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Time to viral clearance, median (IQR):</i> I: 6 (4 to 11) days C: 4 (4 to 6) days P=0.196)</p> <p><i>Proportions of viral clearance at day 28, n/N (%); RR (95% CI):</i> I: 45/61 (73.8); RR 0.96 (95% CI 0.78 to 1.17) P=0.674</p>	
Bainbridge, 2021	<p><u>Type of study:</u> Randomized, double-blinded, placebo-controlled trial.</p> <p><u>Setting:</u> Two hospitals in San Francisco, California.</p> <p><u>Country:</u> United States of America.</p> <p><u>Source of funding:</u> This work was funded by the Marti and Steve Diamond Charitable Foundation and the UCSF COVID-19 Response Fund.</p> <p><u>Conflicts of interest:</u> All authors have submitted the ICMJE Form for</p>	<p><u>Hospitalized, hypoxic, nonventilated adults with confirmed COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients ≥18 years of age • Hospitalized with COVID-19 • Enrolled within 72 hours of hospitalization OR within day 14 from first signs of illness • Pulmonary infiltrates on chest imaging • Oxygenation of <95% on room air • Laboratory confirmed COVID-19 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Contraindication to transfusion due to inability to tolerate additional fluid, such as due to decompensated congestive heart failure • Baseline requirement for oxygen supplementation prior to COVID-19 infection or use of positive pressure 	<p>Convalescent plasma</p> <p>1 unit of convalescent plasma</p>	<p>Non-immune fresh frozen plasma (200–250 mL).</p>	<p><u>Length of follow-up:</u> 29 days.</p> <p><u>Loss-to-follow-up:</u> None.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p>Clinical outcomes <u>Mortality (28-30 day)</u> Not reported.</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u> Not reported.</p> <p>Virological outcomes <u>Viral clearance</u></p> <p>Patients with baseline Vitros IgG results</p> <p><i>IgG reactivity detection before transfusion, n/N (%)</i> 19/28 (67.9%) *there were no differences for any of the 6 assays between participants who</p>	<p><u>Definitions:</u></p> <ul style="list-style-type: none"> • RFU: relative fluorescence units <p><u>Remarks:</u> The investigators and study monitoring committee closed the study before completing target enrolment due to declining COVID-19 cases in San Francisco in October 2020</p> <p><u>Authors conclusion:</u> In summary, CCP specifically selected for higher IgG levels did not promote or inhibit the humoral immune response to SARS-CoV-2 by day 29. These findings may be relevant to the settings in which CCP may have a role for COVID-19 treatment, such as within 72 hours in high-risk elderly patients [10] and in those with impaired humoral immunity, or for COVID-19 use as passive immunization. Future studies of CCP could consider selection of plasma with high neutralizing antibodies in addition to overall high IgG, which correlated with higher avidity, to maximize activity. The contribution of neutralizing activity to the clinical</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.	<p>therapy for sleep disordered breathing</p> <ul style="list-style-type: none"> • Currently experiencing severe hypoxemic failure, as defined in study endpoints • Prior receipt of plasma products, IVIG, or hyperimmune globulin within past 3 months • Not currently enrolled another interventional clinical trial of COVID-19 treatment. <p><u>N total at baseline:</u> N = 34 Intervention: N = 16 Control: N = 18</p> <p><u>Important characteristics:</u> Median (IQR): I: 52 y (40-64) C: 62 y (49-74)</p> <p>Sex, n/N (%) male: I: 6/16 (38%) C: 9/18 (50%)</p> <p>Disease severity, mean (SD): <i>Defined by WHO 8 point ordinal scale score, n/N (%)</i> 3. Hospitalized, no oxygen I: 2/16 (13%) C: 0/18 (0%)</p> <p>4. Hospitalized, low-flow supplemental oxygen I: 10/16 (63%) C: 16/18 (89%)</p> <p>5. Hospitalized, high-flow supplemental oxygen I: 4/16 (25%)</p>				<p>reported ≤7 days of symptoms and those with >7 days.</p> <p><i>Donor plasma median (IQR) IgG compared with baseline</i> 1025.0 (766.0 to 1465.0) RFU versus 38.0 (5.8 to 161.0) RFU</p> <p><i>Median (IQR) IgG avidity in donor plasma than recipients at baseline</i> 69.0% (47.8 to 82.8) versus 0.0% (0.0 to 47.0)</p> <p>CCP recipients</p> <p><i>Median IgG and avidity levels</i> 21.5 RFU (4.3 to 138.8) versus 1679.0 (1006.0 to 2291.0)</p> <p><i>Median Vitros IgG</i> Increase from 0.0% (0.0 to 42.3) to 67.5% (55.5 to 79.5)</p> <p><i>Median neutralizing antibody level</i> Baseline was 295.5 (123.0 to 1288.0) and 1518 (919.3 to 3955) at follow-up</p> <p><i>Quantitative PCR completed, n/N (%)</i> 32/34 (94.1%)</p> <p>Two FFP recipients and 1 CCP recipient had undetectable viral loads at</p>	efficacy of convalescent plasma merits further evaluation.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		C: 3/18 (17%) Groups comparable at baseline? Yes.				baseline, and the median CT was 24.0 (20.4 to 27.9) in the remaining participants.	
Sekine, 2021	<p>Type of study: investigator-initiated, unicentric, open-label RCT</p> <p>Setting: hospital-based in Porto Alegre</p> <p>Country: Brazil</p> <p>Source of funding: The study was funded by Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (Grant 16/2551-0000242-8), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Grants 2020/06409-1 and 2016/20045-7) and Instituto Cultural Floresta.</p> <p>Conflicts of interest: R.R.G.M. receive support from Fundação de Amparo à Pesquisa do Estado de São</p>	<p>severe and critically ill COVID-19 patients admitted to the hospital</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> age ≥ 18 y positive RT-PCR for SARS-CoV-2 symptom onset < 15 days severe respiratory disease* <p>Exclusion criteria:</p> <ul style="list-style-type: none"> impossibility for any reason to perform the first plasma infusion within 14 days of the onset of symptoms use of immunosuppressive drugs for other non-COVID-19 underlying diseases in the last 30 days before enrolment pregnancy history of serious adverse reactions such as transfusion anaphylaxis disagreement of attending physician participation in other interventional randomised clinical trials <p>N total at baseline: Randomized: N = 160</p> <p>Intervention: N = 80 Control: N = 80</p> <p>Important characteristics: Age, median (IQR): I: 59.0 y (48.0-68.5) C: 62.0 y (49.5-68.0)</p>	2 infusions of convalescent plasma + standard care	standard care	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up: -</p>	<p>Prespecified subgroups were defined according to the unit of hospitalization (medical ward [considered severe patients] or ICU [considered critically ill patients]) and mechanical ventilation needed on enrolment</p> <p>Clinical outcomes</p> <p>Mortality</p> <p>Mortality on day 2 I: 18/80 (22.5%) C: 13/80 (16.3%) RR 1.38 (95%CI: 0.73-2.63)</p> <p>Mortality on day 14: I: 10/80 (12.5%) C: 5/80 (6.3%) RR 2.00 (95%CI: 0.72-5.59)</p> <p>Duration of hospitalization</p> <p>Time to being discharged Days (IQR) I: 10 (6-15); n = 44 C: 8 (5-17.8); n = 46 p = 0.869</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support*</p> <p>Duration of invasive ventilatory support Days (IQR) I: 12 (6.5-16.5); n = 15</p>	<p>Definitions: * Severe respiratory disease was defined by the presence of at least one of the following: respiratory rate > 30 breaths/min in room air; O₂ saturation ≤ 93% in room air; P_aO₂/FIO₂ ratio ≤ 300; need for supplemental O₂ to maintain O₂ saturation > 95%; need for supplemental O₂ by high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation</p> <p>† Clinical improvement was defined as hospital discharge or reduction of 2 points in a 6-level ordinal scale. Levels on the scale were defined as follows: a score of 1 indicated not hospitalized; 2, hospitalized and not receiving supplemental oxygen; 3, hospitalized and receiving supplemental oxygen; 4, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or noninvasive ventilation; 5, hospitalized and receiving mechanical ventilation or extracorporeal membrane oxygenation; and 6, death.</p> <p>Remarks: -</p> <p>Authors conclusion: In severe or critically ill COVID-19 patients, almost all receiving corticosteroids as standard care, convalescent plasma and standard care did not result in a higher proportion of clinical improvement on day 28 compared to standard care alone</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Paulo (FAPESP) (2017/24769-2). R.G.G receive research grants from Brazilian Ministry of Health. A.P.Z is a research fellow of the National Council for Scientific and Technological Development (CNPq), Ministry of Science and Technology, Brazil (304226/2018-1), and receives a research grant not related to this work from Pfizer (W1242215 2018). All other authors report no potential conflicts.</p>	<p>Sex, n/N (%) male: I: 49/80 (61.2%) C: 44/80 (55.0%)</p> <p>Groups were comparable at baseline, except for median neutralizing antibody titres (significantly higher in control than in intervention group) and interleukin-6 levels (significantly higher in intervention than in control group).</p>				<p>C: 13 (7-21); n = 17 p = 0.515</p> <p><u>Time alive and free of respiratory support</u> Days (IQR) I: 11 (0-21) C: 7.5 (0-22) p = 0.444</p> <p>Clinical improvement† I: 49/80 (61.3%) C: 52/80 (65.0%) RR 0.94 (95%CI: 0.74-1.19)</p> <p>Safety <u>Grade 3-4 adverse events</u> I: 50/79 (63.3%) C: 44/81 (54.3%) RR 1.14 (95%CI: 0.88-1.48)</p> <p>Virological outcomes <u>Positive RT-PCR on day 7</u> I: 45/59 (76.3%) C: 43/58 (74.1%) RR 1.03 (95%CI: 0.84-1.27)</p> <p>Other prespecified secondary outcomes included clinical status (6-level ordinal scale) on day 14 and 28, P_aO₂/FiO₂ ratio on day 7, sepsis-related organ failure assessment (SOFA) score on day 7, and national early warning score (NEWS) score on day 7 and 14. Other prespecified exploratory outcomes were levels of serum inflammatory markers and cytokines on day 3, 7 and 14.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
O'Donnell, 2021	<p><u>Type of study:</u> RCT <i>[bijzonderheden? Open-label? Double blind?]</i></p> <p><u>Setting:</u> Two hospitals affiliated with New York-Presbyterian Hospital/Columbia University Irving Medical Center in Northern Manhattan and three sites in Rio de Janeiro.</p> <p><u>Country:</u> United States of America and Brazil.</p> <p><u>Source of funding:</u> Amazon Foundation, Skoll Foundation.</p> <p><u>Conflicts of interest:</u> MRO and MJC participated as investigators for clinical trials evaluating the efficacy and safety of remdesivir in hospitalized patients with COVID-19, sponsored by Gilead Sciences. VG is employed by Amazon Care.</p>	<p><u>Hospitalized COVID-19 patients.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Aged 18 years or older; • Evidence of SARS-CoV-2 infection by PCR of nasopharyngeal, oropharyngeal swab or tracheal aspirate sample within 14 days of randomization; • infiltrates on chest imaging and oxygen saturation less than or equal to 94% on room air or requirement for supplemental oxygen; • IMV, or extracorporeal membrane oxygenation at the time of screening. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Participation in another clinical trial of antiviral agent(s) for COVID-19; • Receipt of any antiviral agent with possible activity against SARS-CoV-2 within 24 hours of randomization; • Duration of IMV or ECMO 5 days or longer at time of screening; • Severe multiorgan failure; • History of prior reactions to transfusion blood products. <p><u>N total at baseline:</u> N = 223 Intervention: 150 Control: 73</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 60 y (48 to 71) C: 63 y (49 to 72)</p>	<p>Convalescent plasma</p> <p>Convalescent plasma used at all study sites was collected by the New York Blood Center from patients who had recovered from laboratory-confirmed COVID-19, provided informed consent, had a minimum anti-SARS-CoV-2 total IgG antibody titer of at least 1:400 by quantitative enzyme linked immunosorbent assay against the Spike protein (23), were at least 14 days asymptomatic following resolution of COVID-19, and had a negative PCR test for SARS-CoV-2 from a nasopharyngeal swab.</p>	<p>Control plasma.</p> <p>Control plasma consisted of oldest available plasma at each study site without prior testing for anti-SARSCoV-2 antibodies. All control plasma was collected prior to January 1, 2020, in Rio de Janeiro and February 20, 2020, in New York City.</p>	<p><u>Length of follow-up:</u> 28 days.</p> <p><u>Loss-to-follow-up:</u> Intervention: N = 3 (2.0%) Reasons: N=2 After improving to oxygen saturation >94% on room air N=1 after developing a severe maculopapular rash prior to transfusion.</p> <p>Control: N =1 (1.4%) Reasons: N=1 after improving to oxygen saturation >94% on room air.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p>Clinical outcomes <u>In-hospital mortality, n/N (%)</u> I: 19/150 (12.6%) C: 18/73 (24.6%) OR 0.44 (95% CI 0.22 to 0.91) P=0.034 Adj OR 0.47 (95% CI 0.21 to 1.06) P=0.068</p> <p><u>28-day mortality, n/N (%)</u> I: 19/150 (12.6%) C: 18/73 (24.6%) OR 0.44 (95% CI 0.22 to 0.91) P=0.034 OR 0.47 (95% CI 0.21 to 1.06) P=0.068</p> <p><u>Duration of hospitalization</u> <u>Time to hospital discharge, median (IQR)</u> I: 9 (6 to 28) C: 8 (6 to 22) sHR 1.05 (95% CI 0.77 to 1.43) P=0.756 Adj. sHR 1.02 (95% CI 0.75 to 1.38) P=0.913</p> <p><u>Time to symptom resolution</u> <u>Time to clinical improvement, median (IQR)</u> I: 5/150 (4 to 6) C: 7/73 (5 to 8) sHR 1.21 (95% CI 0.89 to 1.65)</p>	<p><u>Definitions:</u> World Health Organization ordinal scale 1: not hospitalized with resumption or normal activities; 2: not hospitalized, but unable to resume normal activities; 3: hospitalized, not requiring supplemental oxygen; 4: hospitalized, requiring supplemental oxygen; 5: hospitalized, requiring high-flow oxygen therapy or noninvasive mechanical ventilation; 6: hospitalized, requiring ECMO, IMV or both; 7: death.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, although use of convalescent plasma was not associated with improved clinical status at 28 days, mortality at this time point was significantly reduced. This result should be interpreted with caution until full results from larger inpatient trials adequately powered to detect differences in mortality are available.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Sex, n/N (%) male: I: 96/150 (64.0%) C: 51/73 (70.0%)</p> <p>Disease severity, mean (SD): <i>Defined by WHO ordinal scale</i></p> <p>3: <i>hospitalized, not requiring supplemental oxygen</i> I: 5/150 (3%) C: 5/73 (7%)</p> <p>4-5: <i>hospitalized, requiring supplemental oxygen, HFO, NIV</i> I: 125/150 (83%) C: 57/73 (78%)</p> <p>6: <i>hospitalized, requiring IMV, ECMO, or both</i> I: 17/150 (11%) C: 11/73 (15%)</p> <p>Groups comparable at baseline? Yes.</p>				<p>P=0.231 Adj. sHR 1.20 (95% CI 0.87 to 1.64) P=0.261</p> <p><u>Clinical status at 28 days, n/N (%)</u> OR 1.50 (95% CI 0.83 to 2.68) P=0.180 Adj. OR 1.38 (95% CI 0.73 to 2.61) P=0.318</p> <p>1 and 2: <i>not hospitalized</i> I: 108/150 (72.0%) C: 48/73 (65.8%)</p> <p>3: <i>hospitalized, not requiring supplemental oxygen</i> I: 3/150 (2.0%) C: 2/73 (2.7%)</p> <p>4: <i>hospitalized, requiring supplemental oxygen</i> I: 7/150 (4.7%) C: 1/73 (1.4%)</p> <p>5: <i>hospitalized, requiring high-flow oxygen therapy or noninvasive mechanical ventilation</i> I: 1/150 (0.7%) C: 0/73 (0%)</p> <p>6: <i>hospitalized, requiring IMV, ECMO, or both</i> I: 12/150 (12.6%) C: 4/73 (5.5%)</p> <p>7: <i>death</i> I: 19/150 (12.6%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 18/73 (24.6%)</p> <p><u>Respiratory support</u> <u>Time to discontinuation of supplemental oxygen, median (IQR)</u> I: 6 (3 to 16) C: 7 (3 to 11) sHR 1.12 (95% CI 0.80 to 1.56) (95% CO 0.80 to 1.56) P=0.508 Adj. sHR 1.12 (95% CI 0.80 to 1.56) P=0.514</p> <p>Safety <u>Serious adverse events, n/N (%)</u> I: 39/147 (26.5%) C: 26/72 (36.1%)</p> <p><u>Adverse events, n/N (%)</u> I: 4/147 (2.7%) 3/72 (4.2%) * In patients who received convalescent plasma, these events included worsening anemia, urticaria, skin rash, and transfusion-associated circulatory overload.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
AlQahtani, 2021	<p><u>Type of study:</u> RCT <i>(open label pilot study)</i></p> <p><u>Setting:</u></p>	<p><u>Hospitalized COVID-19 patients with hypoxia requiring oxygen support, but no ventilatory support</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Signed informed consent 	400 ml convalescent plasma (CP) transfusion given as 200 ml over 2hrs over 2 successive days. Patients prior to therapy were on standard supportive treatment.	Standard supportive treatment including control of fever (paracetamol) and possible	<u>Length of follow up:</u> Not reported, but adverse event will be reported until 30 days after the patient's final study medication.	<p>Clinical outcomes <u>Mortality (28-30 day)</u> <u>28th day mortality rate, n/N(%)</u> I: 1/20 (5%) C: 2/20 (10%) p=0.55</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Pilot RCT Patients and clinicians unblinded Comparable groups at baseline

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Multicenter: (coordinating centers: Hereditary blood Disorder Centre – Salmaniya Medical Complex, Bahrain Defense Force Hospital Blood Bank, Bahrain Defence Force Royal Medical Services, Military Hospital, Royal College of Surgeons in Ireland – Bahrain; enrolment April 2020 – June 2020)</p> <p><u>Country:</u> Bahrain</p> <p><u>Source of funding:</u> Ministry of Health Bahrain and the College of Surgeons in Ireland-Bahrain</p> <p><u>Conflicts of interest:</u> No competing interests</p>	<ul style="list-style-type: none"> At least 21 years; COVID-19 diagnosis based on polymerase chain reaction (PCR) testing; hypoxia (oxygen saturation of less than or equal 92% on air, or PO₂<60 mmHg arterial blood gas, or arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FIO₂) of 300 or less and the patient requiring oxygen therapy; pneumonia confirmed by chest imaging. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients with mild disease not requiring oxygen therapy; Patients with a normal CXR or CT scan; Patients requiring ventilatory support (non-invasive or mechanical); Patients with a negative PCR test for SARS-CoV-2 Patients with a history of allergy to plasma, sodium citrate or methylene blue, or those with a history of autoimmune disease or selective IGA deficiency <p><u>N total at baseline:</u> N = 40 Intervention: 20 Control: 20</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 52.6 y (14.9) C: 50.7 y (12.5) Sex, n/N (%) male: I: 17/20 (85%) C: 15/20 (15%)</p>		therapy including antiviral medications, Tocilizumab and antibacterial medication.	<p><u>Loss to follow-up:</u> I: 0/20 (0%) Reasons: - C: 0/20 (%) Reasons: - Note: probably none, but not clearly reported</p>	<p><u>Duration of hospitalization</u> <i>Length of (hospital?) stay (only survivors included), mean days (SD)</i></p> <p>I: 14.1 (1.24) C: 18.05 (2.22) p=0.12</p> <p><u>Time to symptom resolution</u> not reported</p> <p><u>Respiratory support</u> <i>Non invasive ventilator (NIV) or mechanical ventilator (MV), n/N(%)</i></p> <p>I: 4/20 (20%) C: 6/20 (30%) p=0.47</p> <p>RR: 0.67 (95%CI 0.22 to 2.0) p=0.72</p> <p>Subgroup analyses: early CP (less than 3 days from admission): 30% late CP (after 3 days from admission): 0%</p> <p><u>Time to ventilation</u> logranktest, p=0.52</p> <p><u>Time on ventilation (for those patients on NIV or MV), mean days (SD)</u></p> <p>I: 8.25 (4.42) C: 10.5 (2.9) p=0.809</p> <p>Safety</p>	<p><u>Authors conclusion:</u> “ There were no significant differences in the primary or secondary outcome measures between CP and standard therapy though fewer patients required ventilation (NIV or MV) and for a shorter period of time, although a larger definitive study is needed for confirmation. However, the study did show that CP therapy appears to be safe in hospitalized COVID-19 patients with hypoxia.”</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Oxygenation device required on admission, n/N (%) nasal cannula or face mask: I: 17/20 (85%) C: 19/20 (95%)</p> <p>Oxygenation device required on admission, n/N (%) nonrebreather mas or high flow nasal cannula: I: 3/20 (95%) C: 1/20 (5%)</p> <p>Groups comparable at baseline? yes, but intervention group showed higher D-dimer and ferritin levels.</p>				<p><u>Adverse events</u> Two patients treated with plasma reported adverse events during the study that were not considered to be related to therapy (diarrhoea and vomiting that settled spontaneously (n=1); desaturated transiently after the infusion (n=1))</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p> <p>Also available: - Use of steroids - Received medication after randomisation Outcomes at discharge (including alive participants: 18 controls and 19 intervention): - CP antibodylevel (available for 13 participants; subgroups for requiring NIV or MV, early or late CP) - WBC (white bloodcell count) - LDH (lactate dehydrogenase) - CRP (c-reactive protein) - Troponin - Ferritin - D-dimer - Procalcitonin</p>	
Bennett-Guerrero, 2021	<u>Type of study:</u> RCT, double-blind	Hospitalized adult patients with mild or severe COVID-19	Convalescent Plasma (CP)	Standard Plasma (SP)	<u>Length of follow up:</u> 90 days	Clinical outcomes <u>Mortality (28-30 day), n/N (%)</u>	<u>Definitions:</u> <u>Ventilator-free days to day 28</u> was defined as the total number of days or

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> One hospital, open to enrolment on April 8, 2020 until August 24, 2020.</p> <p><u>Country:</u> USA (New York)</p> <p><u>Source of funding:</u> Apheresis/Blood Bank staff and Stony Brook Medicine Information Technology (assist in the trial), Health Sciences Renaissance School of Medicine (financial and administrative support)</p> <p><u>Conflicts of interest:</u> Dr. Fries received support for article research from the National Institutes of Health. The remaining authors have disclosed that they do not have any potential conflicts of interest.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Hospitalized adult patients Confirmed diagnosis (PCR) of COVID-19 (mild/severe) 2:1 intubated to no-intubated <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Contraindication to transfusion or history of prior reactions to transfusion blood products Receipt of pooled immunoglobulin or any intravenous polyclonal immunoglobulin in past 30 days Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period In the treating physician's opinion, the patient is unable to tolerate a 450-550 mL infusion of plasma over up to 8 hours (4 hours max per unit) Unable to be randomized within 14 days of admission <p><u>N total at baseline:</u> N = 74 Intervention: 59 Control: 15</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 67 y (15.8) C: 64 y (17.4) Sex, n/N (%) male: I: 36/59 (61.0%) C: 8/15 (53.3%) Disease severity, n/N (%): Any FDA severe COVID-19 sign/symptom</p>	<p>Subjects received a single "dose" of 2 U CP (total volume approximately 480 mL). Each unit of plasma (approx.. 240 mL) was administered over 1–4 hours, using standard hospital procedures.</p> <p>In a randomly selected subset of units, CP had high levels of neutralizing antibodies to SARS-CoV-2. NT50 were median (interquartile range [IQR]) 1:334 (1:192–1:714) in a pseudotype assay and 1:526 (1:359–1:786) in a plaque neutralization assay using SARS-CoV-2.</p>	<p>SP was collected prior to January 2020. Subjects received a single "dose" of 2 U SP (total volume approximately 480 mL). Each unit of plasma (approx.. 240 mL) was administered over 1–4 hours, using standard hospital procedures.</p>	<p><u>Loss to follow-up:</u> I: 0/N (0%) Reasons: C: 0/N (0%) Reasons: n.a.</p>	<p>I: 14/59 (24%) C: 4/15 (27%) HR (95%CI): 0.80 (0.26–2.44)</p> <p><u>Mortality (90 days), n/N (%)*</u> I: 16/59 (27%) C: 5/15 (33%) HR (95%CI): 0.74 (0.27–2.03)</p> <p>*Subgroup analysis for time to death in patients who were intubated at baseline was statistically significant.</p> <p><u>Duration of hospitalization</u> Not reported</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support**</u> <i>Ventilator free days through 28 days, median (IQR)</i> I: 28 (2-28) C: 28 (0-28) P=0.86</p> <p>**Subgroup analysis available for patients which were 1) intubated and 2) non-intubated.</p> <p><u>WHO ordinal scale, n/N (%)</u> <i>Defined as ≥ 2 points of improvement</i></p>	<p>proportions of days during the first 28 days after randomization. Subjects never requiring intubation were assigned a time of 28 days and those who died by day 28 were assigned 0 ventilator-free days.</p> <p>SAE including death, grade 4 or greater organ failure, serious infusion reaction warranting termination of plasma infusion.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Groups were almost similar, except with regard to use of remdesivir/hydroxychloroquine (higher in CP) and supplemental oxygen (higher in CP) In both groups, one patient did not receive the intervention. Study is severely underpowered 80% and 87% of patients in CP and SP arms, respectively, had detectable IgG antibodies to SARS-CoV-2 at baseline. Randomization was stratified by non-intubated vs. intubated patients. <p><u>Authors conclusion:</u> In summary, in this double-blind RCT, administration of 2 U of CP to patients hospitalized in New York with COVID-19 infection increased antibodies to SARS-CoV-2 but was not associated with improved outcome. Results from this and previous trials (18–20) do not support the use of CP for the treatment of hospitalized patients with COVID-19 infection.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 44/59 (74.6%) C: 13/15 (86.7%) <i>In ICU at randomization</i> I: 17/59 (28.8%) C: 3/15 (20.0%) <i>Intubated</i> I: 11/59 (18.6%) C: 3/15 (20.0%) <i>Acute physiology and chronic health evaluation II score*, mean (SD)</i> I: 23.4 (5.6) C: 22.5 (6.6)</p> <p>*A composite index of comorbidities and acute physiologic status</p> <p>Groups comparable at baseline? Groups differed with regard to other COVID-19 treatments and oxygen supplementation.</p>				<p>I: 12 /59 (20%) C: 3/15 (20%) HR (95%CI): 0.75 (0.21–2.68)</p> <p>Safety <u>Serious adverse events in first 28 days, n/N (%) ***</u> I: 16/59 (30%) C: 4/15 (27%)</p> <p>*** Data is also available for first 24h, days 2-7 and days 8-28.</p> <p><u>Infusion related event, n/N (%)</u> I: 1/59 (2%) C: 0/15 (0%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p> <p><u>IgG Antibodies (%) increase from baseline</u> I: 14.4% C: 8.6% P=0.005</p>	
Pouladzadeh, 2021	<p><u>Type of study:</u> RCT hospital-based, parallel-group, single-blind</p> <p><u>Setting:</u> Emergency department in Razi hospital of Ahvaz between March and May 2020</p> <p><u>Country:</u></p>	<p>COVID-19 patients referred to the Emergency department.</p> <p><u>Inclusion criteria (for CP recipient):</u></p> <ul style="list-style-type: none"> COVID-19 patients who had specified COVID-19 symptoms (less than 7 days since the onset of the symptoms) The positive results of PCR test and CT scan Severity WHO score>4 Blood oxygen saturation (SPO2)≤93% in room air. 	<p><u>Plasma (CP group)</u> one unit (500 mL) plasma on the admission day plus standard treatment (Chloroquine phosphate, Lopinavir/Ritonavir, etc.)</p> <p>The first plasma unit was injected in the first 4 h after admission; according to the physician's recommendation, the second unit was</p>	<p><u>Standard treatment</u> Chloroquine phosphate, Lopinavir/Ritonavir, etc</p>	<p><u>Length of follow up:</u> 60-day follow-up</p> <p><u>Loss to follow-up:</u> I: 1/31 (%) Reasons: Lost to follow-up (declined to participate) (n= 1) C: 1/31 (%) Reasons: Lost to follow-up (declined to participate) (n= 1)</p>	<p>Clinical outcomes <u>Mortality, 2-month mortality after admission, n/N (%)</u> I: 3/30 (10%) C: 5/30 (16.7%) P=0.44</p> <p><u>Duration of hospitalization</u> Defined as length of in-hospital day, mean ± SD I: 8.66±3.94 C: 6.66±4.30 P=0.06</p>	<p><u>Definitions:</u> The “cytokine storm” is defined as a high concentration of pro-inflammatory cytokines in severely ill patients.</p> <p><u>Remarks:</u> The frequency of underlying disease in the intervention group [20 (66.6%)] was significantly more than the control group [10 (33.3%)] (p value=0.02). The most common underlying diseases were, respectively, diabetes</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Iran</p> <p><u>Source of funding:</u> Not reported.</p> <p><u>Conflicts of interest:</u> Not reported.</p>	<ul style="list-style-type: none"> Individuals who no exhibit hypersensitivity to plasma intravenous administration <p>Also available: inclusion criteria for CP donors</p> <p><u>Exclusion criteria:</u> Not reported.</p> <p><u>N total at baseline:</u> N = 60 Intervention: 30 Control: 30</p> <p><u>Important characteristics:</u></p> <p>Age, n (%): I: ≤50 y: 11/30 (36.7%) >50 y: 19/30 (63.3%) C: ≤50 y: 12/30 (40%) >50 y: 18/30 (60%)</p> <p>Sex, n/N (%) male: I: 16/30 (53.3 %) C: 17/30 (56.7%)</p> <p>Underlying disease, n/N (%) yes: I: 20/30 (66.7%) C: 10/30 (33.3%)</p> <p>Severity grade of COVID-19*, pre I: Grade 5: 20/30 (66.7%) Grade 6: 10/30 (33.3%) C: Grade 5: 25/30 (83.3%) Grade 6: 5/30 (16.7%)</p> <p>*Not further defined in the article.</p>	prescribed if no improvement was observed after 24 h.			<p><u>Time to symptom resolution</u> Defined as improvement in the 8-point WHO severity score, mean ± SD, difference I: - 0.56±0.935 C: - 0.23±0.81 P=0.14</p> <p><u>Laboratory markers</u> Absolute lymphocytes (mm3), mean ± SD, difference I: - 675.55±969.33 C:- 106.79±654.15 P=0.012</p> <p>IL-10 (pg/ml), mean ± SD, difference I: 4.486±9.579 C: 1.28±7.43 P=0.15</p> <p>IL-6 (pg/ml), mean ± SD, difference I: - 8.98±10.35 C: 1.60±5.34 P<0.001</p> <p>TNF-α (pg/ml), mean ± SD, difference I: - 6.49±15.56 C: 2.79±19.35 P=0.045</p> <p>IFN-γ (pg/ml), mean ± SD, difference I: - 8.49±15.52 C: 1.21±6.65 P= 0.0217</p>	<p>mellitus, hypertension, and ischemic heart disease (IHD). In some cases, asthma, rheumatoid arthritis (RA), and hyperlipidemia were found.</p> <p><u>Authors conclusion:</u> Although CP has a remarkable immunomodulatory and antiviral potential to improve the cytokine storm and disease severity in COVID-19 patients, it did not considerably affect the mortality rate.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline? There was no significant difference between the intervention and control groups in terms of age and sex (p=0.79). The frequency of underlying disease in the intervention group [20 (66.6%)] was significantly more than the control group [10 (33.3%)] (p value=0.02).				<p>Respiratory support Three and five patients in the intervention and control groups needed to intubation. It is noteworthy that these intubated patients were eventually died.</p> <p>Safety <u>Adverse events</u> Defined as CP therapy related side effects. CP therapy had not any serious side effects on patients.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p> <p>Also available: CRP (mg/L); ESR (mm/hr)</p>	
Libster,2020	<p><u>Type of study:</u> RCT; double-blind, placebo-controlled</p> <p><u>Setting:</u> clinical sites and geriatric units, n=13; June 4, 2020, and Oct 25, 2020 (when the last patient completed follow-up)</p> <p><u>Country:</u> Argentina</p> <p><u>Source of funding:</u></p>	<p><u>Hospitalized patients with Covid-19, treated within 72 hours after the onset of mild symptoms, age 65 and up</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ≥75 years of age, irrespective of current coexisting conditions • OR 65-74 years of age with at least one coexisting condition [see supplement; including hypertension, diabetes, obesity, CVD, COPD] • At time of RT- 	<p>Convalescent plasma</p> <p>250 ml of convalescent plasma; IgG titer > 1:1000 against SARS-CoV-2 spike (S) protein (COVIDAR IgG, Instituto Leloir, Argentina)</p> <p>The convalescent plasma was arbitrarily defined as 'high-titer' and included antibody concentrations in the upper 28th percentile.</p> <p>Treatment was administered < 72 hours after onset of symptoms</p>	<p>Placebo</p> <p>250 ml of placebo (0.9% normal saline).</p> <p>Treatment was administered < 72 hours after onset of symptoms</p> <p>Infusions were given over a period of 1.5 to 2.0 hours</p>	<p><u>Length of follow up:</u> 15 days for primary end-point; 25 days for secondary end-points</p> <p><u>Loss to follow-up:</u> I: 0/80 (0%) C: 0/80 (0%)</p> <p><u>Excluded from modified ITT analysis:</u> I: 4/80 (5%) C: 2/80 (2.5%) Reason: Endpoint reached before treatment administration</p>	<p>Clinical outcomes <i>Mod. ITT = modified intention-to-treat; excluding 6 patients that reached the endpoint before treatment administration</i></p> <p><u>Severe respiratory disease, defined as a respiratory rate of ≥30 breaths per minute, oxygen saturation <93% while the patient was breathing ambient air, or both.</u> I: 13/80 (16%) C: 25/80 (31%) RR 0.52 (95% CI 0.29 to 0.94)</p>	<p><u>Definitions:</u> *Modified intention-to-treat analysis: excluded 6 patients who had a primary end-point event before infusion of treatment.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Patients were older adults (from 65 years of age and older) and had mild COVID-19. • 95% confidence intervals are wide • in case minimal clinically important difference set at 25% difference: crossing the threshold for a clinically relevant difference in favour

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Funded by the Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund; Dirección de Sangre y Medicina Transfusional del Ministerio de Salud number, PAEPCC19, Plataforma de Registro Informatizado de Investigaciones en Salud number, 1421, and ClinicalTrials.gov number, NCT04479163.)	<p>PCR screening for SARS-CoV-2</p> <ul style="list-style-type: none"> at least 1 sign/symptom in each of following two categories for < 48 hours: I) temperature $\geq 37.5^{\circ}\text{C}$, unexplained sweating, or chills; II) dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, or rhinorrhea. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> severe respiratory disease (the primary end point) any disease listed in Table S5 <p><u>N total at baseline:</u> N = 160 Intervention: 80 Control: 80</p> <p><u>Important characteristics:</u> Age, mean\pmSD: I: 76.4\pm8.7 C: 77.9\pm8.4 Sex, n/N (%) male: I: 26/80 (32%) C: 34/80 (42%)</p> <p>Vital signs, mean\pmSD: Respiratory rate — breaths/min I: 17\pm2.8 C: 17.3\pm3.0 Oxygen saturation while breathing ambient air — % I: 96.1\pm1.6 C: 96.1\pm1.7</p>	<p>Infusions were given over a period of 1.5 to 2.0 hours.</p> <p>Collection plasma: 479 potential plasma donors who had had SARS-CoV-2 infection for ≥ 10 days and had been asymptomatic for ≥ 3 days and had two negative RT-PCR tests were identified. Potential donors who provided written informed consent were visited at home and screened for SARS-CoV-2 S IgG at a titer greater than 1:1000 in serum. Each of the 135 candidates (28%) with adequate titers donated 750 ml of plasma.</p>			<p>Mod. ITT RR 0.40 (95% CI 0.20; 0.81) <u>Time to development severe respiratory disease</u> I: 15 days (IQR 15 to 15) C: 15 days (IQR 9 to 15)</p> <p><u>Life-threatening respiratory disease</u> I: 4/80 (5%) C: 10/80 (12%) RR 0.40 (95% CI 0.13–1.22) Mod. ITT RR 0.34 (95% CI 0.10; 1.22) <u>Oxygen supplementation at an FiO₂ of 100%</u> I: 4/80 (5%) C: 6/80 (8%) RR 0.67 (95% CI 0.20–2.27) Mod. ITT RR 0.62 (95% CI 0.15; 2.49) <u>Noninvasive ventilation</u> I: 1/80 (1%) C: 6/80 (8%) RR 0.17 (95% CI 0.02–1.35) Mod. ITT RR 0.17 (95% CI 0.02; 1.39) <u>Admission to intensive care unit</u> I: 2/80 (2%) C: 6/80 (8%) RR 0.33 (95% CI 0.07–1.60) Mod. ITT RR 0.21 (95% CI 0.02; 1.72) <u>Mechanical ventilation</u> I: 2/80 (2%) C: 4/80 (5%) RR 0.50 (95% CI 0.09–2.65)</p>	<p>of the control group (<0.8) as well as in favour of the control group (>1.25).</p> <p><u>Authors conclusion:</u> "In our randomized, controlled trial, the administration of high-titer convalescent plasma against SARS-CoV-2 to infected older adults within 72 hours after the onset of mild symptoms reduced the progression of Covid-19 to severe illness. This simple and inexpensive intervention can reduce demands on the health care system and may save lives. Early infusions of convalescent plasma can provide a bridge to recovery for at-risk patients until vaccines become widely available."</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Time since onset symptoms, hr I: 39.6±13.9 C: 38.3±14.3</p> <p>Groups comparable at baseline.</p>				<p>Mod. ITT RR 0.26 (95% CI 0.03; 2.24)</p> <p><u>Critical systemic illness</u> I: 5/80 (6%) C: 6/80 (8%) RR 0.83 (95% CI 0.27–2.62) Mod. ITT RR 0.82 (95% CI 0.23; 2.94)</p> <p><u>Acute respiratory failure</u> I: 2/80 (2%) C: 5/80 (6%) RR 0.40 (95% CI 0.08–2.00) Mod. ITT RR 0.26 (95% CI 0.03; 2.24)</p> <p><u>Shock</u> I: 2/80 (2%) C: 1/80 (1%) RR 2.00 (95% CI 0.19–21.6) Mod. ITT RR 1.03 (95% CI 0.07; 16.11)</p> <p><u>Multiple organ dysfunction syndrome</u> I: 3/80 (4%) C: 5/80 (6%) RR 0.60 (95% CI 0.15–2.43) Mod. ITT RR 0.77 (95% CI 0.18; 3.33)</p> <p><u>Death from Covid-19</u> I: 2/80 (2%) C: 4/80 (5%) RR 0.50 (95% CI 0.09–2.65) Mod. ITT RR 0.34 (95% CI 0.04; 3.22)</p> <p><u>Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I: 7/80 (9%) C: 12/80 (15%) RR 0.58 (95% CI 0.24–1.41) Mod. ITT RR 0.56 (95% CI 0.22; 1.44)</p> <p>Antibody titers <u>Distribution of anti-SARS-CoV-2 serum S IgG titers 24 hours after infusion, median log:</u> I: 5.7 (IQR, 4.9 to 6.3) C: 3.9 (IQR 3.9 to 4.7) <u>Stratified by outcome status yes/no:</u> No IgG correlate of protection for antibodies against SARS-CoV-2 in the serum samples of intervention group</p> <p>Dose-dependent effect was observed for SARS-CoV-2 S IgG titers in plasma bags (Table 3). Donor titers selected on the basis of a median titer of 1:3200 showed a relative risk reduction of 73.3%, with a number needed to treat of 4 (range, 3 to 11) to avoid a worsening of Covid-19 in recipients of antibody concentrations above the median concentration (Table 3). The SARS-CoV-2 S IgG results were replicated with the use of a different</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>SARS-CoV-2 spike S1-RBD IgG commercial assay; this assay provides a potential alternative tool for donor selection ($r = 0.7$; 95% CI, 0.6 to 0.8) (see Fig. S3).</p> <p>Safety, (<u>Serious</u>) <u>adverse events</u>; <i>volume overload, allergic reaction, trombophlebitis, vasovagal syndrome, hematoma at site, nerve injury, tetany (hyperventilation)</i> Inconsistency in table; 0 or 1 adverse events reported: Trombophlebitis in 1 patients of the placebo group.</p>	
Simonovich, 2020	<p><u>Type of study:</u> Double-blind, placebo-controlled multicenter trial</p> <p><u>Setting:</u> 12 clinical sites in Argentina and coordinated by Hospital Italiano de Buenos Aires.</p> <p><u>Country:</u> Argentina</p> <p><u>Source of funding:</u> Supported by the participant institutions (Hospital Italiano de Buenos Aires,</p>	<p><u>Hospitalized adults with COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a respiratory tract sample that was positive for SARS-CoV-2; Radiologically confirmed pneumonia; No previous directives rejecting advanced life support; At least one of the following severity criteria: oxygen saturation below 93% while they were at rest and breathing ambient air, a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg or a 	Single administration of Covid-19 convalescent plasma in addition to standard treatment	Placebo (normal saline solution) in addition to standard treatment	<p><u>Length of follow up:</u> 30 days after enrollment</p> <p><u>Loss to follow-up:</u> No patients were lost to follow-up</p>	<p>Clinical outcomes</p> <p><u>Mortality, n/N (%)</u> I: 25/228 (11%) C: 12/105 (11.4%)</p> <p><u>Time from intervention to hospital discharge, median (IQR) in days</u> I: 13 (8 to 30) C: 12 (7 ND (could not be determined)) Subhazard ratio= 1 (95% CI= 0.76 to 1.32)</p> <p><u>Time from intervention to discharge from the ICU, median (IQR) in days</u> I: ND (8 to ND) C: ND (6 to ND)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> Patients were allowed to receive antiviral agents, glucocorticoids, or both according to the standard of care at the provider health care institution.</p> <p><u>Authors conclusion:</u> In our trial, the use of convalescent plasma therapy in addition to standard treatment in patients with severe pneumonia due to Covid-19 did not reduce mortality or improve other clinical outcomes at day 30 as compared with placebo. We believe the use of convalescent plasma as a standard of care in such patients should be reevaluated. Further studies regarding antibody therapy may be</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Swiss Medical Group, Hospital Universitario Austral, Sanatorio Trinidad de Palermo, Clínica Santa Isabel, Hospital Privado de la Comunidad, Hospital Zonal Ramón Carrillo de Bariloche, Hospital JM Ramos Mejía, Sanatorio Británico de Rosario and Hospital Privado de Córdoba), which provided their own funding for the conduct of this trial.</p>	<p>Sequential Organ Failure Assessment or modified SOFA score of two or more points above baseline status.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Pregnant patients or lactating • Patients of reproductive age who were not willing to use contraceptive measures for a period of 30 days after enrolment; • Patients with history of blood component allergies; • Infectious cause of pneumonia other than SARS-CoV-2; • Requirement for mechanical ventilation; • Multiorgan failure; • Any other condition that would impede the provision or informed consent. <p><u>N total at baseline:</u> N = 333 Intervention: 228 Control: 105</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 62.5 y (53-72.5) C: 62 y (49-71)</p> <p>Sex, n/N (%) female: I: 67/228 (55.3%) female C: 41/105 (51.4%) female</p> <p><u>Oxygen saturation <93% at FiO₂, n/N (%)</u> I: 224/228 (98.2%) C: 100/105 (95.2%)</p> <p><u>mSOFA or SOFA ≥2, n/N (%)</u></p>				<p>Subhazard ratio= 0.94 (95% CI= 0.48 to 1.82)</p> <p><u>Time from intervention to complete restoration of physical functions, median (IQR) in days</u> I: 15 (9 to ND) C: 15 (7 to ND) Subhazard ratio= 0.89 (95% CI= 0.66 to 1.18)</p> <p><u>Time from intervention to start of invasive ventilation, median (IQR) in days</u> I: ND (9 to ND) C: ND Subhazard ratio= 1.14 (95% CI= 0.72 to 1.81)</p> <p><u>Time from intervention to death, median (IQR) in days</u> I: ND C: ND HR= 0.93 (95% CI= 0.47 to 1.86)</p> <p><u>Discharged without full return to baseline physical condition, n/N (%)</u> I: 30/228 (13.2%) C: 8/105 (7.6%)</p> <p><u>Discharged with full return to baseline physical function, n/N (%)</u> I: 141/228 (61.8%) C: 72/105 (68.6%)</p> <p><u>Invasive ventilatory support n/N (%)</u></p>	<p>best focused on other populations or on interventions with other types of preparations, such as intravenous immunoglobulin or anti-SARS-CoV-2 monoclonal antibodies.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		I: 32/228 (14%) C: 17/105 (16.2%) Groups comparable at baseline? Yes				I: 19/228 (8.3%) C: 10/105 (9.5%) <u>Hospitalized with supplemental oxygen requirement n/N (%)</u> I: 5/228 (2.2%) C: 2/105 (1.9%) <u>Hospitalized without supplemental oxygen requirement, n/N (%)</u> I: 8/228 (3.5%) C: 1/105 (1%) <u>Any adverse event, n/N (%)</u> I: 153/228 (67.1%) C: 66/105 (62.9%) <u>Serious adverse event, n/N (%)</u> I: 54/228 (23.7%) C: 19/105 (18.1%) <u>Infusion-related adverse event, n/N (%)</u> I: 13/228 (5.7%) C: 2/105 (1.9%)	
Salman, 2020	<u>Type of study:</u> RCT; double-blinded controlled preliminary study <u>Setting:</u> June - August 2020 at Qena University Hospital, COVID-19 isolation ward, Qena <u>Country:</u> Egypt <u>Source of funding:</u> Funding was not reported; the	Hospitalized COVID-19 patients, all (100%) on oxygen therapy, none (0%) on mechanical ventilation <u>Inclusion criteria:</u> • Hospitalized • age ≥18 years • confirmed positive nasopharyngeal/oropharyngeal covid-19 swab • ≥2 of 4-category illness-severity scale: 1. Respiratory frequency ≥24/min. 2. Blood oxygen saturation ≤ 93% on room air,	Convalescent plasma a single dose of plasma of recovered COVID-19 individuals, 250 ml, plus standard COVID-19 therapy. COVID-19 neutralizing antibodies (Qualitative assay), was measured in donors' serum before donation and in the recipient serum a day before and every day for 5 days after recovered	Standard care Available standard therapy, when appropriate, included: supplemental oxygen, noninvasive and invasive ventilation, antibiotic medication, inotrope drugs, renal-replacement therapy,	<u>Length of follow up:</u> 5 days post transfusion <u>Loss to follow-up:</u> None	Clinical outcomes <u>Illness severity scale, day 5, n (%)</u> ; also reported for day 1-4 <i>Respiratory rate > 24/ min</i> I: 4 (26) * C: 8 (53) <i>Blood oxygen saturation ≤ 93% on room air</i> I: 3 (20) C: 8 (53.3) <i>Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg</i> I: 4 (26.4) C: 9 (60)	<u>Remarks:</u> -this was a pilot study with 30 patients in total -all patients received oxygen therapy, none was on mechanical ventilation of ECMO -the authors also discuss safety of the treatment. However, no data on adverse events or other indicators of safety were reported <u>Authors conclusion:</u> "Plasma of recovered COVID-19 resulted in improvement of laboratory and radiological findings. In RCP group, there was statistically significant improvement of clinical parameters, as well as serum ferritin, D-dimer, c-

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Author declares that there is no conflict of interest.	<p>3. Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg,</p> <p>4. Pulmonary infiltrates occupying more than 50% of both lungs</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • prior allergic history to plasma or plasma products • septic shock • multiple organ failure <p><u>N total at baseline:</u> N = 30 Intervention: 15 Control: 15</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 58.0 (49.0–68.0) C: 57.0 (50.0–67.0) Sex, n/N (%) male: I: 11/15 (73.33%) C: 10/15 (66.6%)</p> <p><u>Days from hospitalization to randomization, median (IQR)</u> I: 13 (10–16) C: 13 (11–17)</p> <p><u>Oxygen therapy</u> I: 15/15 (100) C: 15/15 (100)</p> <p><u>Invasive mechanical ventilation I:</u> 0 (0%) C: 0 (0%)</p> <p><u>ECMO</u> I: 0 (0%) C: 0 (0%)</p> <p><u>Four category illness severity scale -no. (%)</u></p>	COVID-19 plasma transfusion. Neutralizing Antibody, Cusabio, ELISA Kit Catalog Number. CSBEL23253HU for the qualitative determination of (SARS-CoV-2).	anticoagulants, glucocorticoids, intravenous fluids, interferon, and extracorporeal membrane oxygenation (ECMO).		<p><i>Pulmonary infiltrates occupying more than 50% of both lungs.</i> I: 5 (33)* C: 10 (66.3)</p> <p><u>Biomarkers of severe COVID-19, day 5, mean SD,</u> also reported for day 1-4: <i>Serum ferritin>500 mcg/L</i> I: 156 ± 76* C: 609 ± 76 <i>Serum D dimer>1000 ng/ml</i> I: 876 ± 32* C: 2012 ± 32 <i>Serum troponin > 30 ng/L</i> I: 21 ± 92 C: 61 ± 72 <i>Serum lactate dehydrogenase >245 units/L</i> I: 97 ± 27 C: 87 ± 17 <i>Serum creatine phosphokinase >300 units/L</i> I: 169 ± 53 u/L C: 199 ± 54 u/L <i><800 lymphocytes in 1 microliter of blood</i> I: 1098 ± 43/μL* C: 1098 ± 43/μL <i>Serum C-reactive protein >100 mg/L</i> I: 65 ± 45* C: 243 ± 45 * = p value ≤ 0.05</p> <p><u>COVID 19 infection indices, day 5, n (%)</u> Neutralizing antibody</p>	reactive protein, and the size of lung lesion compared to control group (P ≤ 0.05). COVID-19 neutralizing antibodies appeared in serum of RCV patients, but failed to show in the control group patients during 5 days study period. Conclusion: Plasma of recovered COVID-19 individuals is safe and effective therapeutic modality that significantly accelerated clinical improvement in patients with severe COVID-19 Infection.”

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Respiratory rate >24/min – I: 11 (73.0) C: 12 (80)</p> <p>Blood oxygen saturation ≤ 93% on room air I: 9 (60) C: 10 (66.6)</p> <p>Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg, I: 10 (66.6) C: 11 (73.3)</p> <p>Pulmonary infiltrates occupying more than 50% of both lungs. I: 10 (66.6) C: 11(73.3)</p> <p>Groups comparable at baseline.</p>				<p>I: 11/15 (73.3) C: 0 (0%)</p>	
Agarwal, 2020	<p>Type of study: Open-label, parallel arm, phase II, multicentre, randomised controlled trial.</p> <p>Setting: 39 public and private hospitals across India (screened 22 April to 14 July 2020).</p> <p>Country: India</p> <p>Source of funding: This study was funded by Indian Council of Medical Research (ICMR), an autonomous government</p>	<p>Patients aged >18 years who had confirmed covid-19 based on a positive reverse transcriptase polymerase chain reaction for SARS-CoV</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Moderate illness with either a partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air; Availability of a matched donor for convalescent plasma at the point of enrolment. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Pregnant and lactating women; Patients with known hypersensitivity to blood products, recipients of 	convalescent plasma with the best standard of care	Best standard of care alone	<p>Length of follow up: 28 days</p> <p>Loss to follow-up: I: 2/235 (%) Reasons: discharge hospital; discontinued intervention. C: 1/229 (%) Reasons: discharge hospital.</p>	<p>Clinical outcomes</p> <p>Mortality I: 44/235 (19%) C: 41/229 (18%) Unadj RD= 0.008 (95% CI= -0.062 to 0.078). Unadj RR= 1.04 (95 CI= 0.71 to 1.54). Adj RR= 1.07 (95% CI= 0.73 to 1.58).</p> <p>Duration of total hospital days (median; IQR); N with event I: 14 (10-19); N = 227 C: 13 (10-18); N = 224 Unadj RR= 0.2</p> <p>Need for respiratory support (days) (median; IQR); N with event Bijv. I: 9 (6-13); N = 227 C: 10 (6-13); N = 224</p>	<p>Definitions: -</p> <p>Remarks: -</p> <p>Authors conclusion: Although the use of convalescent plasma seemed to improve resolution of shortness of breath and fatigue in patients with moderate covid-19 and led to higher negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment, this did not translate into a reduction in 28 day mortality or progression to severe disease. Areas of future research could include effectiveness of convalescent plasma among neutralising antibody</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>funded medical research council. The Central Implementation Team at ICMR was responsible for study design, study coordination, data analysis, data BMJ: first published as 10.1136/bmj.m3939 on 22 October 2020. Downloaded from http://www.bmj.com/ on 5 November 2020 by guest. Protected by copyright.</p> <p>RESEARCH No commercial reuse. Patient enrolment, data collection, and the conduct of the study was done at public and private hospitals independently, and the investigators in ICMR had no role in these activities. The funding source has no financial interest in the investigational product.</p>	<p>immunoglobulin in the past 30 days;</p> <ul style="list-style-type: none"> • Patients with conditions precluding infusion of blood products, participants in any other clinical trials; • Critically ill patients with <200 mm Hg oxygen ratio or shock. <p><u>N total at baseline:</u> N = 464 Intervention: 235 Control: 229</p> <p><u>Important characteristics:</u> Age, median (range): I: 52 y (42-60) C: 52 y (41-60) Sex, n/N (%) male: I: 177/235 (75%) C: 177/229 77.%)</p> <p>Median symptom onset to admission (days), median (range): I: 4 (3-7) C: 4 (3-7)</p> <p>Groups comparable at baseline? Yes</p>				<p>Unadj RR= 0.7</p> <p><u>Need for respiratory support (days) post enrolment (median; IQR); N with event:</u> I: 6 (3-9); N = 227 C: 6 (4-10); N = 224 Unadj RR= 0.5</p> <p><u>Type of mechanical ventilation during hospital stay (n/N; %)</u></p> <p><i>Invasive</i> I: 19/227 (8%) C: 19/224 (8%) Unadj RR= 0.99 (95% CI= 0.54 to 1.81)</p> <p><i>Non-invasive</i> I: 31/227 (14%) C: 37/224 (16%) Unadj RR= 0.8 (95% CI= 0.5 to 1.3)</p> <p>Also available: - Resolution of symptoms on day 7 (shortness of breath; fever; cough; fatigue); - Negative conversion of SARS-CoV-2 RNA at day 3 and 7.</p>	<p>negative patients and the use of convalescent plasma with high neutralising antibody titres. The challenge will be to find both suitable patients and suitable plasma donors. Additionally, this challenge could limit the use of convalescent plasma to a small subset of patients.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Li, 2020b	<p>Type of study: Open-label, multicenter, randomized clinical trial</p> <p>Setting: 7 medical centers, from February 14, 2020 to April 1, 2020</p> <p>Country: China</p> <p>Source of funding: Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) grants and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences.</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> signed informed consent; aged at least 18 years; COVID-19 diagnosis based on polymerase chain reaction (PCR) testing; positive PCR result within 72 hours prior to randomization; pneumonia confirmed by chest imaging; clinical symptoms meeting the definitions of severe or life-threatening COVID-19; acceptance of random group assignment; hospital admission; willingness to participate in all necessary research studies and be able to complete the study follow-up; no participation in other clinical trials, such as antiviral trials, during the study period. <p>Severe COVID-19 was defined as respiratory distress (≥ 30 breaths/min; in resting state, oxygen saturation of 93% or less on room air; or arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FIO₂) of 300 or less.</p> <p>Life threatening COVID-19 was defined as respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring.</p>	<p>Convalescent plasma added to standard treatment.</p> <p>The transfusion dose was approximately 4 to 13 mL/kg of recipient body weight.</p> <p>Procurement of plasma The plasma products were prepared as fresh-frozen plasma.</p> <p>Only the plasma units with an S-RBD-specific IgG titer of at least 1:640 were used for this study.</p> <p>Convalescent plasma-specific donor screening and selection were based on the following criteria:</p> <ul style="list-style-type: none"> age of 18 through 55 years; suitable for blood donation; initially diagnosed with COVID-19 but with 2 negative PCRtest results from nasopharyngeal swabs (at least 24hours apart) prior to hospital discharge; discharged for more than 2 weeks from the hospital; no persisting COVID-19 symptoms. 	<p>Standard treatment</p> <p>Standard treatment consisted of symptomatic control and supportive care for COVID-19, mostly based on the evolving Chinese national COVID-19 treatment guidelines and hospital practice. Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications.</p>	<p>Final follow-up at April 28, 2020, at least 28 days.</p>	<p>Clinical improvement within 28 days (%) I: 27/52 (51.9) C: 22/51 (43.1) OR (95%CI): 1.20 (0.80-1.81) P= 0.37</p> <p>Subgroup severe disease (%) I: 21/23 (91.3) C: 15/22 (68.2) OR (95%CI): 1.34 (0.98-1.83) P= 0.07</p> <p>Subgroup life-threatening disease (%) I: 6/29 (20.7) C: 7/29 (24.1) OR (95%CI): 0.86 (0.33-2.24) P= 0.75</p> <p>Discharge rate at day 28 (%) I: 26/51 (51.0) C: 18/50 (36.0) OR (95%CI): 1.42 (0.90-2.24) P=0.13</p> <p>Mortality at day 28 (%) I: 8/51 (15.7) C: 12/50 (24.0) OR (95%CI): 0.59 (0.22-1.59) P= 0.30</p> <p>Viral nucleic acid negative rate at 72h (%) I: 41/47 (87.2) C: 15/40 (37.5)</p>	<p>Remarks: Due to decreasing numbers of COVID-19 patients, trial was terminated early after 103 of a planned 200 patients were enrolled. So trial may have been underpowered.</p> <p>According to the authors the study findings should be interpreted cautiously given that practices may vary from country to country, and hospital to hospital, such as the types of standard treatment, supportive care, and thresholds for intubation and hospital admission.</p> <p>Authors conclusion: Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not significantly improve the time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • pregnancy or lactation; • immunoglobulin allergy; • IgA deficiency; • pre-existing comorbidity that could increase the risk of thrombosis; • life expectancy less than 24 hours; • disseminated intravascular coagulation; • severe septic shock; • PaO₂/FIO₂ of less than 100; • severe congestive heart failure; • detection of high titer of S protein–RBD-specific (receptor binding domain) IgG antibody (≥1:640); • other contraindications as determined by the patient’s physicians; • participation in any antiviral clinical trials for COVID-19 within 30 days prior to enrolment. <p><u>N total at baseline:</u> N = 103 Intervention: 52 Control: 51</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 70 (62-80) C: 69 (63-76) P= not reported Sex, n/N (%) male: I: 27/52 (51.9) C: 33/51 (64.7) P= not reported</p>				<p>OR (95%CI):11.39 (3.91-33.18) P= <0.001</p> <p>For two patients transfusion related adverse events were reported. One was determined to be a definite nonsevere allergic transfusion reaction and also a probable nonsevere febrile nonhemolytic transfusion reaction. The was determined to be possible severe transfusion associated dyspnea.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline? Overall and within disease severity strata, the groups were similar at baseline, with the exception of systolic blood pressure in the patients with severe COVID-19 and sex in the patients with life-threatening COVID-19.					
6. Monoclonal antibodies							
6.1. Adalimumab							
Fakharian, 2021	<p><u>Type of study:</u> RCT</p> <p><u>Setting:</u> Affiliated and selected referral center for COVID-19 patients, period of enrolment is not reported</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> Shahid Beheshti University of Medical Sciences</p> <p><u>Conflicts of interest:</u> Authors declare that they have no known competing financial interest or personal relationship that could have appeared to influence the work</p>	<p>Hospitalized adults with severe COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> aged 18-70 years RT-PCR reports or CT scan confirming bilateral pulmonary infiltration severe COVID-19 (pO₂ ≤ 93% at room air, Heart rate ≥ 125 min, respiratory rate ≥ 30/min, the evidence of shock, the need for mechanical ventilation or vasopressors, clinically significant acute hepatic, renal or neurological dysfunction due to COVID-19 and patients with acute respiratory distress syndrome). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> denying to sign the consent form acute or chronic kidney disease history of liver failure history of malignancy history of heart failure latent or active tuberculosis or any active infection 	<p>Adalimumab + standard care</p> <p>40 mg, single-dose, subcutaneously in prefilled syringe form.</p> <p>Days from admission to administration of adalimumab: Mean±SD: 4.35±1.73 Range: 2-11 days</p>	<p>Standard care</p> <p>Oxygen and fluid support, remdesivir 200 mg stat followed by 100 mg IV daily for 5-10 days, and dexamethasone 6 mg IV daily for 10 days or up to the point of discharge.</p>	<p><u>Length of follow-up:</u> Until death or discharge</p> <p><u>Loss-to-follow-up:</u> Intervention: 0 (0%) Reasons: NA</p> <p>Control: 0 (0%) Reasons: NA</p> <p><u>Incomplete outcome data:</u> Intervention: NR Reasons: NA</p> <p>Control: NR Reasons: NA</p> <p>Laboratory results and trends on symptom improvement were not available for all patients (range missing data is N=21 to N=1).</p>	<p>Clinical outcomes</p> <p><u>Mortality (28-30 day)</u> Not reported</p> <p><u>Mortality (other), n/N (%)</u> I: 4/34 (11.7) C: 4/34 (11.7) Effect (95%CI): NR P= 1</p> <p><u>Duration of hospitalization</u> <i>Need for ICU admission, n/N (%)</i> I: 5/34 (14.7) C: 5/34 (14.7) Effect (95%CI): NR P= 1</p> <p><i>Length of ICU stay, median days (IQR)</i> I: 13 (8–18.5) C: 9 (6.5–19.5) Effect (95%CI): NR (-10.5 to 3.73) P= 0.53</p> <p><i>Length of hospital stay, mean days±SD</i> I: 12.18±4.64 C: 10.85±5.29</p>	<p><u>Definitions:</u> Not reported</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> It is not clear whether this study was blinded Allocation concealment is unclear Groups were different at baseline (e.g. medical history and symptoms) <p><u>Authors conclusion:</u> We did not find any therapeutic benefits for adalimumab in combination with remdesivir and dexamethasone in severe COVID-19 cases. It seems that increased levels of TNF-α may lead to better predictions of the efficacy of anti-TNF-α therapy. Our patients did not have increased levels of TNF-α despite being the severe cases of COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	presented in this paper.	<ul style="list-style-type: none"> patients receiving medications affecting IL-6 or TNF-α levels active peptic ulcer disease history of an allergic reaction to adalimumab or developing allergic reaction while receiving the medication mildly ill patients pregnancy or breastfeeding <p><u>N total at baseline:</u> N = 68 Intervention: 34 Control: 34</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 53.2 y (12.9) C: 56.1 y (11.5)</p> <p>Sex, n/N (%) male: I: 22/34 (65%) C: 18/34 (53%)</p> <p>Disease severity, mean (SD): Following symptoms at baseline are reported: fever, cough, dyspnoea, myalgia, chest pain, headache, diarrhoea and sore throat. Chest pain and myalgia were more reported in the control group (difference >10%) and vice versa for cough at baseline. For details, see Table 4 in Fakharian (2021).</p> <p>Groups comparable at baseline? Medical history was different between the treatment groups (more cases with hypertension, diabetes, ischemic heart disease etc. in the control group). Furthermore, symptoms</p>				<p>Effect (95%CI): NR (-1.08 to 3.73) P= 0.27</p> <p><u>Time to symptom resolution</u> <i>More than 50% improvement in chest CT scan, n/N (%)</i> I: 8/34 (23.5) C: 5/34 (14.7) Effect (95%CI): NR P= 0.74</p> <p><u>Respiratory support</u> <i>Mechanical ventilation requirement, n/N (%)</i> I: 4/34 (11.7) C: 3/34 (8.8) Effect (95%CI): NR P=1</p> <p><i>Need for NIV, n/N (%)</i> I: 4/34 (11.7) C: 2/34 (5.8) Effect (95%CI): NR P= 0.67</p> <p><i>Nasal/face mask or nasal oxygen, n/N (%)</i> I: 28/34 (82.3) C: 31/34 (91.1) Effect (95%CI): NR P= 0.42</p> <p>Safety <u>Adverse events</u> Not reported</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		at baseline were different between the groups.				Also available: laboratory results (WBC, D-Dimer, Ferritin, CRP, IL-6 and TNF- α , not available for all patients) and trend of symptom improvement (fever, cough, dyspnoea, myalgia, chest pain, headache, diarrhoea and sore throat, not available for all patients)	
6.2. Antibody JS016							
Dong, 2022	<p><u>Type of study:</u> Randomized controlled trial.</p> <p><u>Setting:</u> Three hospitals in Hebei and Heilongjiang Province, China.</p> <p><u>Country:</u> China.</p> <p><u>Source of funding:</u> This study was funded by the National Key Research and Development Program (2021YFC0863100) from the Ministry of Science and Technology of China, and Beijing Medical and Health Foundation Medical Science Research Fund (B17245-043). However, the</p>	<p>Hospitalized patients with moderate or severe COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients aged 18 to 85 years; • Hospitalized patients with confirmed moderate or severe COVID-19; • Patients who had a duration of symptoms of 7 days or less for moderate disease or a duration of severe disease of 4 days or less. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with critical disease. • Patients tested positive of SARS-CoV-2 specific immunoglobulin G (IgG) or immunoglobulin M (IgM) before enrollment. • Class III or IV heart failure; • Left ventricular ejection fraction lower than 30 percent; • Confirmed or suspected active tuberculosis; • Chronic renal failure requiring renal replacement therapy; • Malignancy; • Pregnancy; • Breastfeeding. 	<p>a single intravenous infusion of 50 mg/kgJS016</p> <p>+</p> <p>Standard care</p>	<p>Standard care</p> <p>Standard care was based on the Eight Edition of Clinical Practice of COVID-19 issued by the China National Health Commission.</p>	<p><u>Length of follow-up:</u> Data were collected on randomization and day 7, 14, 21, and 28 since randomization.</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: N = 1 (1%) Reasons: received convalescent plasma or antiviral drugs.</p> <p>Control: N = 1 (1%) Reasons: received convalescent plasma or antiviral drugs.</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality at 28 days</u> I: 1/99 (1%) C: 0/98 (0%) P=0.99</p> <p><u>Duration of hospitalization</u> <i>Length of hospital stay, median (IQR)</i> I: 13 (11-15) C: 14 (11-17) OR 0.55 (95% CI 0.13 to 2.31)</p> <p><u>Time to symptom resolution</u> <i>Clinical status on day 28, n/N (%)</i> 1: not hospitalized I: 95/99 (96%) C: 97/98 (99%) OR 0.55 (95% CI 0.13 to 2.31)</p> <p>2: hospitalized without supplemental oxygen I: 0/99 (0%) C: 0/98 (0%)</p> <p>3: hospitalized with supplemental oxygen</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Six-level scale of clinical status on 28 days (13-15), which was defined as follows: a score of 1 indicated not hospitalized; 2, hospitalized without supplemental oxygen; 3, hospitalized with supplemental oxygen; 4, hospitalized with noninvasive ventilation or high flow nasal cannula; 5, hospitalized with invasive ventilation or ECMO; and 6, death. <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • 28-day mortality, ventilator free days within 28 days, length of hospital stay, negative conversion rate of SARS-CoV-2 nucleic acid on day 14. Safety outcomes included allergic reaction, secondary infection, elevated alanine or aspartate transaminase, acute kidney injury, acute myocardial infarction, septic shock, and gastrointestinal bleeding. <p><u>Definitions:</u></p> <ul style="list-style-type: none"> • Patients aged 18 to 85 years; • Definitions of disease severity were based on the Eight Edition of Clinical

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>fundes did not have a role in study design, data collection and analysis, decision to publish, or preparation of the article.</p> <p><u>Conflicts of interest:</u> The authors declare that they have no competing interests.</p>	<p><u>N total at baseline:</u> N = 197 Intervention: N = 99 Control: N = 98</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 58 y (47-68) C: 61 y (51-67)</p> <p>Sex, n/N (%) male: I: 59/99 (60%) C: 47/98 (48%)</p> <p>Disease severity, n/N (%) with moderate disease: I: 86/99 (87%) C: 84/98 (86%)</p> <p>Groups comparable at baseline: yes, except for days since hospitalization and IgM antibodies</p>				<p>I: 1/99 (1%) C: 1/98 (1%)</p> <p>4: hospitalized with noninvasive ventilation or high flow nasal cannula I: 0/99 (0%) C: 0/98 (0%)</p> <p>5: hospitalized with invasive ventilation or ECMO I: 2/99 (2%) C: 0/98 (0%)</p> <p>6: death I: 1/99 (1%) C: 0/98 (0%)</p> <p>OR 0.31 (95% CI 0.03 to 3.19) P=0.33</p> <p><u>Invasive respiratory support</u> <i>Ventilator-free days within 28 days, median (IQR)</i> I: 28 (28-28) C: 29 (28-28) OR 0.57 (95% CI 0.27 to 1.24) P=0.16)</p> <p><u>Non-invasive respiratory support</u> Not reported.</p> <p>Safety <u>Serious adverse events</u></p> <p><u>Adverse events</u> <i>Any adverse event at day 28, n/N (%)</i></p>	<p>Practice of COVID-19 issued by China National Health Commission.</p> <ul style="list-style-type: none"> Moderate illness was defined as fever of respiratory symptoms with pulmonary infiltration. Severe illness was defined if patients presented with any of the following conditions: dyspnea or respiratory rate \geq 30 per minute; (2) arterial oxygen saturation \leq 93% on room air at sea level; (3) a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) \leq 300mmHg; (4) progressive exacerbation of symptoms, and pulmonary infiltration progressing by more than 50 percent within 24-48 hours. SARS-CoV-2 nucleic acid was defined as negative if both ORF and N gene turned negative. <p><u>Remarks:</u> None.</p> <p><u>Authors conclusion:</u> Our multicenter, open-label, randomized, controlled trial did not show clinical or virological efficacy of JS016 among Chinese hospitalized patients with moderate or severe COVID-19 illness. Potential benefits remain to be evaluated among groups of patients specified by disease course and severity. Further studies might be needed to assess the efficacy of the neutralizing antibody to prevent disease deterioration.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I: 3/99 (3%) C: 1/98 (1%) OR 3.16 (95% CI 0.30 to 33.64) P=0.34 A detailed record of all adverse events is reported in the article. Virological outcomes <u>Viral clearance</u> <i>Negative conversion rate of SARS-CoV-2 nucleic acid on day 14, n/N (%)</i> I: 80/97 (82%) C: 76/97 (79%) Or 1.35 (95% CI 0.65 to 2.83) <i>ORF gene negative at day 14, n/N (%)</i> I: 80/97 (82%) C: 77/97 (79%) OR 1.27 (95% CI 0.60 to 2.68) <i>N gene, negative at day 14, n/N (%)</i> I: 80/97 (82%) C: 76/97 (78%) OR 1.35 (95% CI 0.65 to 2.83)	
6.3. Anti-granulocyte-macrophage colony-stimulating-factor (anti-GM-CSF)							
Criner, 2022	<u>Type of study:</u> A randomized, multicenter, double-blind, placebo-controlled trial. <u>Setting:</u> Hospitalized patients, between	Hospitalized patients with hypoxemia <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Serum C-reactive protein (CRP) ≥ 50 mg/L or ferritin $\geq 1,000$ ng/mL based on local laboratory measurements 	Gimsilumab: 400 mg was administered intravenously on day 1, and gimsilumab 200 mg was administered intravenously on day 8. The day 8 dose was omitted if the patient was	Placebo: placebo saline was administered intravenously on day 1, and placebo saline was administered	<u>Length of follow-up:</u> 24 weeks <u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: N=7 (6.1%) Reasons: withdrawal by subject (n=2),	Clinical outcomes <u>Mortality (43 day):</u> Mortality, n/N (%): I: 32/113 (28.3%) C: 26/112 (26%) P=0.377 <u>Duration of hospitalization</u> Time to hospital discharge by end of study	Primary outcome: <ul style="list-style-type: none"> Rate of all-cause mortality at day 43 Secondary outcome(s): <ul style="list-style-type: none"> Proportion of patients who survived and were free of invasive ventilation at day 29 Number of invasive ventilator-free days through day 29 Time to hospital discharge

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>April 15, 2020, and October 12, 2020 (BREATHE study)</p> <p><u>Country:</u> 21 hospitals, United States</p> <p><u>Source of funding:</u> The BREATHE study was funded by Kinevant Sciences (Kinevant), a wholly-owned subsidiary of Roivant Sciences (Roivant).</p> <p><u>Conflicts of interest:</u> Transparently reported.</p>	<ul style="list-style-type: none"> Radiographic evidence of bilateral infiltrates, and (4) clinical evidence of substantial hypoxemia [defined as (A) requiring ≥ 4L supplemental O₂ to attempt to maintain $\geq 92\%$ SpO₂, or (B) measured or imputed^{22,23} PaO₂/FiO₂ ≤ 300 mmHg] or acute respiratory distress syndrome (ARDS) per the Berlin definition <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Evidence of multi-organ failure or had received mechanical ventilation for >72 hours <p>The full list of entry criteria is described in the Protocol</p> <p><u>N total at baseline:</u> N = 227 Intervention: N=114 Control: N=113</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 59.9 y (14.7) C: 60.4 y (14.3)</p> <p>Sex, n/N (%) male: I: 73/113 (64.4%) C: 81/112 (72.3%)</p> <p>Disease severity: Illness severity by National Early Warning Score, mean (SD) I: 6.1 (2.3) C: 5.8 (3.0)</p> <p>Groups are comparable at baseline</p>	discharged or no longer required supplemental oxygen	<p>intravenously on day 8.</p> <p>The day 8 dose was omitted if the patient was discharged or no longer required supplemental oxygen</p> <p><i>Medication use before and during the study is reported in the article.</i></p>	<p>adverse event (n=1), 1 protocol violation (n=1), lost to follow-up (n=3)</p> <p>Control: N=6 (5.3%) Reasons: withdrawal by subject (n=3), lost to follow-up (n=3)</p>	<p>HR 1.0 (0.71-1.33)</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Invasive respiratory support</u> Ventilator-free survival rate at day 29, difference (95%CI) 0.02 (-0.09 – 0.14) Favors Gimsilumab</p> <p>Safety <u>Serious adverse events</u> Patients with at least one SAE, n/N (%) I: 47/113 (41.6%) C: 45/112 (40.2)</p> <p>*The full list of adverse events can be consulted in the original publication of the study.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	<p><u>Definitions:</u></p> <p><u>Remarks:</u> Standard of care was not described.</p> <p>Enrollment was halted early for futility based on an interim analysis.</p> <p>High background use of corticosteroids and anticoagulants.</p> <p><u>Authors conclusion:</u> Gimsilumab did not improve mortality or other key clinical outcomes in patients with COVID-19 pneumonia and evidence of systemic inflammation. The utility of anti-GM-CSF therapy for COVID-19 remains unclear.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
6.4. Bamlanivimab (INN, codenamed LY-CoV555, neutralizing monoclonal antibody)							
Lundgren, 2021	<p><u>Type of study:</u> Multigroup, multistage, double-blind randomized, placebo-controlled, clinical trial</p> <p><u>Setting:</u> Multicentre trial, 5 August - 13 October 2020</p> <p><u>Country:</u> 23 trial sites in the USA; 7 trial sites in Denmark; 1 trial site in Singapore.</p> <p><u>Source of funding:</u> Primary funding source: U.S. government Operation Warp Speed and National Institute of Allergy and Infectious Diseases with the support of grant U01-AI136780 from the National Institute of Allergy and ...</p> <p><u>Conflicts of interest</u> <i>Disclosures can be viewed at online version</i></p>	<p>Adult hospitalized patients with COVID-19 without end organ failure.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age ≥ 18 years; Informed consent by the patient or the patient's legally-authorized representative SARS-CoV-2 infection, documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator; Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator; Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Prior receipt of: <ul style="list-style-type: none"> Any SARS-CoV-2 hVIG, convalescent plasma from a person who recovered from COVID-19 or 	<p>bamlanivimab (7000 mg) single intravenous infusion over a 1-hour period on the day of randomization</p> <p>**All patients received high-quality supportive care as background therapy, including remdesivir and, when indicated, supplemental oxygen and glucocorticoids.</p> <p>*** bamlanivimab or placebo was administered as a single intravenous infusion over a 1-hour period.</p>	<p>Placebo</p> <p>**All patients received high-quality supportive care as background therapy, including remdesivir and, when indicated, supplemental oxygen and glucocorticoids.</p> <p>*** bamlanivimab or placebo was administered as a single intravenous infusion over a 1-hour period.</p>	<p><u>Length of follow-up:</u> 90 days</p> <p><u>Loss-to-follow-up:</u> Intervention: 19/163 (11.7%) Reasons (not reported)</p> <p>Control: 15/151 (9.9%) Reasons (not reported)</p>	<p><u>Clinical outcomes</u> <u>Sustained Recovery at 90 days, Overall</u> I: 144/163 (88%) C: 136/151 (90.1%) sHR 0.99 (95% CI, 0.79 to 1.22) P = 0.89</p> <p><u>Mortality (90 day)</u> I: 13/163 (8%) C: 11/151 (7%) HR, 1.09 [CI, 0.49 to 2.43]</p> <p><u>Duration of hospitalization</u> not reported</p> <p><u>Time to symptom resolution</u> Median time to sustained recovery: 19 days sHR, 0.99 [95% CI, 0.79 to 1.22]</p> <p><u>Respiratory support</u> Ordinal scale for primary pulmonary outcome 1 I:19 C:23.2 2 I:31.3 C:29.8 3 I:18.4 C:21.9 4 I:11 C:7.3 5 I:14.7 C:14.6 6 I:7.9 C:3.3 7 I:0.6 C:0.0 Odds Ratio, Adjusted* 0.86 (95% CI: 0.57 to 1.30), P=0.48</p> <p><u>Safety</u> <u>Adverse events</u></p>	<p><u>Definitions:</u> <u>"pulmonary" ordinal outcome:</u> 1. Can independently undertake usual activities with minimal or no symptoms 2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above pre-morbid requirements) 3. Supplemental oxygen (<4 liters/min, or <4 liters/min above pre-morbid requirements) 4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above pre-morbid requirements, but not high-flow oxygen) 5. Non-invasive ventilation or high-flow oxygen 6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy 7. Death <u>"pulmonary+" ordinal outcome:</u> 1. Can independently undertake usual activities with minimal or no symptoms 2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above pre-morbid requirements) 3. Supplemental oxygen (<4 liters/min, or <4 liters/min above pre-morbid requirements) 4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above pre-morbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> ○ SARS-CoV-2 nMAb at any time prior to hospitalization; • Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5; • In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol-specified assessments; • Expected inability to participate in study procedures; • Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through Day 90 of the study. • Men who are unwilling to abstain from sexual intercourse with women of child-bearing potential or who are unwilling to use barrier contraception through Day 90 of the study. <p><u>N total at baseline:</u> N =326 Intervention: 169 Control: 157 <u>ITT</u> N =314</p>				<p>SAE I: 9/163 (5.5%) C: 12/151 (7.9%) HR 0.70 (95% CI 0.29, 1.65) P= 0.41</p> <p>Virological outcomes <u>Viral clearance</u> Subgroup analysis is available at study entry: nAb status and levels of viral measures (plasma antigen and nasal viral RNA)</p> <p><i>Subgroup analysis is also available for Sustained recovery at figure. Additional analysis available at supplementary.</i></p>	<p>infarction, myocarditis, pericarditis, new onset CHF NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events. 5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14) 6. Invasive ventilation, ECMO or mechanical circulatory support; vasopressor therapy; or new receipt of renal replacement therapy 7. Death</p> <p><u>Remarks:</u> Subgroup analysis of a trial prematurely stopped because of futility; small sample size; multiple subgroups analyzed.</p> <p><u>Authors conclusion:</u> Efficacy and safety of bamlanivimab may differ depending on whether an endogenous nAb response has been mounted. The limited sample size of the study does not allow firm conclusions based on these findings, and further independent trials are required that assess other types of passive immune therapies in the same patient setting.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Intervention: 163 Control: 151</p> <p><u>Important characteristics:</u> Age, Median (IQR): 61 (49–71) I: 63 y (50-72) C: 59 y (48-71)</p> <p>Sex, n/N (%) female: I: 66/153 (40%) C: 71/151 (47%)</p> <p>Disease severity, mean (SD): <i>Defined by Oxygen Requirement</i> Not receiving supplemental oxygen I: 44 (27%) C: 42 (28%) Supplemental oxygen < 4 L/min* I: 60 (37%) C: 56 (37%) Supplemental oxygen ≥ 4 L/min* I: 29 (18%) C: 35 (23%) Non-invasive ventilation or HFNC I: 30 (18%) C: 18 (12%) Invasive ventilation or ECMO I: 0 (0%) C: 0 (0%)</p> <p>Groups comparable at baseline? Yes</p>					
Chen, 2021	<p><u>Type of study:</u> Randomized, double-blind, placebo-controlled, single-dose trial</p> <p><u>Setting:</u> 41 centers in the United States</p> <p><u>Country:</u> United States of America</p> <p><u>Source of funding:</u></p>	<p>Patients with positive results on testing for SARS-CoV-2 and presented one or more mild to moderate symptoms, not hospitalized</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age >18 y • Currently not hospitalized; • Have one or more mild to moderate COVID-19; symptoms (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, 	<p>Single intravenous infusion of neutralizing antibody LY-CoV555, 3 different doses:</p> <p>Intervention 1: 700 mg (n=101) Intervention 2: 2800 mg (n=107) Intervention 3: 7000 mg (n=101)</p>	Placebo	<p><u>Length of follow up:</u> Primary outcome was the change from baseline in the SARS-CoV-2 viral load at day 11 (±4 days). Data regarding virologic features and symptoms were collected up to day 29 in this trial.</p> <p><u>Loss to follow-up:</u> No lost to follow-up reported.</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> There were no deaths during the trial</p> <p><u>Hospitalization at day 29, n/N (%)</u> Intervention1: 1/101 (1.0%) Intervention2: 2/107 (1.9%) Intervention3: 2/101 (2.0%)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> The data regarding symptoms (as measured by the change from baseline in the symptom score) were also consistent with the hospitalization results, with findings that supported a possible reduction in symptom severity as early as day 2 in the LY-CoV555 group. This effect was maintained over</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Not reported.	<p>shortness of breath with exertion);</p> <ul style="list-style-type: none"> • Sample collection for first positive SARS-CoV-2 viral infection determination <3 days prior to start of the infusion; • Males or non-pregnant woman; • Understanding and agreement to comply with planned study procedures; • Agreement for collecting nasopharyngeal swabs and venous blood; • Signed informed consent. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Have SpO2 ≤93% on room air at sea level or PaO2/Fio2 <300, respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute; • Require mechanical ventilation or anticipated impending need for mechanical ventilation; • Have known allergies to any of the components used in the formulation of the interventions; • Have hemodynamic instability requiring use of pressors within 24 hours of randomization; • Suspected or proven serious, active bacterial, fungal, viral, or other infection that in the opinion of the investigator could constitute a risk when taking intervention; • Have any co-morbidity requiring surgery within <7days, or that is considered life-threatening within 29 days; • Have any serious concomitant systematic disease, condition or 				<p>Pooled doses: 5/309 (1.6%) Control: 9/143 (6.3%)</p> <p><u>Mean change from baseline in viral load at day 11 (95% CI)</u> Intervention1: -3.67 Intervention2: -4.00 Intervention3: -3.38 Pooled doses: -3.70 Control: -3.47</p> <p>Int1 vs control MD= -0.20 (95% CI= -0.66 to 0.25) Int2 vs control MD= -0.53 (95% CI= -0.98 to -0.08) Int3 vs control MD= 0.09 (95% CI= -0.37 to 0.55) Pooled MD= -0.22 (-0.60 to 0.15)</p> <p><u>Mean change from baseline in viral load at day 3 (95% CI)</u> Intervention1: -1.27 Intervention2: -1.50 Intervention3: -1.27 Pooled doses: -1.35 Control: -0.85</p> <p>Int1 vs control MD= -0.42 (95% CI= -0.89 to 0.06) Int2 vs control MD= -0.64 (95% CI= -1.11 to -0.17) Int3 vs control MD= -0.42 (95% CI= -0.90 to 0.06) Pooled MD= -0.49 (95% CI= -0.87 to -0.11)</p> <p><u>Mean change from baseline in viral load at day 7 (95% CI)</u></p>	<p>time and across doses, which further supports the validity of a treatment effect on symptoms and suggests a mechanistic link between a lower viral load and a lower frequency of hospitalization. Although the differences in the effects of the three doses of LY-CoV555 were not clear, the 2800-mg dose was the only one to show evidence of accelerated viral clearance. Nevertheless, further studies should continue to assess the efficacy of lower doses. The safety profile of patients who received LY-CoV555 was similar to that of placebo-treated patients. These data indicate that the treatment is safe. In this interim analysis, the patients who received LY-CoV555 had fewer hospitalizations and a lower symptom burden than those who received placebo, with the most pronounced effects observed in high-risk cohorts. If these results are confirmed in additional analyses in this trial, LY-CoV555 could become a useful treatment for emergency use in patients with recently diagnosed Covid-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>disorder that, in the opinion of the investigator, should preclude participation in this study.</p> <p>*For other exclusions see chapter 5.2 of the <u>study protocol</u></p> <p><u>N total at baseline:</u> N = 452 Intervention1: N = 101 Intervention2: N = 107 Intervention3: N = 101 Control: 143</p> <p><u>Important characteristics:</u> Age, median (range): I: 45 y (18-86) C: 46 y (18-77)</p> <p>Sex, n/N (%) female: I: 171/309 (55.3%) C: 78/143 (54.5%)</p> <p>Mild disease status, n/N (%) I: 232/309 (75.1%) C: 113/143 (79.0%)</p> <p>Moderate disease status, n/N (%) I: 77/309 (24.9%) C: 30/143 (21.0%)</p> <p>Number of days since onset of symptoms, median: I: 4.0 days C: 4.0 days</p> <p>Viral load – cycle threshold of the reverse-transcriptase-polymerase-chain-reaction assay, mean: I: 23.9 C: 23.8</p>				<p>Intervention1: -2.82 Intervention2: -3.01 Intervention3: -2.85 Pooled doses: -2.90 Control: -2.56</p> <p>Int1 vs control MD= -0.25 (95% CI= -0.73 to 0.23) Int2 vs control MD= -0.45 (95% CI= -0.92 to 0.03) Int3 vs control MD= -0.28 (95% CI= -0.77 to 0.20) Pooled MD= -0.33 (95% CI= -0.72 to 0.06)</p> <p><u>Safety: Serious adverse events, n/N (%)</u> Intervention1: 0/101 Intervention2: 0/107 Intervention3: 0/101 Pooled doses: 0/309 Control: 1/143 (0.7%) *The serious adverse event in the placebo group was upper abdominal pain.</p> <p><u>Safety: Any adverse event, n/N (%)</u> Intervention1: 24/101 (23.8%) Intervention2: 23/107 (21.5%) Intervention3: 22/101 (21.8%) Pooled doses: 69/309 (22.3%) Control: 35/143 (24.5%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline? Yes					
Lundgren, 2020	<p>Type of study: Multigroup, multistage, double-blind randomized controlled trial.</p> <p>Setting: Hospital</p> <p>Country: 23 trial sites in the USA; 7 trial sites in Denmark; 1 trial site in Singapore.</p> <p>Source of funding: Not reported</p>	<p>Hospitalized COVID-19 patients</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Age ≥ 18 years; Informed consent by the patient or the patient's legally-authorized representative SARS-CoV-2 infection, documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator; Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator; Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19, per the responsible investigator, and NOT for purely public health or quarantine purposes. <p>Exclusion criteria: Prior receipt of:</p> <ul style="list-style-type: none"> Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from COVID-19 or • SARS-CoV-2 nMAb at any time prior to hospitalization; 	<p>7000 mg LY-CoV555 *7000 mg was chosen on the basis of pharmacokinetic and preliminary safety data</p> <p>**All patients received high-quality supportive care as background therapy, including remdesivir and, when indicated, supplemental oxygen and glucocorticoids.</p> <p>***LY-CoV555 or placebo was administered as a single intravenous infusion over a 1-hour period.</p>	<p>Placebo</p> <p>*All patients received high-quality supportive care as background therapy, including remdesivir and, when indicated, supplemental oxygen and glucocorticoids.</p> <p>**LY-CoV555 or placebo was administered as a single intravenous infusion over a 1-hour period.</p>	<p>Length of follow up: At least 28 days</p> <p>Loss to follow-up: No lost to follow-up reported.</p>	<p>Clinical outcomes</p> <p>Mortality (through oct. 26), n/N (%) I: 9/163 (6%) C: 5/151 (3%) Comparison: <i>Pre-specified analysis:</i> Rate ratio= 2.00 (95% CI= 0.67 to 5.99) P=0.22</p> <p>Mortality through day 28, n/N (%) I: 6/163 (3.7%) C: 4/151 (2.6%)</p> <p><i>No adj or stratify:</i> Rate ratio= 1.75 (95% CI= 0.59 to 5.24) <i>Adjusted:</i> Rate ratio= 1.96 (95% CI= 0.64 to 5.97) 2.00 (95% CI= 0.67 to 5.99)</p> <p>Sustained recovery through oct. 26, n/N (%) I: 71/87 (82%) C: 64/81 (79%) Rate ratio= 1.06 (95% CI= 0.77 to 1.47)</p> <p>Hospital discharge at 28 days follow-up, n/N (%) I: 143/163 (88%) C: 136/151 (90%) <i>Pre-specified analysis:</i> Rate ratio= 0.97 (95% CI= 0.78 to 1.20).</p>	<p>Definitions: -</p> <p>Remarks:</p> <ul style="list-style-type: none"> Adjusted rate ratio: adjustment for baseline risk score in addition to covariates in primary analysis. Dates of organ dysfunction events and serious infections are reported at the time of hospital discharge or death. These data are currently missing for 11 participants given LY-CoV555 and 10 participants given placebo. All other events are reported through Day 28. <p>Authors conclusion: "Monoclonal antibody LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure."</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5; • In the opinion of the responsible investigator, any condition for which, participation would not be in the best interest of the participant or that could limit protocol-specified assessments; • Expected inability to participate in study procedures; • Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through Day 90 of the study. • Men who are unwilling to abstain from sexual intercourse with women of child-bearing potential or who are unwilling to use barrier contraception through Day 90 of the study. • [stage 1 only] Presence at enrollment of any of the following: a. stroke b. meningitis c. encephalitis d. myelitis e. myocardial infarction f. myocarditis g. pericarditis h. symptomatic congestive heart failure (NYHA class III-IV) i. arterial or deep venous thrombosis or pulmonary embolism 9. • [stage 1 only] Current or imminent requirement for any 				<p><i>No adj or stratify: Rate ratio= 0.93 (95% CI= 0.75 to 1.16)</i> <i>Adjusted: Rate ratio= 1.05 (95% CI= 0.84 to 1.31)</i></p> <p><u>Organ dysfunction events, n/N (%)</u> I: 24/163 (15.8%) C: 18/151 (12.8%)</p> <p><u>Serious co-infections, n/N (%)</u> I: 4/163 (2.6%) C: 4/151 (2.8%)</p> <p><u>Safety</u> <i>Composite safety outcome through day 28, n/N (%)</i> I: 38/163 (23%) C: 30/151 (20%) Rate ratio= 1.22 (95% CI= 0.75 to 1.98) P=0.42</p> <p><i>Composite safety outcome, organ dysfunction, or serious coinfection through day 28, n/N (%)</i> I: 49 /163(30%) C: 37/151 (25%) Rate ratio= 1.25 (95% CI= 0.81 to 1.93) P=0.31</p> <p><i>*Most of the organ-dysfunction (10% and 11% respectively), whereas other rarer events (i.e. seen in <4%) were thromboembolic events, acute delirium, and hypotension leading to</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>of the following: a. invasive mechanical ventilation b. ECMO c. mechanical circulatory support d. vasopressor therapy e. commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy).</p> <p><u>N total at baseline:</u> N = 314 Intervention: 163 Control: 151</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 63 y (50-72) C: 59 y (48-71)</p> <p>Sex, n/N (%) male: I: 97/163 (60%) C: 80/151 (53%)</p> <p>Oxygen requirement, n (%): <i>None</i> I: N = 44 (27%) C: N = 42 (28%)</p> <p><4 liter/min I: N = 60 (37%) C: N = 57 (38%)</p> <p>>4 liter/min I: N = 29 (18%) C: N = 34 (23%)</p> <p>Groups comparable at baseline? Yes</p>				<p><i>vasopressor treatment. Intercurrent serious coinfection was seen in only 3% of the cohort.</i></p> <p><u>Serious adverse events, n/N (%)</u> I: 5/163 (3.1%) C: 5/151 (3.3%)</p>	
6.5. Bamlanivimab and Etesevimab (LY-CoV016; recombinant fully human monoclonal neutralizing antibody; together is combination of two monoclonal antibodies)							
Chen, 2022 (BLAZE-1 trial)	<u>Type of study:</u> Double-blind, placebo-controlled,	Symptomatic patients with mild to moderate COVID-19 and	Bamlanivimab + etesevimab	Placebo	<u>Length of follow-up:</u> 85 days	Clinical outcomes Mortality Not reported.	Chen, 2022 (BLAZE-1 trial)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>randomized, controlled phase 3 trial</p> <p><u>Setting:</u> Outpatient setting, 104 trial sites in the USA, between December 9, 2020, and January 7, 2021</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> Funded by Eli Lilly and Company.</p> <p><u>Conflicts of interest:</u> Most of the authors are employees and shareholders of Eli Lilly and Company. Furthermore, several authors reported grants or payment from pharmaceutical companies.</p>	<p>increased risk for severe illness in outpatient setting</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ambulatory adolescent (12-17 y) and adult (≥ 18 y) • ≥ 1 risk factor for progression to severe COVID-19 • presented ≤ 3 days of the positive test (RT-PCR or direct antigen test); • ≥ 1 mild or moderate COVID-19 symptom(s) <p>Full list is available online in the supplementary materials.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • ≥ 1 dose of a COVID-19 vaccine • SpO₂ $\leq 93\%$ or PaO₂/FIO₂ < 300, respiratory rate ≥ 30/min, heart rate ≥ 125/min • require mechanical ventilation or anticipated need for it • known allergies to any components of the interventions • hemodynamic instability within 24 hours of randomization • serious active infection that could be of risk when taking the intervention • comorbidity requiring surgery within 7 days/is life threatening within 29 days • serious concomitant systemic disease, condition or disorder • pregnant or breast feeding 	<p>Single intravenous infusion of 700 mg bamlanivimab and 1400 mg etesevimab together. Each patient was infused within 3 days of their first positive test and was monitored for ≥ 1 hour post infusion.</p>	<p>0.9% sodium chloride solution. Each patient was infused within 3 days of their first positive test and was monitored for ≥ 1 hour post infusion.</p>	<p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: NR Reasons: NA</p> <p>Control: NR Reasons: NA</p> <p>The first interim database lock occurred when patients reached day 29 (safety population: placebo n = 258, bamlanivimab and etesevimab n = 511; efficacy population: placebo n = 258, bamlanivimab and etesevimab n = 510). The second interim database lock occurred when patients reached day 85 (efficacy population: placebo n = 258, bamlanivimab and etesevimab n = 513).</p>	<p><u>Duration of hospitalization</u> Days, mean (SD)</p> <p><i>At day 29</i> I: 7.3 (3.3) C: 13.5 (7.5) $p = 0.161$</p> <p><i>At day 85</i> I: 7.3 (3.3) C: 14.5 (9.1) $p = 0.165$</p> <p><u>Time to symptom resolution</u> By day 29 and day 85, a higher proportion of patients in the bamlanivimab and etesevimab treatment group experienced sustained resolution of each symptom compared with the placebo group (Figure 3). At day 29 and day 85, the median time to first sustained symptom resolution was significantly decreased among the bamlanivimab and etesevimab group compared with placebo for body aches and pain ($P = .007$ and $P = .022$, respectively), chills ($P = .001$ and $P = .003$), fatigue ($P = .01$ and $P = .009$), feeling feverish ($P = .016$ and $P = .02$), headache ($P = .009$ and $P = .018$), and</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Full list is available online in the supplementary materials.</p> <p><u>N total at baseline:</u> Randomized: N = 769 Intervention: 511 Control: 258</p> <p><u>Important characteristics:</u> Age, median (range): I: 57 y (12-93) C: 55 y (13-89)</p> <p>Sex, n/N (%) male: I: 247/511 (48.3%) C: 114/258 (44.2%)</p> <p>Disease severity, n (%): <i>Mild:</i> I: 380/511 (74.4%) C: 202/258 (78.3%)</p> <p><i>Moderate</i> I: 131/511 (25.6%) C: 56/258 (21.7%)</p> <p>High-risk status for severe COVID-19 illness <i>High</i> I: 485/511 (94.9%) C: 247/258 (95.7%)</p> <p><i>Low</i> I: 26/511 (5.1%) C: 11/258 (4.3%)</p> <p>Groups were comparable at baseline.</p>				<p>shortness of breath (P = .016 and P = .022).</p> <p><u>Invasive respiratory support</u> <u>Mechanical ventilation</u> I: 0/511 (0%) C: 1/258 (0.4%)</p> <p><u>Non-invasive respiratory support</u> <u>Supplemental oxygen therapy</u> <i>At day 29</i> I: 1/511 (0.2%) C: 9/258 (3.5%) p = 0.003</p> <p><i>At day 85</i> I: 1/511 (0.2%) C: 10/258 (3.0%) p = 0.002</p> <p><u>Other</u> A total of 5 patients were admitted to the ICU (1 from the bamlanivimab and etesevimab group and 4 from the placebo group). Treatment with bamlanivimab and etesevimab together significantly reduced the time to admission to ICU compared with placebo (P = .027).</p> <p><u>Safety</u> A total of 16 grade 3 or 4 adverse events (7 in the convalescent-plasma group and 9 in the control plasma group) occurred in</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						participants who were not hospitalized. Virological outcomes Not reported.	
Dougan, 2021a BLAZE-I trial	<p><u>Type of study:</u> RCT, phase 2/3, double-blind, placebo-controlled</p> <p><u>Setting:</u> Outpatient setting, between 09 December 2020 - 07 January 2021.</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> Eli Lilly and Company</p> <p><u>Conflicts of interest:</u> Most of the authors are employees and shareholders of Eli Lilly and Company. Furthermore, several authors reported grants or payment from pharmaceutical companies.</p>	<p><u>Non-hospitalized adolescents and adults with COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Ambulatory adolescents (12-17 years) and adults (≥18 years); ≥1 risk factor for progression to severe illness* presented ≤ 3 days of the positive test (RT-PCR or direct antigen test); ≥1 mild or moderate COVID-19 symptom(s) <p><i>*Full list is available online in the supplementary materials</i></p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> SpO₂ ≤ 93% or PaO₂/FiO₂ < 300, respiratory rate ≥30/min, heart rate ≥125/min; Require mechanical ventilation or anticipated need for it; Known allergies to any components of the interventions; Hemodynamic instability within 24 hours of randomization; Serious active infection that could be of risk when taking the intervention; Co-morbidity requiring surgery within 7 days/is life threatening within 29 days; Serious concomitant systemic disease, condition or disorder; Pregnant or breast feeding. <p><i>*Full list is available online in the supplementary materials.</i></p>	<p>Bamlanivimab and etesevimab (together)</p> <p>Single intravenous (IV) infusion of 700 mg bamlanivimab and 1400 mg etesevimab. Each patient was infused within 3 days of their first positive test and was monitored for ≥1 hour post infusion.</p>	<p>Placebo</p> <p>0.9% sodium chloride solution. Each patient was infused within 3 days of their first positive test and was monitored for ≥1 hour post infusion.</p>	<p><u>Length of follow-up:</u> 29 days</p> <p><u>Loss-to-follow-up:</u> Intervention: 3 (1,2%)</p> <p>Control: 0</p> <p><u>Incomplete outcome data:</u> Intervention: NR Reasons: NA</p> <p>Control: NR Reasons: NA</p>	<p>Clinical outcomes <u>Mortality (28-30 day), n/N (%)</u> I: 0/511 (0) C: 4/258 (1.6) Effect (95%CI): NR P=NR</p> <p><u>COVID-19-related hospitalization or all-cause deaths (29-day), n/N (%)*</u> I: 4/511 (0.8) C: 15/258 (5.8) Difference (95%CI): -5.0 (-8.0 to -2,1) P<0.001</p> <p><i>*Subgroup analysis are available for age and BMI.</i></p> <p><u>COVID-19-related hospitalization, emergency room visit or death, n/N (%)</u> I: 6/511 (1.2) C: 15/258 (5.8) Difference (95%CI): -4.6 (-7.6 to -1.6) P<0.001</p> <p><u>Duration of hospitalization</u> Not reported</p> <p><u>Time to symptom resolution</u> <i>Sustained symptom resolution, days (95%CI)</i> I: 8.0 (7.0 to 9.0) C: 9.0 (9.0 to 10.0)</p>	<p><u>Definitions:</u> <i>Sustained symptom resolution</i> Two consecutive assessments with a score of 0 for shortness of breath, feeling feverish, body aches and pains, sore throat, chills, and headache; and a score of 0 or 1 for fatigue or cough. <i>SARS-CoV-2 clearance (yes/no)</i> Two consecutive negative tests for the SARS-CoV-2 virus.</p> <p><u>Remarks:</u> The study was sponsored by Eli Lilly and company. Furthermore, large part of the authors is employee and shareholder at Eli Lilly and company. Eli Lilly and company designed the study, provided assistance with data acquisition and carried out statistical analyses. This might have had introduced risk of bias.</p> <p>No intention to treat analysis, patients receiving other intervention than randomized were excluded from analysis.</p> <p>There was a 1:2 randomization between placebo and antibody treatment.</p> <p><u>Authors conclusion:</u> Overall, data from this portion of BLAZE-1 confirm the efficacy of 700/1400mg of bamlanivimab and etesevimab on both clinical and viral outcomes in high-risk patients with mild-to-moderate COVID-19 and</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>N total at baseline:</u> N = 769 (782 randomized) Intervention: 511 (520 randomized) Control: 258 (262 randomized)</p> <p><u>Important characteristics:</u> Age, median (range): 56 (12-93) I: 57 y (12-93) C: 55 y (13-89)</p> <p>Sex, n/N (%) male: 361 (46.9) I: 247/511 (48.3%) C: 114/258 (44.2%)</p> <p>Disease severity, n (%): <i>No definition reported</i> <i>Mild: 582 (75.7)</i> I: 202 (78.3) C: 380 (74.4) <i>Moderate: 187 (24.3)</i> I: 56 (21.7) C: 131 (25.6)</p> <p>High-risk status for severe COVID-19 illness <i>No definition reported</i> <i>High: 732 (95.2)</i> I: 247 (95.7) C: 485 (94.9) <i>Low: 37 (4.8)</i> I: 11 (4.3) C: 26 (5.1)</p> <p>Groups comparable at baseline? Yes</p>				<p>HR (95%CI): 1.1 (NR) P=0.13</p> <p><u>Respiratory support</u> Not reported</p> <p>Safety* <u>Serious Adverse events, n/N (%)</u> I: 6/511 (1.2) C: 2/258 (0.8)</p> <p><u>Treatment emergent adverse events, n/N (%)</u> <i>Total</i> I: 46/511 (9.0) C: 25/258 (9.7)</p> <p><i>Mild</i> I: 26/511 (5.1) C: 15/258 (5.8)</p> <p><i>Moderate</i> I: 16/511 (3.1) C: 8/258 (3.1)</p> <p><i>Severe</i> I: 4/511 (0.8) C: 1/258 (0.4)</p> <p><i>*list of adverse events is available online in the supplementary material.</i></p> <p>Virological outcomes <u>Viral clearance</u> I: NR C: NR HR (95%CI): NR P=0.185</p> <p><u>Reduction in viral load from T0 to day 7</u> I: NR</p>	<p>support the use of this dose in the ongoing fight against COVID-19. The utility of bamlanivimab and etesevimab together, as well as other antibodies and antibody combinations, can clearly be impacted by the development of resistant viral variants. Due to the prevalence of specific resistant variants, the distribution of bamlanivimab and etesevimab was temporarily restricted in the United States between June-September, 2021. Regardless, as the pandemic evolves globally and the burden on health care settings continues, reducing deaths, hospitalizations and clinical severity of disease will be crucial.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: NR Difference (95%CI): -0.99 (-1.3 to -0.66) P=<0.0001</p> <p><u>Persistent high viral load, n/N (%)</u> I: 76/510 (14.9) C: 106/258 (41.1) Difference (95%CI): -26.2 (-32.9 to -19.4) P<0.0001</p> <ul style="list-style-type: none"> Also available: time to first symptom improvement (no HR reported), time to first symptom resolution (no HR reported), time to complete symptom resolution (no HR reported) and time to sustained complete symptom resolution (no HR reported) and post-hoc analysis on persistent high viral load and hospitalization/ death. 	
Dougan, 2021b	<p><u>Type of study:</u> RCT, phase 2-3, randomized, double-blind, placebo-controlled, single-dose trial</p> <p><u>Setting:</u> Ambulatory setting, between 4 September and 8 December 2020</p> <p><u>Country:</u></p>	<p>Ambulatory patients with mild or moderate Covid-19 within 3 days after they had tested positive for SARS-CoV-2</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> ≥12 years of age at the time of screening Ambulatory patients who were 12-17 years of age and who had at least one of the following risk factors: <ul style="list-style-type: none"> a BMI in at least the 85th percentile for age and sex, 	<p>Single intravenous infusion of bamlanivimab and etesevimab</p> <p>Single intravenous infusion of a neutralizing monoclonal-antibody combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together) within 3 days after a laboratory diagnosis of SARS-CoV-2 infection.</p>	<p>Placebo (intravenous)</p> <p>Single intravenous infusion of placebo within 3 days after a laboratory diagnosis of SARS-CoV-2 infection.</p>	<p><u>Length of follow-up:</u> 29 days</p> <p><u>Loss-to-follow-up:</u> 62 Intervention: 26/518 (5.0%) Reasons (describe): - did not complete the 29-day treatment period, - did not yet transition to follow-up period,</p>	<ul style="list-style-type: none"> Subgroup analysis for adolescents (12-17) and adults (≥18 years) <p>Clinical outcomes <u>Mortality (day 29)</u> I: 0/518 (2.1%) C: 10/517 (7.0%) RR: 0.05 (95%CI 0.00 to 0.81)</p> <p><u>Hospitalization</u> I: 11/518 (2.1%) C: 33/517 (6.4%)</p>	<p><u>Definitions:</u> Difference between mild and moderate Covid-19 was not defined. Persistently high SARS-CoV-2 viral load: a log viral load >5.27, corresponding to a mean PCR cycle-threshold [Ct] value of <27.5</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Groups are comparable regarding disease severity Subgroup analysis for adolescents and adults separately are mentioned in methods, but not reported

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>United States</p> <p><u>Source of funding:</u> Supported by Eli Lilly (pharmaceutical company)</p> <p><u>Conflicts of interest:</u> Several authors report financial conflicts of interest.</p>	<p>according to CDC growth charts;</p> <ul style="list-style-type: none"> - sickle cell disease; - congenital or acquired heart disease; - neurodevelopmental disorders such as cerebral palsy; - dependence on a medical-related mechanical device or procedure such as tracheostomy, gastrostomy, or positive pressure ventilation (not related to Covid-19); - asthma, a reactive airway, or another chronic respiratory disease; - type 1 or type 2 diabetes mellitus; - and an immunocompromised condition or receipt of an immunosuppressive treatment. <ul style="list-style-type: none"> • Ambulatory patients who were at least 18 years of age and who presented with at least one of the following risk factors: <ul style="list-style-type: none"> - age of at least 65 years, - a BMI of at least 35, - chronic kidney disease, - diabetes mellitus type 1 or type 2, - immunosuppressive disease or receipt of immunosuppressive treatment, - and an age of at least 55 years with cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease. 			<p>- or the trial site did not update the disposition status at time of data lock</p> <p>- 2 were lost to follow-up</p> <p>Control: 36 (7.0%) Reasons (describe):</p> <ul style="list-style-type: none"> - Discontinued placebo - 1 was lost to follow-up <p><u>Incomplete outcome data:</u> Intervention: N (%) Reasons (describe)</p> <p>Control: N (%) Reasons (describe)</p>	<p>RR: 0.33 (95%CI 0.17 to 0.65)</p> <p><u>Covid-19-related hospitalization or death (day 29)</u> I: 11/518 (2.1%) C: 36/517 (7.0%) RR: 0.30% (95%CI 0.16 to 0.59)</p> <p><u>Time to symptom resolution</u> I: 8 days (95%CI 7 to 9) C: 9 days (95%CI 8 to 10)</p> <p><u>Respiratory support</u> Not reported</p> <p>Also available: a composite of a Covid-19–related hospitalization, a visit to an emergency department, or death from any cause by day 29; duration of hospitalization, symptom resolution at day 2-11 among high risk patients</p> <p>Safety <u>Adverse events</u> I: 69/518 (13.3%) C: 61/517 (11.6%) RR: 1.13 (95%CI 0.82 to 1.56)</p> <p><u>Serious adverse events</u> I: 7/518 (1.4%) C: 5/517 (1.0%) RR: 1.40 (95%CI 0.45 to 4.37)</p> <p>Virological outcomes</p>	<ul style="list-style-type: none"> • An employee of Eli Lilly is especially thanked for the medical-writing and editorial support. • Several employees of Eli Lilly are co-authors • Data sharing statement only included that they will not share the collected data, without any explanation. • No information on randomization, concealment of allocation or blinding procedures. <p><u>Authors conclusion:</u> These data from the latest portion of the phase 3 BLAZE-1 clinical trial show the clinical benefit of early testing for SARS-CoV-2 infection coupled with prompt intervention with neutralizing antibody therapy in high-risk ambulatory patients. This trial also provides context for the recent FDA emergency use authorization granted for the use of bamlanivimab plus etesevimab in the treatment of outpatients who have mild or moderate Covid-19 and a high risk of progression to more severe disease, hospitalization, or both.</p> <p>While society moves toward ending the Covid-19 pandemic with widespread vaccination campaigns and efforts to achieve herd immunity, antibody therapy provides a potential treatment option to reduce the incidence of illness and death among vulnerable patients.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> Mild or moderate Covid-19 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> a peripheral oxygen saturation of 93% or less while breathing ambient air, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 300, a respiratory rate of at least 30 breaths per minute, and a heart rate of 125 or more beats per minute. <p><u>N total at baseline:</u> N = 1035 Intervention: 518 Control: 517</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 54.3 y (17.1) C: 53.3 y (16.4)</p> <p>Sex, n/N (%) male: I: 239/518 (46.1%) C: 258/517 (49.9%)</p> <p>Disease severity, mean (SD): <i>Mild or moderate Covid-19 (not defined)</i> Mild n/N (%) I: 397/518 (76.6%) C: 403/517 (77.9%) Moderate n/N (%) I: 121/518 (23.4%) C: 114/517 (22.1%)</p> <p>Groups are not completely comparable at baseline. The intervention groups seems to be slightly older, less males and have</p>				<p><u>Change in viral load (day 0-7)</u> Reported in figure <i>(difference from placebo in the decrease from baseline: -1.20 (95% CI -1.46 to -0.94)</i></p> <p><u>Persistently high SARS-CoV-2 viral load on day 7</u> I: 50/508 (9.8%) C: 147/499 (29.5%) RR: 0.33 (95% CI 0.25 to 0.45)</p> <p><u>Time to viral clearance</u> Not reported</p> <p>Also available: a reduction in the SARS-CoV-2 viral load from baseline to days 3 and 5, the time to viral clearance</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		better peripheral oxygen saturation.					
Gottlieb, 2021 (BLAZE-1 trial)	<p><u>Type of study:</u> Randomized, double-blind, placebo-controlled, phase 2-3 trial</p> <p><u>Setting:</u> 49 centers in the United States</p> <p><u>Country:</u> United States of America</p> <p><u>Source of funding:</u> Sabo.</p>	<p><u>In- and exclusion criteria:</u> See Chen, 2021</p> <p><u>N total at baseline:</u> N = 592 Intervention1: 104 Intervention2: 109 Intervention3: 104 Intervention4: 114 Control: 161</p> <p><u>Important characteristics:</u> Age, median (IQR): I1: 39 y (31-58) I2: 45 y (31-56) I3: 46 y (34-55) I4: 44 y (30-60) C: 46 y (35-57)</p> <p>Sex, n/N (%) female: I1: 63/101 (62.4%) I2: 51/107 (47.7%) I3: 58/101 (57.4%) I4: 58/112 (51.8%) C: 85/156 (54.5%)</p> <p>Mild disease status, n/N (%) I1: 83/101 (82.2%) I2: 79/107 (73.8%) I3: 70/101 (69.3%) I4: 82/112 (82.1%) C: 125/156 (80.1%)</p> <p>Moderate disease status, n/N (%) I1: 18/101 (17.8%) I2: 28/107 (26.2%) I3: 31/101 (30.7%) I4: 20/112 (17.9%) C: 31/156 (19.9%)</p>	<p>Single intravenous infusion of neutralizing antibody LY-CoV555, 3 different doses: Intervention 1: 700 mg (n=104) Intervention 2: 2800 mg (n=109) Intervention 3: 7000 mg (n=104) ----- Intervention 4: 2800 mg of neutralizing antibody LY-CoV555 and 2800 mg of etesevimab (n=114)</p>	Placebo (n=161)	<p><u>Length of follow up:</u> See Chen, 2021</p> <p><u>Loss to follow-up:</u></p> <p><i>Included in efficacy analysis</i> (at least 1 postbaseline viral load) Intervention1: 101 Intervention2: 107 Intervention3: 101 Intervention4: 109 Control: 152</p> <p><i>Included in primary analysis</i> (data on viral load for both baseline and at day 11) Intervention1: 100 Intervention2: 103 Intervention3: 95 Intervention4: 102 Control: 146</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> There were no deaths during the trial</p> <p><u>Hospitalization at day 29, n/N (%)</u> Intervention1: 1/101 (1.0%) Intervention2: 2/107 (1.9%) Intervention3: 2/101 (2.0%) Pooled doses: 1/109 (0.9%) Control: 9/143 (5.8%)</p> <p><u>Mean (SD) viral load at day 11 (95% CI)</u> Intervention1: 2.64 (1.80) Intervention2: 2.21 (1.73) Intervention3: 2.85 (1.73) Intervention4: 2.16 (1.82) Control: 2.46 (1.73)</p> <p>Int1 vs control MD= 0.09 (95% CI= -0.35 to 0.52) Int2 vs control MD= -0.27 (95% CI= -0.71 to 0.16) Int3 vs control MD= 0.31 (95% CI= -0.13 to 0.76) Int4 vs control MD= -0.57 (95% CI= -1.00 to -0.14)</p> <p><u>Viral load (AUC) at day 29 mean (SD)</u> Intervention1: 70.17 (29.68) Intervention2: 63.74 (28.97)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy. Further ongoing clinical trials will focus on assessing the clinical benefit of antispikes neutralizing antibodies in patients with COVID-19 as a primary end point.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Number of days since onset of symptoms, median (IQR): I: 5 (3-6) days I: 4 (3-6) days I: 4 (2-7) days I: 4 (3-5) days C: 4 (3-6) days</p> <p>Viral load – cycle threshold of the reverse-transcriptase-polymerase-chain-reaction assay, mean (SD): I: 23.8 (6.5) I: 24.5 (7.6) I: 23.4 (6.8) I: 22.7 (8.0) C: 23.8 (7.8)</p> <p>Groups comparable at baseline? Yes, except COVID-19 severity.</p>				<p>Intervention3: 71.53 (30.15) Intervention4: 61.69 (28.39) Control: 74.45 (35.30)</p> <p><u>Number of viral clearance</u> <u>At day 7</u> Intervention1: 10/99 Intervention2: 12/101 Intervention3: 8/99 Intervention4: 14/100 Control: 16/145</p> <p><u>At day 22</u> Intervention1: 41/85 Intervention2: 43/93 Intervention3: 37/86 Intervention4: 40/82 Control: 56/122</p> <p><u>Safety: Serious adverse events, n/N (%)</u> Intervention1: 0/101 Intervention2: 0/107 Intervention3: 0/101 Intervention4: 1/112 Control: 1/156 The serious adverse event observed in the combination group was a urinary tract infection. The serious adverse event in the placebo group was upper abdominal pain.</p> <p><u>Safety: Any adverse event, n/N (%)</u> Intervention1: 27/101 (26.7%) Intervention2: 26/107 (24.3%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Intervention3: 22/101 (21.8%) Intervention4: 17/112 (17.0%) Control: 42/156 (26.9%)</p> <p><u>Safety: Adverse event, n (mild/ moderate/ severe)</u> Intervention1: 17/ 7/ 2 Intervention2: 18/ 5/ 3 Intervention3: 10/ 7/ 5 Intervention4: 15/ 3/ 1 Control: 21/ 18/ 3</p> <p><u>Symptom resolution, n/N (%)</u> <u>At day 7</u> Intervention1: 47/101 (46.5%) Intervention2: 37/107 (34.6%) Intervention3: 46/101 (45.5%) Intervention4: 50/112 (45.9%) Control: 62/156 (40.8%)</p> <p><u>At day 22</u> Intervention1: 68/101 (67.3%) Intervention2: 63/107 (58.9%) Intervention3: 62/101 (61.4%) Intervention4: 75/112 (68.8%) Control: 88/156 (57.9%)</p>	
6.6. Casirivimab and imdevimab (REGN-COV2; combination of two noncompeting, neutralizing human IgG1 antibodies)							
RECOVERY Collaborative Group, 2022	<u>Type of study:</u> Multicenter, open-label RCT	Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection	Casirivimab + imdevimab + usual care	Usual care	<u>Length of follow-up:</u> 28 days	Clinical outcomes <u>Mortality</u> <u>All-cause mortality at day 28</u>	Primary outcome: • 28-day all-cause mortality Secondary outcome(s):

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Setting: 127 hospitals, between September 18, 2020 and May 22, 2021</p> <p>Country: UK</p> <p>Source of funding: UK Research and Innovation (Medical Research Council) and National Institute of Health Research. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Regeneron Pharmaceuticals supported the study through supply of casirivimab and imdevimab and DMW provided comments on the manuscript as a member of the writing committee.</p> <p>Conflicts of interest: One author is DMW is an employee of</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> hospitalized clinically suspected or laboratory-confirmed SARS-CoV-2 infection no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial <p>Exclusion criteria:</p> <ul style="list-style-type: none"> received i.v. immunoglobulin treatment during the current admission children weighing < 40 kg or aged <12 y <p>N total at baseline: N = 9784 Intervention: N = 4839 Control: N = 4946</p> <p>Important characteristics:</p> <p>Seronegative patients Age, mean (SD): I: .63.2 y (15.5) C: 64.0 y (15.2)</p> <p>Sex, n/N (%) male: I: 995/1633 (61%) C: 879/1520 (58%)</p> <p>Respiratory support <i>No oxygen received</i> I: 182/1633 (11%) C: 148/1520 (10%)</p> <p><i>Simple oxygen</i> I: 1085/1633 (66%) C: 995/1520 (65%)</p> <p><i>Non-invasive ventilation</i></p>	<p>Casirivimab 4 g and imdevimab 4 g were administered together in 250 ml 0,9% saline infused intravenously over 60 min (plus or minus 15 min) as soon as possible after randomization.</p> <p>Usual care is not further specified.</p>	<p>Usual care is not further specified.</p>	<p>Incomplete outcome data & loss-to-follow-up: Intervention: 49/4839 (1%) Reasons not provided.</p> <p>Control: 30/4946 (< 1%) Reasons not provided.</p>	<p><i>Seronegative patients</i> I: 396/1633 (24%) C: 452/1520 (30%) RR 0.79 (95%CI: 0.69-0.91)</p> <p><i>All patients</i> I: 943/4839 (19%) C: 1029/4946 (21%) RR 0.94 (95%CI: 0.86-1.02)</p> <p>Death within 28 days (in patients not on invasive mechanical ventilation at randomisation) <i>Seropositive patients</i> I: 383/1599 (24%) C: 435/1484 (29%) RR 0.82 (95%CI: 0.73-0.92)</p> <p><i>All patients</i> I: 836/4556 (18%) C: 905/4642 (19%) RR 0.94 (95%CI: 0.86-1.02)</p> <p>Duration of hospitalization Duration of hospitalisation Days, median (IQR) <i>Seropositive patients</i> I: 13 (7 to > 28) C: 17 (7 to > 28)</p> <p><i>All patients</i> I: 10 (6 to > 28) C: 10 (5 to > 28)</p> <p>Discharged from hospital within 28 days <i>Seropositive patients</i> I: 1049/1633 (64%) C: 878/1520 (58%) RR 1.19 (95%CI: 1.09-1.31)</p>	<ul style="list-style-type: none"> time to discharge from hospital invasive mechanical ventilation or death (in patients not on invasive mechanical ventilation at randomisation) <p>Definitions: -</p> <p>Remarks: -</p> <p>Authors conclusion: In patients admitted to hospital with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab reduced 28-day mortality in patients who were seronegative (and therefore had not mounted their own humoral immune response) at baseline but not in those who were seropositive at baseline.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Regeneron Pharmaceuticals and holds shares or share options in the company. All other authors declare no competing or financial relationships relevant to the submitted work. No form of payment was given to anyone to produce the manuscript.</p>	<p>I: 332/1633 (20%) C: 341/1520 (22%)</p> <p><i>Invasive mechanical ventilation</i> I: 34/1633 (2%) C: 36/1520 (2%)</p> <p>All patients Age, mean (SD): I: .61.9 y (14.6) C: 61.9 y (14.4)</p> <p>Sex, n/N (%) male: I: 3033/4839 (70%) C: 3454/4946 (70%)</p> <p>Respiratory support <i>No oxygen received</i> I: 332/4839 (7%) C: 309/4946 (6%)</p> <p><i>Simple oxygen</i> I: 2980/4839 (62%) C: 3016/4946 (61%)</p> <p><i>Non-invasive ventilation</i> I: 1244/4839 (26%) C: 1317/4946 (27%)</p> <p><i>Invasive mechanical ventilation</i> I: 283/4839 (6%) C: 304/4946 (6%)</p> <p>Groups comparable at baseline.</p>				<p><i>All patients</i> I: 3389/4839 (70%) C: 3420/4946 (69%) RR 1.02 (95%CI: 0.97-1.07)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Invasive respiratory support</u> <u>Use of invasive mechanical ventilation (in patients not on invasive mechanical ventilation at randomisation)</u> <i>Seropositive patients</i> I: 190/1599 (12%) C: 202/1484 (14%) RR 0.87 (95%CI: 0.73-1.05)</p> <p><i>All patients</i> I: 484/4556 (11%) C: 488/4642 (11%) RR 1.01 (95%CI: 0.90-1.14)</p> <p><u>Use of invasive mechanical ventilation (in patients not on any ventilation at randomisation)</u> <i>Seropositive patients</i> I: 90/1267 (7%) C: 120/1143 (10%) RR 0.68 (95%CI: 0.52-0.88)</p> <p><i>All patients</i> I: 183/3312 (6%) C: 211/3325 (6%) RR 0.87 (95%CI: 0.72-1.06)</p> <p><u>Successful cessation of invasive mechanical ventilation within 28 days</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>(in patients on <u>invasive mechanical ventilation at randomisation</u>) <i>Seropositive patients</i> I: 10/34 (29%) C: 10/36 (28%) RR 1.19 (95%CI: 0.49-2.88)</p> <p><i>All patients</i> I: 104/283 (37%) C: 114/304 (38%) RR 0.99 (95%CI: 0.76-1.30)</p> <p><u>Non-invasive respiratory support</u> <u>Use of non-invasive ventilation (in patients not on any ventilation at randomisation)</u> <i>Seropositive patients</i> I: 348/1267 (27%) C: 362/1143 (32%) RR 0.87 (95%CI: 0.77-0.98)</p> <p><i>All patients</i> I: 733/3312 (22%) C: 771/3325 (23%) RR 0.95 (95%CI: 0.87-1.04)</p> <p><u>Other</u> <u>Invasive mechanical ventilation or death within 28 days (in patients not on invasive mechanical ventilation at randomisation)</u> <i>Seropositive patients</i> I: 488/1599 (31%) C: 544/1484 (37%) RR 0.86 (95%CI: 0.75-0.92)</p> <p><i>All patients</i> I: 1094/4556 (24%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 1155/4642 (25%) RR 0.97 (95%CI: 0.90-1.04)</p> <p><u>Use of any ventilation (in patients not on any ventilation at randomisation)</u> <i>Seropositive patients</i> I: 360/1267 (28%) C: 373/1143 (33%) RR 0.87 (95%CI: 0.77-0.98)</p> <p><i>All patients</i> I: 756/3312 (23%) C: 799/3325 (24%) RR 0.95 (95%CI: 0.87-1.04)</p> <p><u>Use of renal replacement therapy</u> <i>Seropositive patients</i> I: 67/1614 (4%) C: 65/1498 (4%) RR 0.96 (95%CI: 0.69-1.34)</p> <p><i>All patients</i> I: 203/4779 (4%) C: 200/4884 (4%) RR 1.04 (95%CI: 0.86-1.26)</p> <p>Safety <u>Serious adverse events</u> <u>Any major cardiac arrhythmia</u> <i>Seropositive patients</i> I: 54/1633 (3%) C: 69/1520 (5%)</p> <p><i>All patients</i> I: 188/4839 (4%) C: 218/4946 (4%)</p> <p><u>Any thrombotic event</u> <i>Seropositive patients</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I: 59/1633 (4%) C: 65/1520 (4%)</p> <p><i>All patients</i> I: 253/4839 (5%) C: 250/4946 (5%)</p> <p><u>Any major bleeding</u> <i>Seropositive patients</i> I: 22/1633 (1%) C: 21/1520 (1%)</p> <p><i>All patients</i> I: 72/4839 (1%) C: 90/4946 (2%)</p> <p><u>Potential infusion reactions within 72 h after randomisation</u> <u>Any worsening in respiratory status</u> <i>Seropositive patients</i> I: 167/645 (26%) C: 140/528 (57%)</p> <p><i>All patients</i> I: 369/1792 (21%) C: 372/1715 (22%)</p> <p><u>Any severe allergic reaction</u> <i>Seropositive patients</i> I: 1/645 (< 1%) C: 0/528 (0%)</p> <p><i>All patients</i> I: 4/1792 (< 1%) C: 1/1715 (< 1%)</p> <p><u>Temperature > 39C or ≥2C rise above baseline</u> <i>Seropositive patients</i> I: 48/645 (7%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 23/528 (4%)</p> <p><i>All patients</i> I: 79/1792 (4%) C: 52/1715 (3%)</p> <p><u>Any sudden hypotension</u> <i>Seropositive patients</i> I: 39/645 (6%) C: 17/528 (3%)</p> <p><i>All patients</i> I: 66/1792 (4%) C: 39/1715 (2%)</p> <p><u>Clinical haemolysis</u> <i>Seropositive patients</i> I: 14/645 (2%) C: 9/528 (2%)</p> <p><i>All patients</i> I: 26/1792 (1%) C: 31/1715 (2%)</p> <p><u>Any thrombotic event</u> <i>Seropositive patients</i> I: 10/645 (2%) C: 7/528 (1%)</p> <p><i>All patients</i> I: 31/1792 (2%) C: 24/1715 (1%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Weinreich, 2021	<p><u>Type of study:</u> RCT; double-blind, placebo-controlled</p> <p><u>Setting:</u> Multi-centre; randomization</p>	<p>Symptomatic, non-hospitalized COVID-19 patients</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age ≥18 years confirmed SARSCoV-2 infection by RT-PCR 	REGN-COV2	Placebo (saline)	<p>At baseline (day 1), REGN-COV2 (at the high dose or low dose) was administered</p> <p>At baseline (day 1), saline placebo was administered</p>	<p><u>Length of follow up:</u> Virological outcomes: 7 days, adverse events: 29 days</p> <p><u>Loss to follow-up:</u> I: 12/92 (13.0%)</p> <p>Clinical outcomes</p> <p><u>Safety</u> <i>In safety population</i> I: n=88 II: n=88 I+II: n=176</p>	<p><u>Authors conclusion:</u> In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>between June 16, 2020, and August 13, 2020; data cut-off for this interim analysis was September 4, 2020</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> Funded by Regeneron Pharmaceuticals and the Biomedical Research and Development Authority of the Department of Health and Human Services;</p>	<ul style="list-style-type: none"> • SARS-CoV-2–positive test result received ≤ 72 hours before randomization • experiencing >1 of the following symptoms at randomization: fever, cough, shortness of breath • symptom onset ≤ 7 days before randomization • maintains O2 saturation ≥93% on room air • willing and able to provide informed consent signed by study patient or legally acceptable representative • willing and able to comply with study procedures, including providing samples for viral shedding testing after discharge <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • admitted to a hospital prior to randomization, or hospitalized (inpatient) at randomization, due to COVID-19 • participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, monoclonal antibodies against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit • history of COVID-19 investigational or Emergency Use Authorization (EUA)-approved treatments in the past 30 days or less than 5 half-lives of the investigational 	<p>intravenously in a 250-ml normal saline solution over a period of 1 hour.</p> <p>Each of the two antibodies that make up REGN-COV2 — casirivimab (REGN10933) and imdevimab (REGN10987) — is given in equal doses in the cocktail.</p> <p>I: 2.4 grams (low dose) II: 8.0 grams (high dose)</p>	<p>intravenously in a 250-ml normal saline solution over a period of 1 hour.</p>	<p>Reasons: currently in ongoing trial (n=3) or discontinued (n=9, of which 1 was withdrawn by sponsor, 3 were lost to follow-up, 4 withdrew and 1 is unknown)</p> <p>II: 6/90 (6.7%) Reasons: currently in ongoing trial (n=2) or discontinued (n=4, of which 1 was lost to follow-up and 3 withdrew)</p> <p>C: 5/93 (5.4%) Reasons: currently in ongoing trial (n=1) or discontinued owing to being lost to follow-up (n=4)</p>	<p>C: n=93</p> <p><i>Any serious adverse event</i> I: 1 (1) II: 0 I+II: 1 (1) C: 2 (2)</p> <p><i>Any adverse event of special interest (*Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions.)</i> I: 0 II: 2 (2) I+II: 2 (1) C: 2 (2)</p> <p><i>Any serious adverse event of special interest*</i> All groups: 0</p> <p><i>Grade ≥2 infusion-related reaction within 4 days</i> I: 0 II: 2 (2) I+II: 2 (1) C: 1 (1)</p> <p><i>Grade ≥2 hypersensitivity reaction within 29 days</i> I: 0 II: 1 (1) I+II: 1 (1) C: 2 (2)</p> <p><i>Adverse events that occurred or worsened during the observation period†</i> <i>Grade 3 or 4 event</i> I: 1 (1) II: 0 I+II: 1 (1) C: 1 (1)</p> <p><i>Event that led to death</i> All: 0</p>	<p>in the combined REGN-COV2 dose groups and the placebo group.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>product (whichever is longer) prior to the screening visit.</p> <ul style="list-style-type: none"> • Current use of any COVID-19 investigational or EUA-approved treatment • Requires IVIG for medical condition other than COVID-19 • known allergy or hypersensitivity to components of study drug • Has been discharged, or is planned to be discharged, to a quarantine center • Pregnant or breastfeeding women <p><u>N total at baseline:</u> N = 275 Intervention-II: 92 Intervention-I: 90 Intervention I+II: 182 Control: 93</p> <p><u>Important characteristics:</u> <i>Age, Median age (IQR) — yr:</i> I: 43.0 (33.5–51.0) II: 44.0 (36.0–53.0) I+II: 43.0 (35.0–52.0) C: 45.0 (34.0–54.0) <i>Sex, n/N (%) male:</i> I: 46/92 (50) II: 38/90 (42) I+II: 84/182 (46) C: 50/93 (54) Positive baseline qualitative RT-PCR — no. (%) I: 73/92 (79) II: 74/90 (82) I+II: 147/182 (81) C: 81/93 (87)</p>				<p><i>Event that led to withdrawal from the trial</i> All: 0 <i>Event that led to infusion interruption*</i> I: 0 II: 1 (1) I+II: 1 (1) C: 1 (1)</p> <p>Virological outcomes <u>Time-weighted average change in viral load from day 1 through day 7†</u> <i>Measured in patients with positive RT_PCR at baseline, number per group:</i> I: 70 II: 73 I+II: 143 C: 78 <u>Least-squares mean change — log₁₀ copies/ml (95% CI)</u> I: -1.60±0.14 (-1.87 to -1.32) II: -1.90 ±0.14 (-2.18 to -1.62) I+II: -1.74±0.11 (-1.95 to -1.53) C: -1.34±0.13 (-1.60 to -1.08) <u>Difference vs. placebo at day 7 — log₁₀ copies/ml</u> Least-squares mean (95% CI) I: -0.25±0.18 (-0.60 to 0.10) II: -0.56±0.18 (-0.91 to -0.21)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Median time from symptom onset to randomization, (range) — days</i> I: 3.5 (0–7) II: 3.0 (0–8) I+II: 3.0 (0–8) C: 3.0 (0–8)</p> <p><i>Baseline viral load in nasopharyngeal swab</i> Measured in - No. of patients: I: 84 II: 83 I+II: 167 C: 91</p> <p><i>Mean viral load — log10 scale of copies/ml</i> I: 5.04±2.495 II: 5.00±2.527 I+II: 5.02±2.503 C: 4.67±2.366</p> <p><i>Median viral load (range) — log10 scale of copies/ml</i> I: 5.41 (0.0–7.9) II: 5.29 (0.0–7.9) I+II: 5.30 (0.0–7.9) C: 4.70 (0.0–7.9)</p> <p><i>Baseline serum antibody status — no. (%)</i> Negative: I: 41 (45) II: 39 (43) I+II: 80 (44) C: 33 (35) Positive I: 37 (40) II: 39 (43) I+II: 76 (42) C: 47 (51) Unknown** I: 14 (15) II: 12 (13)</p>				<p>I+II: -0.41±0.15 (-0.71 to -0.10)</p> <p><i>Sub group analysis based on baseline serum antibody status</i> Negative: <u>Time-weighted average change in viral load from day 1 through day 7+</u> <i>Measured in patients with positive RT_PCR at baseline, number per group:</i> I: 34 II: 35 I+II: 69 C: 28 <u>Least-squares mean change — log10 copies/ml (95% CI)</u> I: -1.89±0.18 (-2.24 to -1.53) II: -1.96±0.18 (-2.33 to -1.60) I+II: -1.94±0.13 (-2.20 to -1.67) C: -1.37±0.20 (-1.76 to -0.98) <u>Difference vs. placebo at day 7 — log10 copies/ml</u> Least-squares mean (95% CI) I: -0.52±0.26 (-1.04 to 0.00) II: -0.60±0.26 (-1.12 to -0.08) I+II: -0.56±0.23 (-1.02 to -0.11) Positive <u>Time-weighted average change in viral load from day 1 through day 7+</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I+II: 26 (14) C: 13 (14) **status could not be evaluated or that the results were borderline.</p> <p>Groups comparable at baseline.</p>				<p><i>Measured in patients with positive RT_PCR at baseline, number per group:</i> I: 27 II: 29 I+II: 56 C: 37</p> <p><u>Least-squares mean change — log₁₀ copies/ml (95% CI)</u> I: -1.24±0.19 (-1.61 to -0.86) II: -1.63±0.20 (-2.03 to -1.24) I+II: -1.45±0.13 (-1.71 to -1.18) C: -1.24±0.16 (-1.55 to -0.93)</p> <p><u>Difference vs. placebo at day 7 — log₁₀ copies/ml Least-squares mean (95% CI)</u> I: 0.00±0.24 (-0.48 to 0.49) II: -0.39±0.25 (-0.89 to 0.11) I+II: -0.21±0.20 (-0.62 to 0.20)</p> <p><u>At least one Covid-19-related, medically attended visit within 29 days¶</u> <i>Measured in all patients, no. per group:</i> I: 92 II: 90 I+II: 182 C: 93 <i>Patients with ≥1 visit within 29 days — no. (%)</i> I: 3 (3) II: 3 (3)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I+II: 6 (3) C: 6 (6) <i>Difference vs. placebo — percentage points (95% CI)</i> I: -3 (-18 to 11) II: -3 (-18 to 11) I+II: -3 (-16 to 9)</p> <p><i>Sub group analysis based on baseline serum antibody status</i> Negative: I: 41 II: 39 I+II: 80 C: 33 <i>Patients with ≥1 visit within 29 days — no. (%)</i> I: 2 (5) II: 3 (8) I+II: 5 (6) C: 5 (15) <i>Difference vs. placebo — percentage points (95% CI)</i> I: -10 (-32 to 13) II: -8 (-30 to 16) I+II: -9 (-29 to 11) Positive: I: 37 II: 39 I+II: 76 C: 47 <i>Patients with ≥1 visit within 29 days — no. (%)</i> I: 1 (3) II: 0 I+II: 1 (1) C: 1 (2) <i>Difference vs. placebo — percentage points (95% CI)</i> I: 1 (-21 to 22) II: -2 (-23 to 19) I+II: -1 (-19 to 17)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
6.7. CERC-002							
Perlin, 2021	<p>Type of study: multicenter, double-blind, randomized controlled phase 2 trial</p> <p>Setting: hospital-based, 11 centres, July 17, 2020 - January 19, 2021</p> <p>Country: USA</p> <p>Source of funding: The study was sponsored by Avalo Therapeutics. The Data and Safety Monitoring Board and the sponsor judged the serious AEs to be symptoms of COVID-19 and unrelated to study drug.</p> <p>Conflicts of interest: Three authors are employees of the study sponsor. Another author has received consulting fees and stock options from the study sponsor, and is an inventor and</p>	<p>hospitalized patients with COVID-19-related pneumonia and mild to moderate ARDS</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age ≥ 18 y • diagnosed with COVID-19 infection through an approved testing method • clinical evidence of pneumonia with acute lung injury* • hospitalized • if data on O₂ saturation were available, the value at rest in ambient air must have been below 93% • patients were permitted to receive high-flow O₂ or positive-pressure O₂ prior to randomization <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • intubated with mechanical ventilation • currently taking immunomodulators or anti-rejection medications • received an immunomodulating biologic drug within 60 days of baseline • septic shock† • received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit • pregnant or lactating females <p>N total at baseline: Randomized: N = 83 Intervention: N = 41</p>	<p>CERC-002 16 mg/kg (maximum: 100 mg)</p> <p>CERC-002 (AVTX-002) is a human LIGHT-neutralizing antibody.</p>	placebo	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up or incomplete data: I: 1/41 (2.4%) C: 0/42 (0%)</p> <p>Reason for loss-to-follow-up is not provided.</p>	<p>As specified a priori, the primary endpoint was evaluated among patients who did not receive high-flow O₂ or positive-pressure O₂ prior to randomization, although patients receiving non-invasive O₂ support was not excluded from the study or other secondary endpoints</p> <p>Clinical outcomes</p> <p>Mortality</p> <p>Mortality at day 28 I: 3/39 (7.7%) C: 6/42 (14.3%)</p> <p>Mortality at day 60 I: 4/37 (10.8%) C: 9/40 (22.5%)</p> <p>Duration of hospitalisation Not reported</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support Not reported</p> <p>Other</p> <p>Alive and free of respiratory failure at day 28 (primary endpoint) I: 26/31 (83.9%) C: 20/31 (64.5%) p = 0.044</p>	<p>Definitions: * Acute lung injury was defined as diffuse bilateral radiographic infiltrates with a P_aO₂/F_iO₂ above 100 and below 300 (i.e., mild to moderate ARDS).</p> <p>† Septic shock was defined as persistent hypotension requiring vasopressors to maintain mean arterial pressure of 65 mmHg or higher and a serum lactate level above 2 mmol/l (18 mg/dl) despite adequate volume resuscitation.</p> <p>Remarks: -</p> <p>Authors conclusion: This phase 2 proof-of-concept study provides initial evidence that using a specific monoclonal antibody (CERC-002) to neutralize the LIGHT cytokine might provide therapeutic benefit, including reducing mortality rates, for patients with COVID-19-related ARDS and CRS. Future studies in larger populations are needed to verify these findings.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	holds a patent related to anti-LIGHT.	<p>Control: N = 42</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 59.2 y (14.5) C: 58.1 y (14.2)</p> <p>Sex, n/N (%) male: I: 25/41 (61.0%) C: 32/42 (76.2%)</p> <p>Baseline free LIGHT pg/ml, mean (range) I: 329 (22-1050) C: 276 (37-834)</p> <p>Concomitant medication <i>Systemic corticosteroids</i> I: 37/41 (90.2%) C: 36/42 (85.7%)</p> <p><i>Remdesivir</i> I: 21/41 (51.2%) C: 27/42 (64.3%)</p> <p>Patients in the intervention group were more often female, black or African American, had a higher mean free LIGHT concentration at baseline, and less often received concomitant remdesivir.</p>				<p>Safety</p> <p><u>Adverse events</u> <u>≥ 1 treatment-emergent adverse event</u> Grade 1-2 I: 11/40 (27.5%) C: 9/42 (21.4%)</p> <p>Grade 3-5 I: 5/40 (12.5%) C: 12/42 (28.6%)</p> <p><u>≥ 1 treatment-related adverse event</u> I: 8/40 (20.0%) C: 6/42 (14.3%)</p> <p><u>≥ 1 serious adverse event</u> I: 8/40 (20.0%) C: 12/42 (28.6%)</p> <p><u>Leucocytosis</u> I: 2/40 (5.0%) C: 2/42 (4.8%)</p> <p><u>Pyrexia</u> I: 2/40 (5.0%) C: 2/42 (4.8%)</p> <p><u>Hepatitis</u> I: 2/40 (5.0%) C: 0/42 (0%)</p> <p><u>Bradycardia</u> I: 1/40 (2.5%) C: 2/42 (4.8%)</p> <p><u>Pleural effusion</u> I: 2/40 (5.0%) C: 0/42 (0%)</p> <p>Virological outcomes Not reported</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
6.8. Etanercept							
6.9. Gimsilumab							
6.10. Golimumab							
6.11. Infliximab							
Fisher, 2021 (CATALYST trial)	<p><u>Type of study:</u> randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial</p> <p><u>Setting:</u> hospital-based, between June 15, 2020 and February 18, 2021</p> <p><u>Country:</u> 9 hospitals in the UK</p> <p><u>Source of funding:</u> This trial was supported by the Medical Research Council. This paper presents independent research supported by the NIHR Birmingham Biomedical Research Centres at Birmingham, Oxford, Imperial College London, and University College London. The views expressed in this paper are those of</p>	<p>hospitalized patients with COVID-19 pneumonia and CRP \geq 40 mg/L</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age \geq 16 y admitted to hospital with a clinical picture strongly suggestive of SARS-CoV-2 pneumonia (confirmed by chest x-ray or CT scan, with or without a positive RT-PCR assay) CRP concentration of 40 mg/L or greater* <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> planned palliative care pregnancy or breastfeeding women of childbearing potential non-vasectomised men who were unwilling to use effective contraception for the duration of the trial and throughout the drug-defined post-trial period known HIV or chronic hepatitis B or C infection concurrent immunosuppression with biological agents history of haematopoietic stem cell or solid organ transplant known hypersensitivity to drug products or excipients tuberculosis or other severe infections such as (non-SARS-CoV-2) sepsis, abscesses, and opportunistic infections requiring treatment 	<p><u>Intervention 1:</u> namilumab (single intravenous dose of 150 mg given over 1 h on day 1) + usual care</p> <p><u>Intervention 2:</u> infliximab (single intravenous dose of 5 mg/kg given over 2 h on day 1) + usual care</p>	usual care	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> I1: 5/57 (8.8%) I2: 7/38 (18.4%) C: 9/54 (16.7%)</p> <p><u>Reasons</u></p> <ul style="list-style-type: none"> withdrawal pretreatment and only one CRP measure available (n = 2) post-treatment CRP not available (n = 3) withdrawal pretreatment and only one CRP measure available (n = 6) post-treatment CRP not available (n = 1) <p><u>Reason</u> post-treatment CRP not available (n = 9)</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> <u>Hospital survival status at day 28</u> I1 vs. C1: 6/55 (11%) vs. 10/54 (19%) I2 vs. C2: 4/29 (14%) vs. 5/34 (15%)</p> <p><u>Duration of hospitalisation</u> <u>Hospital-free days</u> Median (IQR) I1 vs. C1: 20 (3-23) vs. 17 (0-23) I2 vs. C2: 17 (3-23) vs. 17 (0-23)</p> <p><u>Length of hospital stay</u> Days, median (range) I1 vs. C1: 8 (2-28) vs. 10 (1-28) I2 vs. C2: 11 (2-28) vs. 10 (1-28)</p> <p><u>Proportion of patients discharged at day 28</u> I1 vs. C1: 43/55 (78%) vs. 33/54 (61%) I2 vs. C2: 22/29 (76%) vs. 22/34 (65%)</p> <p><u>Destination of discharge</u> Data were non-informative and, therefore, these data are not shown.</p> <p><u>Time to symptom resolution</u></p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> * The requirement for raised CRP concentration replaced an inclusion criterion for low oxygenation status (oxygen saturation \leq94% while breathing ambient air or a ratio of partial pressure of oxygen to the fraction of inspired oxygen of \leq300 mmHg) early in the course of recruitment, following a change in primary outcome.</p> <p>† Each intervention group was compared with the control group independently, including only control patients for whom that intervention was a randomisation option; ie, patients in the usual care group who were randomly assigned after the infliximab group closed or at the single study site where infliximab was not a randomisation option were not included in the infliximab comparison.</p> <p>Following a data monitoring committee review on Jan 21, 2021, where recommendations on both groups were made on the basis of the primary outcome analysis, the trial steering committee advised to stop the infliximab group for futility (probability of benefit 21%) but to continue to recruit to usual care and namilumab, which met the criteria for success (probability of benefit 99%), to collect further secondary outcome clinical data. A subsequent data monitoring</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care. Namilumab was provided free of charge by Izana Bioscience. Infliximab was provided free of charge by Celltrion. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.</p> <p><u>Conflicts of interest:</u> One author reports consultancy for Novartis, Bristol Myers Squibb, Servier, Galapagos, and Janssen and research funding from Servier and Galapagos. One author is currently undertaking a Senior Clinical Fellowship financed by Roche. One author reports consultancy for Bristol Myers</p>	<ul style="list-style-type: none"> • moderate or severe heart failure (NYHA class III/IV) • any other indication or medical history, that in the opinion of the patient’s local investigator, made the patient unsuitable for trial participation • co-enrolment into other interventional trials, except the RECOVERY-Respiratory Support trial <p><u>N total at baseline:</u> Randomized: N = 146</p> <p>Intervention 1: N = 57 Intervention 2: N = 35 Control: N = 54</p> <p><u>Important characteristics:†</u> <u>I1 vs. C1</u> Age, median (IQR): I1: 56.2 (47.6-63.3) C1: 62.8 (51.9-70.5)</p> <p>Sex, n/N (%) male: I1: 34/57 (60%) C1: 37/54 (69%)</p> <p>Clinical frailty score level 4-8, n/N (%): I1: 4/57 (7%) C1: 7/54 (13%)</p> <p><u>I2 vs. C2</u> Age, median (IQR): I2: 55.4 (46.1-70.5) C2: 64.5 (51.9-71.9)</p> <p>Sex, n/N (%) male: I2: 19/35 (54%) C2: 21/34 (62%)</p>				<p>Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p><u>Other</u> <u>Improvement in inflammation (primary endpoint)</u> The probabilities that the interventions were superior to usual care alone in reducing CRP concentration over time were 97% for namilumab and 15% for infliximab; the point estimates for treatment–time interactions were -0.09 (95%CI: -0.19 to 0.00) for namilumab and 0.06 (95%CI: -0.05 to 0.17) for infliximab.</p> <p><u>WHO clinical progression scale</u> In the namilumab group, for patients recruited from both wards and ICUs, the probability of having lower WHO clinical progression scale scores was consistently increased over time compared with usual care alone.</p> <p><u>S_pO₂:F_iO₂ ratio</u> Trends to improvement in oxygenation status were observed in the namilumab group.</p>	<p>committee meeting on Feb 23, 2021, advised closing the remaining groups as the trial was close to maximal recruitment and recent changes to standard of care with routine use of tocilizumab would affect the conduct of the trial.</p> <p><u>Authors conclusion:</u> Namilumab, but not infliximab, showed proof-of-concept evidence for reduction in inflammation – as measured by CRP concentration – in hospitalised patients with COVID-19 pneumonia. Namilumab should be prioritised for further investigation in COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Squibb and AstraZeneca, and research funding from Bayer and Pfizer. One author is a former employee of GlaxoSmithKline. All other authors declare no competing interests.	Clinical frailty score level 4-8, n/N (%): I2: 5/35 (14%) C2: 5/54 (15%) Patients in the intervention groups were slightly older. Furthermore, fewer patients in the infliximab group had remdesivir at enrolment than in the namilumab or usual care groups.				<u>Respiratory rate</u> Data were non-informative and, therefore, these data are not shown. <u>Body temperature</u> Data were non-informative and, therefore, these data are not shown. Safety <u>Adverse events</u> I1 vs. C1: 134 adverse events occurred in 30 (55%) of 55 patients in the namilumab group compared with 145 in 29 (54%) of 54 in the usual care group. I2 vs. C2: 102 adverse events occurred in 20 (69%) of 29 patients in the infliximab group compared with 112 in 17 (50%) of 34 in the usual care group. Virological outcomes Not reported	
6.12. Itolizumab (humanized monoclonal antibody (IgG1 kappa anti-CD6))							
Kumar, 2021	<u>Type of study:</u> RCT; open-label, <u>Setting:</u> multi-center; initiated May 2 nd , 2020, completed July 7 th , 2020 <u>Country:</u> India <u>Source of funding:</u>	Hospitalized COVID-19 patients with moderate to severe disease. <u>Inclusion criteria:</u> • Age >18 years • tested positive for virologic diagnosis of SARS-CoV-2 infection (RT-PCR) • hospitalized due to clinical worsening with oxygen saturation ≤94% at rest in ambient air	Itolizumab + standard of care • Itolizumab diluted in 250 ml of normal (0.9%) saline and was allowed to reach room temp. prior to infusion. • Itolizumab infusion started after pre-medication with Hydrocortisone 100 mg i.v (or equivalent short	Standard of care Oxygen, antibiotics, hydroxychloroquine, antivirals, steroids, low-molecular-weight heparin, and vitamin supplements	<u>Length of follow up:</u> 30 days <u>Loss to follow-up:</u> 0 <u>Excluded from analysis:</u> I: 2/22 (9.1%) Reasons: discontinued intervention C: 0/10 (0%; 3 patients discontinued	Clinical outcomes <u>Mortality , 30 days</u> I: 0/20 C: 3/10 (p = 0.029; 95% CI = -0.3 [-0.61, -0.08]) <u>Duration of hospitalization</u> not reported <u>Time to symptom resolution</u>	<u>Definitions:</u> - <u>Remarks:</u> • Relative small study • Gender does not seem balanced at baseline • Number of patients differ per moment in time; patients that are discharged or died are not included in the analysis <u>Authors conclusion:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>The study was funded by Biocon Biologics India Limited and the funders did not have any role in patient recruitment and management.</p> <p><u>Conflicts of interest:</u> Ashwani Marwah, Subramanian Loganathan and Sandeep N. Athalye are employees of Biocon Biologics Ltd. and hold stocks in Biocon. Shashank R. Joshi has received Speaker/Advisory/Research Grants from Abbott, Astra, Biocon, Boehringer Ingelheim, Eli Lilly, Franco Indian, Glenmark, Lupin, Marico, MSD, Novartis, Novo Nordisk, Roche, Sanofi, Serdia and Zydus. Sivakumar Vaidyanathan is an employee of Biocon Biologics Ltd.</p>	<ul style="list-style-type: none"> either moderate to severe ARDS (PaO₂/Fio₂ ratio of <200 or more than 25% deterioration from the immediate previous value) and/or high levels of proinflammatory markers (baseline serum ferritin level ≥400 ng/mL or IL-6 levels >4x upper normal limit). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> known severe allergic reactions to monoclonal antibodies active tuberculosis (TB) infection/inadequately treated tuberculosis/latent tuberculosis oral anti-rejection or any immunosuppressive drug in the last 6 months participated in any drug clinical trial using anti-IL-6 therapy known history of Hepatitis B, Hepatitis C or HIV, absolute neutrophil count (ANC) <1000/mm³, platelet count <50,000/mm³ and absolute lymphocyte count (ALC) <500/mm³ <p><u>N total at baseline:</u> N = 32 Intervention: 22 Control: 10</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 49.55 (12.49) C: 48.30 (14.62) Sex, n/N (%) male: I: 19 (95%) C: 7 (70%)</p>	<p>acting glucocorticoid) and Pheniramine 30 mg i.v. about 30 ± 10 minutes prior to infusion. Patients were initiated on 1.6 mg/kg i.v infusion of Itolizumab and continued with a 0.8 mg/kg dose weekly regimen, if required, based on previous clinical experience, as stated above. If patient recovered, subsequent doses were modified, deferred, or stopped as per investigator's discretion. As Itolizumab was being used in COVID-19 indication for the first time, post first infusion, second Itolizumab dose was repeated after 7 days, as per investigator's discretion, and so were subsequent doses. Investigators' decision was based on levels of inflammatory markers, clinical status, oxygen requirement and safety concerns (if any). The maximum number of administered doses was 4.</p> <ul style="list-style-type: none"> Itolizumab infusion was administered over period of not less than 120 min, using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 	<p>were used as a part of the best supportive care in both treatment arms.</p>	<p>intervention due to death)</p>	<p><i>Reduction in the proportion of patients with deteriorating lung functions, as measured by:</i></p> <p><i>Patients with Stable/Improved SpO₂ without Increasing Fio₂</i> Day 7, n (%) I: 17 (85) C: 5 (50), p= 0.0778</p> <p><i>Day 30, n (%)</i> I: 20 (100) C: 7 (70), p= 0.0296</p> <p><i>Patients with Stable/Improved PaO₂ Without Increasing Fio₂</i> Day 7, n (%) I: 18 (90) C: 6 (60), p=0.1413</p> <p><i>Day 30, n (%)</i> I: 20 (100) C: 7 (70), p= 0.0296</p> <p><u>Respiratory support</u> Free of NIV among patients on NIV at baseline I: 5/5 C: 1/4</p> <p>Safety <u>Adverse events</u> <i>Treatment emergent adverse event, n of patients that experienced at least one event:</i> I: 18 (81.8%) C: 4 (40%) <i>All events specified in table 5.</i></p> <p>Virological outcomes <u>Viral clearance</u> not reported</p>	<p>Itolizumab is a promising, safe and effective immunomodulatory therapy for treatment of ARDS due to cytokine release in COVID-19 patients, with survival and recovery-benefit.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Duration of COVID-19 related symptoms at enrollment</i> (in Days, mean (SD)) I: 8.55 (6.21) C: 5.60 (2.59) Groups comparable at baseline?</p>	<p>of 1.2 µm or less). Approx. 50 mL of infusion solution was administered during first hour, followed by remaining solution (approx. 200 mL) in next hour. Infusion period could be extended up to 8 hours for medical reasons, particularly if patient experienced infusion-related reactions, which needed medical attention prior to re-initiation of infusion. Itolizumab was not infused concomitantly in the same i.v line with any other agents.</p>			<p><i>Also reported: Reduction in inflammatory markers: Ferritin, D-dimer, LDH, CRP. Biomarkers such as IL-6, TNF-α, IL-17A; Absolute lymphocyte count; PaO2/FiO2 ratio calculated from arterial blood gas analyses</i></p>	
6.13. Lenzilumab							
Temesgen,2021	<p><u>Type of study:</u> Randomized, double-blind, placebo-controlled, phase 3 trial</p> <p><u>Setting:</u> 29 sites, 85% of patients enrolled from US sites, May 5, 2020 - Jan 27, 2021</p> <p><u>Country:</u> USA, Brazil</p> <p><u>Source of funding:</u> Humanigen <i>The study sponsor funded all aspects of the study,</i></p>	<p>hospitalised with COVID-19 pneumonia not requiring invasive mechanical ventilation</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y who are capable of providing informed consent or have a proxy capable of giving consent for them • Virologic confirmation of SARS-CoV-2 infection via any FDA authorized diagnostic test for SARS-CoV-2 • Pneumonia diagnosed by Chest X-ray or Computed Tomography revealing infiltrates consistent with pneumonia • SpO2 ≤ 94% on room air and/or require low-flow supplemental 	<p>lenzilumab plus standard of care group</p> <p>three intravenous doses of lenzilumab (600 mg per dose)</p>	<p>placebo plus standard of care group</p> <p>delivered 8 h apart.</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up:</u> Intervention: 5 (2.1%) Control: 6 (2.5%) seven had recovered and were discharged and subsequently lost to follow-up, and four patients withdrew from the study before day 28 (two lenzilumab and two placebo).</p>	<p>The primary efficacy endpoint was survival without ventilation (sometimes referred to as ventilator-free survival) by day 28.</p> <p>Clinical outcomes <u>Mortality (28 day)</u> I: 24 (10%; 6–14) C: 34 (14%; 10–19) HR 0.72 (0.42–1.23) P=0.24</p> <p><u>Survival without ventilation to day 28</u> I: 198 (84%; 79–89) C: 190 (78%; 72–83) HR 1.54 (1.02–2.32) P= 0.04</p>	<p><u>Definitions:</u> 8-point ordinal scale ((Hospitalized, not requiring supplemental oxygen-no longer requires ongoing medical care; Not hospitalized, limitation on activities and/or requiring home oxygen; Not hospitalized, no limitations on activities).</p> <p>Adverse events were graded by means of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0)</p> <p><u>Remarks:</u> The study sponsor funded all aspects of the study, participated in data collection, data analysis, data</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><i>participated in data collection, data analysis, data interpretation, and writing of the report and the decision to submit the manuscript for publication.</i></p> <p><u>Conflicts of interest:</u> ZT has received research support from Humanigen and unrestricted education support from Gilead, ViiV, and Merck (all to the institution). CRL has received research support from Gilead, Pfizer, and NIAID (ACTIV-2–A5401). <i>Other authors declared their conflict of interests. Please see full text.</i></p>	<p>oxygen and/or require high-flow oxygen support or NIPPV</p> <ul style="list-style-type: none"> • Hospitalized, not requiring invasive mechanical ventilation during this hospitalization • Have not participated in other clinical trial for COVID-19 using an immunomodulatory monoclonal antibody or kinase inhibitor (use of remdesivir, corticosteroids, convalescent plasma, hydroxychloroquine or chloroquine is permitted) • Females of childbearing potential must have a negative serum or urine pregnancy test <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Requiring invasive mechanical ventilation or extracorporeal membrane oxygenation prior to randomization • Confirmed diagnosis of bacterial pneumonia or other active/uncontrolled fungal or viral infections at screening/baseline • Known active tuberculosis (TB), history of incompletely treated TB or suspected or known extrapulmonary TB • Currently receiving treatment for hepatitis A, hepatitis B, hepatitis C or HIV infection • History of pulmonary alveolar proteinosis (PAP) • Women of childbearing potential who are pregnant or breastfeeding 				<p><u>Duration of hospitalization</u> ICU stay(days) I: 6 (10) C: 7 (11) P= 0.16</p> <p><u>Time to symptom resolution</u> Time to recovery (median number of days per quartile) 25% I: 5 (4–5) C: 5 (5–5) P= 0.43 50% I: 8 (7–9) C: 8 (7–9) 75% I: 15 (11–20) C: 19 (13–NA)</p> <p><u>Respiratory support</u> Incidence of invasive mechanical ventilation, extracorporeal membrane oxygenation, or death I: 35 (15%; 11–21) C: 51 (21%; 16–27) HR 0.67 (0.41–1.10) P= 0.11</p> <p>Invasive mechanical ventilation I: 26 (11%; 8–16) C: 49 (20%; 16–26) HR 0.52 (0.32–0.82) P= 0.0059</p> <p>Safety <u>Adverse events</u> Any adverse event ≥grade 3 I: 68 (27%) C: 84 (33%)</p> <p>Virological outcomes</p>	<p>interpretation, and writing of the report and the decision to submit the manuscript for publication.</p> <p><u>Authors conclusion:</u> Lenzilumab significantly improved survival without invasive mechanical ventilation in hospitalised patients with COVID-19, with a safety profile similar to that of placebo. The added value of lenzilumab beyond other immunomodulators used to treat COVID-19 alongside steroids remains unknown.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Known hypersensitivity to lenzilumab or any of its components • Use of any FDA authorized anti-IL-6 (e.g., tocilizumab, sarilumab, sitlukimab), anti-IL-1 (e.g., anakinra, canakinumab), kinase inhibitor (e.g., baracitinib, ibrutinib, acalabrutinib), or neutralizing monoclonal antibody (e.g. bamlanivimab or casirivimab/imdevimab) therapy to treat COVID-19 within 8 weeks prior to randomization • Use of GM-CSF agents (e.g., sargramostim) within prior 2 months of randomization • Expected survival < 48h in the opinion of the investigator • Any condition that, in the opinion of the investigator, is likely to interfere with the safety and efficacy of the study treatment or puts the patient at unacceptably high risk from the study <p><u>N total at baseline:</u> N = 520 Intervention: 261 Control: 259</p> <p>Modified ITT Intervention: 236 Control: 243</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 61 y (14)</p>				<p><u>Viral clearance</u> not reported</p> <p><i>* Sensitivity analyses of primary endpoint in the intention-to-treat population is also done.</i></p> <p><i>**Secondary outcomes are reported in supplementary file.</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: 61 y (14)</p> <p>Sex, n/N (%) male: I: 153 /236 (65%) C: 158/243 (65%)</p> <p>Disease severity, mean (SD): <i>Defined by</i> Room air (clinical ordinal score=5) I: 24 (10%) C: 17 (7%) Low-flow oxygen (clinical ordinal score=4) I: 120 (51%) C: 121 (50%) High-flow oxygen or non-invasive positive pressure ventilation (clinical ordinal score=3) I: 92 (39%) C: 105 (43%)</p> <p>Groups comparable at baseline? Yes</p>					
6.14. Mavrilimumab (human monoclonal antibody; anti-GM-CSF-Rα; human isoform IgG4)							
Cremer, 2021 MASH-COVID study	<p><u>Type of study:</u> RCT; double-blind, placebo-controlled</p> <p><u>Setting:</u> seven hospitals in the USA (three referral centres and four community hospitals)</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> Kiniksa Pharmaceuticals;</p>	<p>Hospitalized COVID-19 patients with documented COVID-19 pneumonia; not mechanically ventilated</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • In-patient hospitalisation for COVID-19; • documented COVID-19 pneumonia defined as positive upper respiratory tract specimen for SARS-CoV-2 with associated abnormalities or infiltrates on chest x-ray or chest CT; • active fever or documented fever within 48 h or antipyretic use; 	<p>Mavrilimumab</p> <p>Mavrilimumab 6 mg/kg was administered as a single intravenous infusion.</p> <p>Concomitant medications included antiviral drugs related to COVID-19, corticosteroids, convalescent plasma, other immunosuppressive agents, and antimicrobial drugs related to non-COVID-19 infections.</p>	<p>Placebo</p> <p>For placebo, an equal volume of diluent was given intravenously via the same infusion pump that was used for mavrilimumab.</p> <p>Concomitant medications included antiviral drugs related</p>	<p><u>Length of follow up:</u> 14-28 days, some of exploratory variables 60 days</p> <p><u>Loss to follow-up:</u> I: 0 C: 1 (5.3%), missed visit</p>	<p>Clinical outcomes</p> <p><u>Mortality (28-30 day)</u> Mortality at day 28 I: 1 (5%) C: 3 (16%), p= 0.22 HR 3-72 [0.39–35.79]</p> <p>Mortality at day 60 I: 1 (5%) C: 4 (21%), p=0.11</p> <p><u>Duration of hospitalization</u> Duration of hospitalisation, days, median (IQR) I: 7.5 (6.0–11.0) C: 8.0 (6.0–10.0), p=0.92</p>	<p><u>Definitions:</u></p> <p>*7-category ordinal scale: (1) not hospitalised, not on supplemental oxygen; (2) not hospitalised but on supplemental oxygen; (3) hospitalised, not requiring supplemental oxygen; (4) hospitalised, requiring supplemental oxygen; (5) hospitalised, requiring nasal high-flow oxygen or non-invasive mechanical ventilation, or both; (6) hospitalised, requiring invasive mechanical ventilation, ECMO, or both; and (7) death</p> <p>RRR: Adjusted recovery rate ratios (RRRs) with</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>“the funder of the study provided the study drug, facilitated formation of the investigator consortium, assisted with study design and interpretation of the data, and had a role in editing the report. The investigator consortium and the funder conceived of the study. The funder of the study had no role in data analysis or data collection.”</p> <p><u>Conflicts of interest:</u> Interest reported in publication</p>	<ul style="list-style-type: none"> hypoxaemia, defined as room air oxygen saturation < 92% or requirement of supplemental oxygen; C-reactive protein concentration > 5 mg/dL <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> age < 18 years, absolute neutrophil count less than 1500/mm³, home oxygen therapy, mechanical ventilation, uncontrolled systemic bacterial infection onset of symptoms more than 14 days before hospital admission and enrolment <p><u>N total at baseline:</u> N = 40 Intervention: 21 Control: 19</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 54·8 (49·7–68·1) C: 59·0 (41·0–69·3) Sex, n/N (%) male: I: 14 (67%) C: 12 (63%) Time from symptom onset to hospitalisation, days I: 5 (2–8) C: 7 (5–8) Time from symptom onset to random assignment, days I: 9 (6–10) C: 9 (7–11) Hospitalised requiring nasal highflow oxygen, non-invasive ventilation, or both I: 10 (48%)</p>	<p>[Mavrilimumab is a monoclonal antibody that binds to the α subunit of the GM-CSF receptor and blocks intracellular signalling of GM-CSF]</p>	<p>to COVID-19, corticosteroids, convalescent plasma, other immunosuppressive agents, and antimicrobial drugs related to non-COVID-19 infections.</p>		<p>Discharge from hospital and no oxygen support by day 28 I: 15/21 (71%) C: 9/18 (50%)</p> <p><u>Time to symptom resolution</u> Time to clinical improvement; defined as time from randomisation to 2-point improvement on 7-category ordinal scale* or discharge from hospital; median I: 5 days [95% CI 3–7] C: 6 days [4–10]; RRR 1·47 [95% CI 0·75–2·87]; p=0·26;</p> <p><u>Respiratory support</u> Need for mechanical ventilation I: 5/21 (24%) C: 4/19 (21%) OR 1·2 [95% CI 0·26–5·21] Patients alive and off supplemental oxygen therapy at day 14 I: 12 (57%) C: 9 (47%), p= 0·76 OR 1·48 [95% CI 0·43–5·16]; Patients alive and without respiratory failure at day 28 I: 20 (95%) C: 15 (79%), p=0·43 OR 5·33 [0·54–52·7]</p> <p>Safety <u>Adverse events</u></p>	<p>95% CIs were calculated from a Cox proportional hazards model. The RRR is similar to the hazard ratio (HR) in survival analysis except for the beneficial outcome of clinical improvement; therefore, an RRR greater than 1 indicates clinical improvement.</p> <p><u>Remarks:</u> “A trial of 60 patients was planned, but given slow enrolment, the study was stopped early to inform the natural history and potential treatment effect.”</p> <p><u>Authors conclusion:</u> “Mavrilimumab did not show a statistically significant increase in the proportion of patients free of supplemental oxygen at day 14 among those with severe COVID-19 pneumonia, hypoxaemia, and systemic hyperinflammation, although this positive outcome was numerically more likely in patients treated with mavrilimumab. By day 28, patients who received mavrilimumab were also numerically more likely to be alive and without respiratory failure. Based on these hypothesis-generating results, larger trials should be completed.”</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		C: 10 (53%) Hospitalised requiring supplemental oxygen I: 11 (52%) C: 9 (47%) Baseline PaO2 to FiO2 ratio I: 138 (83–172) C: 136 (103–221) Baseline SOFA score I: 2 (2–3) C: 2 (2–3) Groups comparable at baseline.				Any serious adverse event I: 5 (24%), C: 4 (21%) Circulatory shock: I: 2 (10%), C: 1 (5%) Acute kidney injury I: 4 (19%), C: 3 (16%) Bacterial pneumonia I: 2 (10%), C: 1 (5%) Bacteraemia: I: 0, C: 0 Neutropenia: I: 0, C: 0 Alanine aminotransferase more than 3 times normal value I: 5 (24%), C: 3 (16%) Aspartate aminotransferase more than 3 times normal value I: 6 (29%), C: 4 (21%) Virological outcomes <u>Viral clearance</u> not reported	
6.15. Namilumab							
Fisher, 2021	See evidence table of Fisher (2021) by infliximab.						
6.16. Regdanvimab							
Streinu-Cercel, 2022	<u>Type of study:</u> 2-part, phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study <u>Setting:</u> Outpatients, enrolment between October 07, 2020 and December 18, 2020 <u>Country:</u> 23 centers across South Korea,	Outpatients with mild-to-moderate COVID-19 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • ≤18 years • Diagnosed with SARS-CoV-2 (RT-PCR) • Oxygen saturation ≥94% on room air • Not requiring supplemental oxygen • Patients who has one or more of the SARS-CoV-2 infection associated symptoms within 7 days prior to the study drug administration <u>Exclusion criteria:</u>	Intervention I: Single dose of regdanvimab (IV) 40 mg/kg on study day 1 Intervention II: Single dose of regdanvimab (IV) 80 mg/kg on study day 1 Patients could receive standard-of-care treatment, excluding	Placebo: 250 mL of 0.9% sodium chloride	<u>Length of follow-up:</u> 180 days <u>Incomplete outcome data & loss-to-follow-up:</u> Intervention (40 mg/kg): N=3 (2.9%) Reasons: investigator decision (n=1), patient withdrawal (n=2) Continuing on study n=102 (97.1%) Intervention (80 mg/kg):	Clinical outcomes <u>Mortality (28 day):</u> Mortality, n/N (%): 0 cases <u>Duration of hospitalization</u> Not reported <u>Patients requiring hospital admission, n/N (%)</u> I (40 mg/kg): 4/100 (4%) I (80 mg/kg): 5/103 (4.9%) C: 9/104 (8.7%) <u>Time to symptom resolution</u> Patients achieving clinical recovery, n/N (%) day 7	Primary outcome: <ul style="list-style-type: none"> • Time to conversion to negative nasopharyngeal swab specimen up to 28 • Time to clinical recovery up to day 14 Secondary outcome(s): <ul style="list-style-type: none"> • Proportion of patients with clinical symptoms requiring hospitalization, oxygen therapy, or death due to COVID-19 up to day 28 • Proportion of patients with conversion to negative RT-qPCR result • Proportion of patients requiring hospital admission • Proportion of patients requiring supplemental oxygen

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Romania, Spain and the United States</p> <p><u>Source of funding:</u> This work was supported by Celltrion, Inc. (Incheon, Republic of Korea). This research was also supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HQ20C0045).</p> <p><u>Conflicts of interest:</u> Yes, transparently reported</p>	<ul style="list-style-type: none"> Patients with a current serious health condition, or with ongoing or history of active or severe infections, were excluded. <p><u>N total at baseline:</u> N = 327 Intervention I (40 mg/kg): N=105 Intervention II (80 mg/kg): N=111 Control: N=111</p> <p><u>Important characteristics:</u> Age, median (IQR): I (40 mg/kg): 51 y (42-60) I (80 mg/kg): 51 y (40-60) C: 52 y (41-61)</p> <p>Sex, n/N (%) male: I (40 mg/kg): 59/105 (56.2%) I (80 mg/kg): 59/111 (53.2%) C: 48/111 (43.2%)</p> <p>Disease severity, Moderate disease Based on the presence of x-ray-confirmed or computed tomography-confirmed pneumonia at screening, n/N (%) I (40 mg/kg): 64/105 (61%) I (80 mg/kg): 65/111 (58.6%) C: 60/111 (54.1%)</p> <p>Groups comparable at baseline</p>	antiviral drugs and/or possible SARS-CoV-2 active drugs (only to be administered as rescue therapies).	Patients could receive standard-of-care treatment, excluding antiviral drugs and/or possible SARS-CoV-2 active drugs (only to be administered as rescue therapies).	<p>N=3 (2.7%) Reason: patient withdrawal (n=3)</p> <p>Continuing on study n=108 (97.3%)</p> <p>Control: N=2 (1.8%) Reason: patient withdrawal (n=2)</p> <p>Continuing on study n=109 (98.2%)</p>	<p>I (40 mg/kg): 53/94 (56.4%) I (80 mg/kg): 46/92 (50%) C: 37/99 (37.4%)</p> <p>Patients achieving clinical recovery, n/N (%) day 14 I (40 mg/kg): 72/94 (76.6%) I (80 mg/kg): 72/92 (78.3%) C: 63/99 (63.6%)</p> <p>Patients achieving clinical recovery, n/N (%) day 28 I (40 mg/kg): 82/94 (87.2%) I (80 mg/kg): 79/92 (85.9%) C: 71/99 (71.7%)</p> <p><u>Invasive respiratory support</u> mechanical ventilation n/N (%) I (40 mg/kg): 0/100 (0%) I (80 mg/kg): 1/103 (1%) C: 0/104 (0%)</p> <p><u>Non-invasive respiratory support</u> supplemental oxygen n/N (%) I (40 mg/kg): 4/100 (4%) I (80 mg/kg): 4/103 (3.9%) C: 9/104 (8.7%)</p> <p>Safety <u>Serious adverse events</u> 0 cases</p> <p>Virological outcomes <u>Viral clearance</u></p>	<ul style="list-style-type: none"> Proportion of patients with mechanical ventilation use Proportion of patients requiring rescue therapy Proportion of patients with ICU admission Proportion of patients with all-cause mortality Treatment-emergent adverse events and treatment-emergent serious adverse events <p><u>Definitions:</u> Conversion to negative RT-qPCR result was defined as a negative nasopharyngeal swab specimen based on RT-qPCR result at 2 or more consecutive time points (the first time point was taken as the time to conversion to negative RT-qPCR result).</p> <p><u>Remarks:</u> *Statistical tests are stratified by age (≥60 vs <60 years) and baseline comorbidities (yes vs no), therefore p-values are not reported here.</p> <p><u>Authors conclusion:</u> Regdanvimab showed a trend toward a minor decrease in time to negative conversion of RT-qPCR results compared with placebo and reduced the need for hospitalization and oxygen therapy in patients with mild-to-moderate COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Time to negative RT-qPCR result to day 28, median (95% CI), d I (40 mg/kg): 12.8 (9-12.9%) I (80 mg/kg): 11.9 (8.9-12.9) C: 12.9 (12.7-13.9) ¹	
6.17. Sotrovimab							
Gupta, 2022	<p>Type of study: Phase 3, double-blind, placebo-controlled, multicenter randomized clinical trial</p> <p>Setting: Non-hospitalized, between August 27, 2020 and March, 2021</p> <p>Country: 57 participating centers (6 sites in Brazil; 2 sites in Canada; 1 site in Peru; 3 sites in Spain; and 45 sites in the US).</p> <p>Source of funding: This study was sponsored by Vir Biotechnology Inc in collaboration with GlaxoSmithKline.</p>	<p>Non-hospitalized patients with symptomatic, mild to moderate COVID-19 at high-risk for progression requiring hospitalization or death</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≤18 years • RT-PCR-or antigen test confirmed COVID-19 • <5 days prior symptom onset • At least 1 of the following risk factors: <ul style="list-style-type: none"> - age of 55 years or older - diabetes requiring medication - obesity (body mass index >30) - chronic kidney disease - congestive heart failure - chronic obstructive pulmonary disease - moderate to severe asthma <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Hospitalized • Signs or symptoms of severe COVID-19 (shortness of breath at rest, oxygen saturation level <94%, or 	single intravenous infusion with 500 mg of sotrovimab over 1 hour on day 1.	single intravenous infusion with 500 mg of saline placebo over 1 hour on day 1.	<p>Length of follow-up: 29 days</p> <p>Incomplete outcome data & loss-to-follow-up: Intervention: N=6/528 (1.1%) Reasons: did not receive intervention as randomized (n=4), withdrawn based on physician decision (n=2)</p> <p>528 included in analysis of primary analysis at 29 d</p> <p>Control: N=2/529 (0.37%) Reason: did not receive intervention as randomized (n=2)</p> <p>529 included in analysis of primary analysis at 29 d</p>	<p>Clinical outcomes</p> <p>Mortality: All-cause mortality at 29 d, n/N (%) I: 0/528 (0%) C: 2/529 (0.37%)</p> <p>Duration of hospitalization Length of hospital stay, days (%) <u>0 d</u> I: 521 (99) C: 499 (94) <u>1-≤24 h</u> I: 1 (<1) C: 0 <u>1-≤8 d</u> I: 3 (<1) C: 19 (4) <u>9-≤15 d</u> I: 2 (<1) C: 3 (<1) <u>16-≤22 d</u> I: 1 (<1) C: 4 (<1) <u>23-≤29 d</u> I: 0 C: 4 (<1)</p> <p>Time to symptom resolution Not reported</p> <p>Invasive respiratory support Mechanical ventilation or extracorporeal membrane oxygenation</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Proportion of patients with COVID-19 progression through day 29 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Composite all-cause emergency department visit • Hospitalization of any duration for acute illness management • Death through day 29 • Progression to severe or critical respiratory COVID-19 requiring supplemental oxygen or mechanical ventilation <p>Definitions: ¹Defined as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity. In addition, there were possible Hy Law cases (alanine transaminase≥3 times upper limit of normal or total bilirubin2 times upper limit of normal) and patients with international normalized ratios greater than 1.5 considered to be serious adverse events.</p> <p>Remarks:</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> Transparently reported</p>	<p>required supplemental oxygen)</p> <p><u>N total at baseline:</u> N = 1057 Intervention: N=528 Control: N=529</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 53 y (41.5-62) C: 53 y (43-63)</p> <p>Sex, n/N (%) male: I: 229/528 (43%) C: 256/529 (48%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline? Yes</p>				<p>I: 0/528 (0%) C: 4/529 (0.8%)</p> <p><u>Non-invasive respiratory support</u> Low-flow nasal cannula or face mask I: 7/528 (1.3%) C: 12/528 (2.3%)</p> <p>Nonbreather mask, high-flow nasal cannula, or non-invasive ventilation I: 0/528 (0%) C: 10/529 (1.9%)</p> <p>Safety <u>Serious adverse events</u>¹ I: 11/523 (2.1%) C: 32/526 (6.1%)</p> <p>Virological outcomes <u>Viral clearance</u> Nasal SARS-CoV-2 viral detection at 8 d Negative I: 36/59 (61%) C: 39/68 (57%)</p> <p>Nasal SARS-CoV-2 viral detection at 29 d Negative I: 64/68 (94%) C: 72/68 (94%)</p>	<p>Standard of care is not described.</p> <p><u>Authors conclusion:</u> Among nonhospitalized patients with mild to moderate COVID-19 and at risk of disease progression, a single intravenous dose of sotrovimab, compared with placebo, significantly reduced the risk of a composite end point of all-cause hospitalization or death through day 29. The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.</p>
Self (2021)	<p><u>Type of study:</u> Multinational, double-blind, randomised, placebo-controlled, clinical trial.</p>	<p><u>Severely ill adults hospitalised with COVID-19.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Aged 18 years and older; • Admitted to hospital for acute medical care for COVID-19 with 	<p>Intervention 1: Sotrovimab</p> <p>Patients in the sotrovimab group received a single 500 mg dose of sotrovimab.</p>	<p>Control: placebo</p> <p>Patients in the placebo group received an intravenous</p>	<p><u>Length of follow-up:</u> 90 days.</p> <p><u>Loss-to-follow-up:</u> Intervention 1: N =5</p>	<p>Clinical outcomes <u>Mortality (up to day 90)</u> I1: 14/182 (8%) I2: 15/176 (9%) C: 13/178 (7%) I1 vs C: aHR 1.02 (95% CI 0.48 to 2.17)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> - The doses of sotrovimab and BRIL-196 plus BRIL-198 were selected on the basis of in-vitro and in-vivo animal model data suggesting that these doses</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> A total of 43 hospitals located in the USA, Denmark, Switzerland, and Poland.</p> <p><u>Country:</u> USA, Denmark, Switzerland, and Poland.</p> <p><u>Source of funding:</u> US National Institute of Health and Operation Warp Speed.</p> <p><u>Conflicts of interest:</u> See page 13 of the original article (too much information to mention).</p>	<p>laboratory-confirmed SARS-CoV-2 infection;</p> <ul style="list-style-type: none"> COVID-19 symptoms for up to 12 days. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients that received any SARS-CoV-2 neutralising monoclonal antibodies, hyperimmune immunoglobulin to SARS-CoV-2, or convalescent plasma from a person recovered from COVID-19 any time before admission to hospital. <p><u>N total at baseline:</u> N = 546 Intervention 1: N = 184 Intervention 2: N = 179 Control: N = 183</p> <p><u>Important characteristics:</u> Age, median (IQR): I1: 61 (50 to 74) I2: 61 (50 to 71) C: 60 (49 to 70)</p> <p>Sex, n/N (%) male: I1: 107/182 (59%) I2: 98/176 (56%) C: 103/178 (58%)</p> <p>Disease severity, mean (SD): <i>Defined by the Pulmonary ordinal scale category</i></p> <p><i>Category 2: unable to do usual activities and no supplemental oxygen</i> I1: 64/182 (35%) I2: 60/176 (34%) C: 52/178 (29%)</p>	<p>Intervention 2: BR11-196 plus BR11-198</p> <p>Patients in the BR11-196 plus BR11-198 group received 1000 mg of BR11-196 immediately followed by 1000 mg of BR11-198.</p>	<p>infusion of 0.9% sodium chloride solution in a manner that mimicked administration of either sotrovimab or BR11-196 plus BR11-198, depending on their matched group assignment.</p>	<p>Reasons: not described.</p> <p>Intervention 2: N = 5 Reasons: not described.</p> <p>Control: N = 9 Reasons: not described.</p>	<p>P=0.96 I2 vs C: aHR 1.15 (95% 0.54 to 2.41) P=0.72</p> <p><u>Duration of hospitalization</u> <i>Not reported.</i></p> <p><u>Time to symptom resolution</u> <i>Sustained clinical recovery by day 90:</i> I1: 160/182 (88%) I2: 155/176 (88%) C: 151/178 (85%)</p> <p>I1 vs C: RR 1.12 (95% CI 0.91 to 1.37) I2 vs C: 1.08 (95% CI 0.88 to 1.32)</p> <p><u>Respiratory support</u> Pulmonary ordinal outcome scale at day 5 (futility assessment)</p> <p><i>Category 1: can independently do usual activities</i> I1: 42/181 (23%) I2: 44/173 (25%) C: 40/178 (22%)</p> <p><i>Category 2: no supplemental oxygen; symptomatic and unable to do usual activities</i> I1: 66/181 (36%) I2: 58/173 (34%) C: 58/178 (33%)</p> <p><i>Category 3: supplemental oxygen < 4 L/min</i> I1: 42/181 (23%)</p>	<p>would provide lung concentrations with maximal antiviral activity for at least 3 weeks;</p> <ul style="list-style-type: none"> - Longer-term assessments, including at 6 months, 12 months, and 18 months, are planned for the future and are not reported here. <p><u>Authors conclusion:</u> In conclusion, in this multinational, double-blind, placebo-controlled, randomised clinical trial, the neutralising anti-SARS-CoV-2 monoclonal antibodies sotrovimab and BR11-196 plus BR11-198 did not show efficacy over placebo for improving clinical outcomes among adults hospitalised with COVID-19. Prespecified subgroup analyses suggested heterogeneity of treatment effect in the BR11-196 plus BR11-198 group by baseline endogenous neutralising antibody status, suggesting potential opportunity for monoclonal antibody therapies to be targeted to patients hospitalised with COVID-19 who have not developed endogenous antibodies.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Category 3: supplemental oxygen <4 L/min</i> I1: 76/182 (42%) I2: 74/176 (42%) C: 80/178 (45%)</p> <p><i>Category 4: supplemental oxygen ≥4 L/min</i> I1: 42/182 (23%) I2: 42/176 (24%) C: 46/178 (26%)</p> <p>Groups comparable at baseline? Yes.</p>				<p>I2: 33/173 (19%) C: 42/178 (24%)</p> <p><i>Category 4: supplemental oxygen ≥4 L/min</i> I1: 19/181 (10%) I2: 15/173 (9%) C: 14/178 (8%)</p> <p><i>Category 5: high-flow nasal canula or non-invasive ventilation</i> I1: 10/181 (6%) I2: 15/173 (9%) C: 14/178 (8%)</p> <p><i>Category 6: invasive ventilation, ECMO, mechanical circulatory support, or RRT</i> I1: 2/181 (1%) I2: 1/173 (1%) C: 1/178 (1%)</p> <p><i>Category 7: death</i> I1: 0/181 (0%) I2: 1/173 (1%) C: 1/178 (1%)</p> <p>Overall OR's: I1 vs C: aOR 1.07 (95% CI 0.74 to 1.56) P=0.72 I2 vs C: aOR 0.98 (95% CI 0.67 to 1.43) P=0.91</p> <p>Pulmonary-plus ordinal outcome scale at day 5 (futility assessment)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Category 1: can independently do usual activities</i> I1: 42/181 (23%) I2: 44/173 (25%) C: 40/178 (22%)</p> <p><i>Category 2: no supplemental oxygen; symptomatic and unable to do usual activities</i> I1: 66/181 (36%) I2: 58/173 (34%) C: 57/178 (32%)</p> <p><i>Category 3: supplemental oxygen <4 L/min</i> I1: 40/181 (22%) I2: 32/173 (18%) C: 42/178 (24%)</p> <p><i>Category 4: supplemental oxygen ≥4 L/min or extrapulmonary manifestations</i> I1: 20/181 (11%) I2: 18/173 (10%) C: 21/178 (12%)</p> <p><i>Category 5: high-flow nasal canula or non-invasive ventilation or severe stroke</i> I1: 9/181 (5%) I2: 15/173 (9%) C: 14/178 (8%)</p> <p><i>Category 6: invasive ventilation, ECMO, mechanical circulatory support, RTT, or vasopressor</i> I1: 4/181 (2%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I2: 5/173 (3%) C: 3/178 (2%)</p> <p><i>Category 7: death</i> I1: 0/181 (0%) I2: 1/173 (1%) C: 1/178 (1%)</p> <p>Overall OR's: I1 vs C: aOR 1.08 (95% CI 0.74 to 1.58) P=0.68 I2 vs C: aOR 1.00 (95% CI 0.68 to 1.46) P=0.99</p> <p>Safety <u>Adverse events</u> <i>Composite safety outcomes up to day 5:</i> I1: N = 36 (20%) I2: N = 46 (26%) C: N = 44 (25%)</p> <p>I1 vs C: aOR 0.75 (95% CI 0.44 to 1.26) P=0.28 I2 vs C: 1.14 (95% CI 0.69 to 1.86) P=0.62</p> <p><i>Composite safety outcomes up to day 28:</i> I1: N = 51 (28%) I2: N = 58 (33%) C: N = 57 (32%)</p> <p>I1 vs C: aHR 0.87 (95% CI 0.60 to 1.27) P=0.48 I2 vs C: aHR 1.10 (95% CI 0.76 to 1.59) P=0.62</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Composite safety outcomes up to day 90:</i> I1: N = 42 (23%) I2: N = 45 (26%) C: N = 48 (27%)</p> <p>I1 vs C: aHR 0.84 (95% CI 0.55 to 1.27) P=0.40 I2 vs C: 1.00 (95% CI 0.66 to 1.51) P>0.99</p> <p><i>Infusion reaction</i> I1: N = 19 (10%) I2: N = 23 (13%) C: N = 14 (8%)</p> <p>I1 vs C: aOR 1.30 (95% CI 0.61 (2.76) P=0.50 I2 vs C: aOR 1.83 (95% CI 0.89 to 3.77) P=0.10</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Gupta, 2021b	<p><u>Type of study:</u> Multi-center, double-blind, phase 3, RCT</p> <p><u>Setting:</u> 37 trial sites Enrollment August 27, 2020 through March 4, 2021.</p> <p><u>Country:</u></p>	<p>Non-hospitalized with symptomatic Covid-19 and at least one risk factor for disease progression</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ≥18 years of age • a positive result on reverse-transcriptase–polymerase-chain-reaction or antigen SARS-CoV-2 testing • onset of Covid-19 symptoms ≤5 days 	<p>Single intravenous infusion of sotrovimab (500 mg)</p> <p>a single 500-mg, 1-hour infusion of sotrovimab</p> <p>The trial design did not mandate any treatment for Covid-19 other than sotrovimab or placebo; as a result, the patients received treatment at the discretion of their</p>	<p>Placebo</p> <p>500 mg of saline placebo.</p> <p>The trial design did not mandate any treatment for Covid-19 other than sotrovimab or placebo; as a result, the patients</p>	<p><u>Length of follow-up:</u> 24 weeks</p> <p><u>Loss-to-follow-up:</u> Intervention: N=4 (1.4%) Reasons: Withdrawal of consent: n=3 Unknown reason: n=1</p> <p>Control: N=4 (1.4%)</p>	<p>Clinical outcomes <u>Mortality (through day 29)</u> I: 0/291 (0%) C: 1/292 (0%) RR: 0.33 (95%CI 0.01-8.18)</p> <p><u>Duration of hospitalization >24 hr</u> I: 3/291 (1%) C: 21/292 (7%) RR: 0.14 (95%CI 0.04-0.48)</p> <p><u>Time to symptom resolution</u></p>	<p><u>Definitions:</u> Severe Covid-19: defined as shortness of breath at rest, an oxygen saturation below 94%, or the use of supplemental oxygen Adverse events of special interest: infusion-related reactions (including hypersensitivity reactions)</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Prespecified interim analysis • No information on allocation concealment, blinding of care providers or outcome assessors.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Unites States, Canada, Brazil and Spain</p> <p><u>Source of funding:</u> Vir Biotechnology in collaboration with GlaxoSmithKline.</p> <p><u>Conflicts of interest:</u> Financial compensation by funders to authors. Some authors are employees of the funders.</p>	<ul style="list-style-type: none"> at least one of the following risk factors: <ul style="list-style-type: none"> ≥55 years diabetes obesity chronic kidney disease congestive heart failure COPD moderate-to-severe asthma <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> severe Covid-19 <p><u>N total at baseline:</u></p> <p><u>Efficacy</u> N = 583 Intervention: 291 Control: 292</p> <p><u>Safety</u> N = 868 Intervention: 430 Control: 438</p> <p><u>Important characteristics:</u></p> <p><u>Efficacy</u> Age, median (range): I: 53.0 y (18-96) C: 52.5 y (18-88)</p> <p>Sex, n/N (%) male: I: 135/291 (46%) C: 131/292 (45%)</p> <p>Disease severity, mean (SD): not reported</p> <p><u>Safety</u> Age, median (range): Not reported Sex, n/N (%) male: Not reported</p> <p>Disease severity, mean (SD): not reported</p>	physicians according to the local standard of care.	received treatment at the discretion of their physicians according to the local standard of care.	<p>Reasons: Withdrawal of consent: n=1 Unknown reason: n=3</p> <p><u>Incomplete outcome data: not reported</u> Intervention: N (%) Reasons (describe)</p> <p>Control: N (%) Reasons (describe)</p>	<p>Not reported</p> <p><u>Respiratory support (use of supplemental oxygen):</u> <u>Low-flow nasal cannula or face mask</u> I: 2/291 (0%) C: 19/292 (7%) RR: 0.11 (95%CI 0.02-0.45)</p> <p><u>Nonbreather mask, high-flow nasal cannula or noninvasive ventilation</u> I: 0/291 (0%) C: 5/292 (2%) RR: 0.09 (95%CI 0.01-1.64)</p> <p><u>Invasive mechanical ventilation</u> I: 0/291 (1%) C: 2/292 (0%) RR: 0.20 (95%CI 0.01-4.16)</p> <p>Safety <u>Adverse events</u> I: 73/291 (17%) C: 85/292 (19%) RR: 0.86 (95%CI 0.66-1.13)</p> <p><u>Serious adverse events</u> I: 7/291 (2%) C: 26/292 (6%) RR: 0.27 (95%CI 0.12-0.61)</p> <p><u>Adverse events of special interest</u> I: 6/291 (1%) C: 5/292 (1%) RR: 1.20 (95%CI 0.37-3.90)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<ul style="list-style-type: none"> No information on comparability of groups for the safety analysis No information on loss-to-follow up for safety analysis. The sponsors designed the trial, and the sponsors and trial investigators participated in data collection, analysis, and interpretation. Medical writers who were funded by Vir Biotechnology assisted in drafting the manuscript under the authors' direction. All the authors had confidentiality agreements with the sponsors. <p><u>Authors conclusion:</u> The results of this interim analysis of COMET-ICE indicate that sotrovimab can be a therapeutic agent for outpatients with Covid-19. Notably, a 500-mg dose may also permit intramuscular administration, which may increase the convenience of and access to therapeutic antibody agents for patients with Covid-19. Studies are currently under way to evaluate this route of administration. Given its in vitro activity against variants of interest and concern,¹⁴ as well as its ability to neutralize other sarbecoviruses, we speculate that sotrovimab has the potential to remain therapeutically active even as SARSCoV-2 continues to evolve.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline? For efficacy: As far as possible to assess using the information provided, yes. However, disease severity unknown. For safety: No information was provided on group level, no comparison was possible.					
6.18. Tixagevimab and cilgavimab (AZD7442)							
NA	NA	NA	NA	NA	NA	Na	NA
6.19. Vilobelimab (Anti-C5a antibody IFX-1; monoclonal anti-human complement factor C5a antibody)							
Vlaar, 2021	<p><u>Type of study:</u> Pragmatic adaptive, open-label, randomized phase 2/3 multicentre trial</p> <p><u>Setting:</u> Three academic hospitals (Amsterdam UMC, location AMC; UMC location VUmc; and Maastricht UMC)</p> <p><u>Country:</u> Netherlands</p> <p><u>Source of funding:</u> The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the</p>	<p><u>Patients with severe COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age 18 years or older; Severe pneumonia with pulmonary infiltrates consistent with pneumonia; A clinical history of severe shortness of breath within the past 14 days; A need for non-invasive or invasive ventilation; Severe disease defined as a ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air between 100 mm Hg and 250 mm Hg in the supine position; SARS-CoV-2 infection confirmed by RT-PCR. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Invasive mechanical ventilation for more than 48h; Improvement in PaO₂/FiO₂ or more than 30% in the past 24h; Known history of progressed chronic obstructive pulmonary disease; 	<p><u>Maximum of seven doses of IFX-1 800 mg intravenously plus best supportive care</u></p> <p>*Five doses of IFX-1 (days 1, 2, 4, 8, and 15) were administered to all patients assigned to the IFX-1 group who were admitted to hospital alive. A dose at day 22 was administered to patients who were still intubated on day 22. One additional dose of IFX-1 could be given between days 11 and 13 at the discretion of the investigator if signs of weakening of any clinical improvement were detected. Treatment with IFX-1 was discontinued if patients were discharged from hospital. IFX-1 (vilobelimab) was provided by InflaRx</p>	<p><u>Best supportive care only</u></p> <p>*Best supportive care in the participating centres consisted of intensive care therapy according to current guidelines, evidence, and best practice, including but not limited to lung protective ventilation, thrombosis prophylaxis, renal replacement therapy when indicated, and access to</p>	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: 0/15 (0%) Reasons: - C: 0/15 (0%) Reasons: -</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality, Kaplan-meier estimates (95% CI) at 28 days:</u> I: 13% (95% CI= 0 to 31) C: 27% (95% CI= 4 to 49) Adj. HR= 0.65 (95% CI= 0.10 to 4.14)</p> <p><u>Mortality for patients intubated within 6h after randomisation, Kaplan-meier estimates (95% CI) at 28 days:</u> I: 20% (95% CI= 0 to 45) C: 40% (95% CI= 10 to 70) HR= 0.48 (95% CI= 0.07 to 3.35)</p> <p><u>PaO₂/FiO₂ at day 5, mean (SD) (range)</u> I: 158 (63) mm Hg (95% CI= 84 to 265) C: 189 (89) mm Hg (95% CI= 71 to 329)</p> <p><u>PaO₂/FiO₂ at day 5 in supine position, mean (range)</u> I: 148 mm Hg (0 to 263)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> The safety and tolerability analysis of this phase 2 part of the study did not result in any signals of concern. We believe that the totality of observed safety and preliminary efficacy signals support continuation to the phase 3 part. Ultimately, the phase 2 part of the PANAMO trial was exploratory in nature and efficacy of IFX-1 in patients with COVID-19 must be confirmed in an adequately and separately powered controlled phase 3 part of the PANAMO study.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	data in the study and had final responsibility for the decision to submit for publication.	<ul style="list-style-type: none"> • Severe congestive heart failure; • Known pregnancy; • Chronic dialysis; • Cancer; • Other lifelimiting disease with life expectancy less than 6 months; • Renal replacement therapy; • Cardiac resuscitation in the past 14 days; • Organ or bone marrow transplantation in the past 3 months; • Anticancer therapy for oncological disease in the past 4 weeks; • Corticosteroid treatment equivalent to 10 mg prednisone or more per day; • Treatment with other biological therapy for COVID-19 in the past 14 days; • Use of viral replication inhibitor in the past 3 days. <p><u>N total at baseline:</u> N = 30 Intervention: 15 Control: 15</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 58 y (9) C: 63 y (8)</p> <p>Sex, n/N (%) male: I: 11/15 (73%) C: 11/15 (73%)</p> <p><u>Disease severity</u> Not reported.</p> <p>Groups comparable at baseline?</p>		advanced therapies including extracorporeal membrane oxygenation		<p>C: 182 mm Hg (61 to 329) *16% change in the IFX-1 group vs 32% change in the control group) Difference: -16 (95% CI= -53 to 20)</p> <p>** Subgroup analyses of patients intubated at baseline or within 6 h after randomisation showed similar results</p> <p><u>Safety</u> <i>Patients with serious adverse events, n/N (%):</i> I: 9/15 (60%) C: 7/15 (47%)</p> <p><i>Total number of serious adverse events:</i> I: N = 23 C: N = 19</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Baseline characteristics were well balanced between treatment groups, although the IFX-1 group had more patients with two or more risk-associated comorbidities (four [27%] of 15) than the control group (one [7%] of 15).					
6.20. Secukinumab							
Resende (2022)	<p><u>Type of study:</u> Investigator-initiated, randomized, open-label, single-centre, phase-II controlled (without placebo) trial.</p> <p><u>Setting:</u> Hospital Risoleta Tolentino Neves, referral centre for treatment of COVID-19 in the northern region of Belo Horizonte city.</p> <p><u>Country:</u> Brazil.</p> <p><u>Source of funding:</u> Novartis Brazil supported this research providing expert input in the development of the project, drug supply, data management, and monitoring. This project was also</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Adult patients aged 18 years or older; • Patients admitted to the hospital; • SARS-CoV-2 infection confirmed by RT-PCR of nasopharyngeal swab; • Severe acute respiratory syndrome (SARS), according to the Brazilian Ministry of Health criteria (dyspnoea/respiratory discomfort OR persistent chest pressure OR oxygen saturation less than 95% in room air OR cyanosis of lips or face). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Functional classes III and IV of congestive heart failure; • Chronic obstructive pulmonary disease, • Stages 4 and 5 of chronic kidney disease (GFR <30 mL/min); • Diabetic ketoacidosis; • Known history of HIV/AIDS infection; • Chronic or acute HBV or HCV infection; • Unrestrained bacterial or fungal co-infections (defined by hemodynamic instability, prior 48h of antimicrobial covering, 	<p>Secukinumab plus standard of care</p> <p>300 mg of secukinumab subcutaneously at day-0 plus standard of care. A second dose of 300 mg of secukinumab could be administered at day 7, according to the judgement of the attending medical team and if all enrolment criteria still remained met.</p>	<p>Standard of care alone</p> <p>Standard of care was not further explained.</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: N=0 (0%)</p> <p>Control: N=2 (8%) Reasons: N=1 withdrew consent, alleging intolerable discomfort with sequential blood and nasopharyngeal swab collection. N=1 was excluded due to a protocol deviation (only after enrolment, the patient was found to be receiving post-transplant immunosuppression).</p>	<p>Clinical outcomes – all outcomes were reported at 28 days follow-up</p> <p><u>Mortality</u> I: 1/25 (4.0%) 1/23 (4.4%) P=1.00</p> <p><u>Duration of hospitalization</u> <i>Hospital days, mean (SD)</i> I: 9.3 (8.1) days C: 11.0 (7.4) days P=0.34</p> <p><i>Number of patients admitted to the intensive care unit, n/N (%)</i> I: 7/25 (28%) C: 9/23 (39%) P=0.54</p> <p><i>Intensive care unit days, mean (SD)</i> I: 4.0 (9.0) days C: 3.2 (6.3) days P=0.55</p> <p><u>Time to symptom resolution</u> <i>WHO scale ≤1, n/N (%)</i> I: 12/25 (48%) C: 6/23 (26%)</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Ventilator-free days at day 28 (defined as 28 – x, where x is the number of days spent receiving mechanical ventilation). <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Mortality rate; • Length of hospitalisation; • Need and length of critical care in the ICU; • WHO scale; • Adverse events (any undesirable event associated at least with prolongation of hospitalization); • Secondary bacterial and fungal infections (culture-confirmed); • Incidence of renal failure; • Circulatory shock or need for vasopressors; • Pulmonary thromboembolism; • Reactions at the injection site. <p><u>Definitions:</u> WHO ordinal scale: 1=can independently undertake usual activities with minimal or no symptoms; 2=no supplemental oxygen, symptomatic and unable to undertake usual activities; 3=supplemental oxygen <4 L/min;)</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>supported by CNPq.</p> <p><u>Conflicts of interest:</u> GGR received personal payments for lectures from Abbvie, Janssen, Lilly, Novartis and UCB; support for attending meetings and/or travel from Abbvie, Janssen, Lilly, Novartis and UCB; and personal payments for participation on a data safety monitoring board or advisory board Abbvie, Janssen, Lilly and Novartis. RCL received honoraria for presentations and speakers bureaus; and support for attending meetings, including travel and hotel expenses from Novartis. RT and FF were Novartis employees until this submission. ADCS, AFM, ATNS, AJAO, DS, HCG, ICG, MMT, SQL, RSA, JSSBF and RPS declare no competing interests.</p>	<p>or at the discretion of the study's medical coordinator);</p> <ul style="list-style-type: none"> • Active tuberculosis; • History of malignancy in the last year; • Current use (or in the previous 15 days) of other immunosuppressants; • Baseline neutrophils count (<1000/mm³); • Pregnancy; • Breastfeeding woman. <p><u>N total at baseline:</u> N = 50 Intervention: N=25 Control: N=25</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 54 y (45-65) C: 54 y (40-63)</p> <p>Sex, n/N (%) male: I: 10/25 (40%) C: 16/25 (64%)</p> <p>Disease severity, mean (SD): <i>Defined by WHO scale, median (IQR):</i> I: 4 (4-4) C: 4 (4-4) P=0.48</p> <p>Groups comparable at baseline. of Groups not comparable at baseline: Yes.</p>				<p>P=0.14</p> <p><i>WHO scale mean score, mean (SD)</i> I: 2.3 (2.1) C: 2.1 (1.5) P=0.31</p> <p><u>Invasive respiratory support</u> <i>Mechanical ventilation, n/N (%)</i> I: 5/25 (20%) C: 5/23 (22%) P=1.00</p> <p><u>Non-invasive respiratory support</u> Not reported.</p> <p>Safety <u>Serious adverse events</u> <i>Number of patients with SAE, n/N (%)</i> I: 5/25 (20%) C: 6/23 (26%) P=0.73</p> <p><i>Any SAE, n/N (incidence/100 patients-days)</i> I: 16 (2.3) C: 11 (1.7) P=0.56</p> <p><u>Adverse events</u> Not reported.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	<p>4=supplemental oxygen \geq4 L/min or symptoms/signs of extra-pulmonary conditions;</p> <p>5=non-invasive ventilation, high-flow oxygen, or symptoms and signs of acute stroke (National Institute of Health Stroke Scale >14)</p> <p>6=invasive ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy; 7=death)</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> The efficacy of secukinumab in the treatment of Covid19 was not demonstrated. Secukinumab decreased pulmonary embolism in male patients. There was no difference between groups in adverse events and no unexpected events were observed.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
7. Polyclonal antibodies							
<p>Loipardo, 2021</p>	<p><u>Type of study:</u> Phase 2/3, double-blind, placebo-controlled, multicenter clinical trial.</p> <p><u>Setting:</u> Nineteen clinical sites of Argentina. August 1st - October 26th, 2020</p> <p><u>Country:</u> Argentina</p> <p><u>Source of funding:</u> The study was funded by Inmunova S.A. and grants from the Ministries of Science and Production of Argentina: "Ministerio de Desarrollo Productivo - Programa solucion. Reactivacion de la economía del conocimiento" and "Agencia Nacional de Promocion de la Investigacion, el Desarrollo Tecnológico y la Innovacion del Ministerio de Ciencia, Tecnología e Innovacion".</p>	<p><u>Hospitalized adult COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Positive RT-PCR for SARS-CoV-2; Between 18 and 79 years old; Within 10 days from the initiation of symptoms; Hospitalized with a diagnosis of moderate or severe COVID-19 disease and provided a voluntary undelegated written informed consent. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Pregnant woman or during lactation period; History of treatment with SARS-CoV-2 convalescent plasma; Participation in other therapeutic clinical trial for COVID-19; History of anaphylaxis; Severe allergic reaction to equine sera or to contact or exposure to horse proteins; Hospitalization in ICU and/or requirement of mechanical ventilation; Likelihood of death due to clinical reasons other than COVID-19 	<p>Starting within 24 h from patient enrollment, two INM005 doses of 4 mg/kg</p> <p>*Each were administered as intravenous infusion of 100 ml over a period of fifty minutes with an interval of 48 h between them.</p> <p>**All patients received supportive care according to the standard of care of each participating hospital.</p>	<p>Matching placebo.</p> <p>*Each were administered as intravenous infusion of 100 ml over a period of fifty minutes with an interval of 48 h between them.</p> <p>**All patients received supportive care according to the standard of care of each participating hospital.</p>	<p><u>Length of follow up:</u> 28 days period after the first dose.</p> <p><u>Loss to follow-up:</u> No patients were lost to follow-up, neither discontinued study treatment due to a treatment emergent adverse event.</p>	<p><u>Clinical outcomes</u> <u>Mortality (overall), n/N (%)</u> I: 8/118 (6.9%) C: 14/123 (11.4%) HR 0.575 (95% CI 0.241 to 1.371).</p> <p><u>Duration of hospitalization</u> <u>Time until discharge (days), mean (SD)</u> I: 8.7 (0.6) C: 10.2 (0.7) HR 1.26 (95% CI 0.96 to 1.66) P=0.09</p> <p><u>Time until discharge from ICU (days), mean (SD)</u> I: 24.7 (0.8) C: 23.6 (0.8) HR 0.67 (95% CI 0.35 to 1.28) P=0.22</p> <p><u>Time to symptom resolution</u> <u>Improvement in at least two categories in WHO ordinal clinical scale at day 28 or discharge</u> I: 106/118 (89.8%) C: 104/123 (84.5%) RD 5.28% (95% CI -3.95 to 14.50) P=0.15</p> <p><u>Time to achieve improvement in at least two categories on the ordinal clinical scale (days), mean (SD)</u> I: 14.2 (7.0)</p>	<p><u>Definitions:</u> Moderate illness was defined as patients who had any of the various symptoms and signs of COVID-19 plus evidence of lower respiratory disease during clinical assessment or imaging and who had oxygen saturation (SpO2) >93% on room air at sea level.</p> <p>Severe illness was defined for individuals who had SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%.</p> <p>AE: Adverse event; TEAE: Treatment-emergent adverse event; SAE: Serious adverse event; AESI: Adverse event of special interest.</p> <p><u>Remarks:</u> -</p> <p><u>Author's conclusion:</u> In summary, as shown in this randomized clinical trial, INM005 appears as an attractive and safe agent for the treatment of patients with severe COVID-19 disease that deserves further evaluation. Future studies will help to define a more precise role of this treatment in the context of current COVID-19 pandemic.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> MC, SS, VZ, LM, LS, FG received grants from Ministries of Science and Production of Argentina. MD, JF, GV, AB, FC, MFA, LB, RT, SL, DS, MI, VS, RS, PC, MMC, LA, HLL, AC, DC declare reimbursement for conduct of clinical trial as investigator of the study. PC, OS, YK report other funds from Inmunova S.A. EN, GL, WHB, SPLL report personal fees from Inmunova S.A. SM reports non-financial support from Inmunova S.A. AP, B de M, Gabriel L declare no competing interests. SPLL declare personal fees from Movement Disorders Society, Laboratorio Elea and Merck pharmaceuticals. MC, SS, VZ, LM, LS are employed by Inmunova S.A.</p>	<p>within the following 30 days;</p> <ul style="list-style-type: none"> Expected transfer to other healthcare institutions. <p><u>N total at baseline:</u> N = 241 Intervention: N =118 Control: N = 123</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 54 (43 to 63) C: 54 (45 to 65)</p> <p>Sex, n/N (%) male: I: 80/118 (67.8%) C: 77/123 (62.6%)</p> <p>Disease severity (ordinal scale): <i>Category 3 (not requiring oxygen)</i> I: 54/118 (45.8%) C: 55/123 (44.7%)</p> <p><i>Category 4 (requiring supplemental oxygen)</i> I: 61/118 (51.7%) C: 64/123 (52.0%)</p> <p><i>Category 5 (receiving non-invasive mechanical ventilation or high-flow oxygen devices)</i> I: 3/118 (2.5%) C: 4/123 (3.3%)</p> <p>Disease severity: COVID-19 classification: <i>Moderate</i> I: 74/118 (62.7%) C: 73/123 (59.3%)</p> <p><i>Severe</i></p>				<p>C: 16.3 (0.7) HR 1.31 (95% CI 1.00 to 1.74) P=0.05</p> <p><i>Improvement in at least two categories in WHO ordinal clinical scale at day 28 (%), mean (SD)</i> I: 87.3 (3.1) C: 79.7 (3.6) P=0.08</p> <p><i>Improvement in at least two categories in WHO ordinal clinical scale or discharge at day 7 (%), mean, (SD)</i> I: 64.1 (4.4) C: 58.3 (4.5) P=0.26</p> <p><i>Improvement in at least two categories in WHO ordinal clinical scale or discharge at day 14 (%), mean (SD)</i> I: 87.3 (3.1) C: 79.7 (3.6) P=0.05</p> <p><i>Improvement in ordinal scale for clinical status scale (AUC), mean (SD)</i> I: 60.5 (41.7) C: 73.7 (49.4) MD -13.14 (95% CI -1.56 to -24.72) P=0.02</p> <p><u>Respiratory support</u> <i>Patients requiring ICU admission at day 28 (%)</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	ClinicalTrials.gov NCT04494984	I: 44/118 (37.3%) C: 50/123 (40.7%) Groups comparable at baseline? Yes.				<p>I: 12.7 (3.1) C: 17.8 (3.5) P=0.11</p> <p><i>Patients requiring invasive mechanical ventilation at day 28 (%)</i> I: 9.3 (2.6) C: 13.9 (2.9) P=0.19</p> <p>Safety <u>Adverse events</u> <i>Subjects with any AE, n/N (%)</i> I: 52/119 (43.7%) C: 55/124 (44.3%)</p> <p><i>Subjects with any SAE, n/N (%)</i> I: 16/119 (13.4%) C: 25/124 (20.1%)</p> <p><i>Subjects with any related treatment-emergent SAE, n/N (%)</i> I: 2/119 (0.8%) C: 1/124 (0.8%)</p> <p><i>Subjects with any treatment-emergent AESI, n/N (%)</i> I: /119 (7.6%) C: 2/124 (1.6%)</p> <p><i>Subjects with a related TEAE, n/N (%)</i> I: 21/119 (17.6%) C: 12/124 (9.7%)</p> <p><i>Subjects with any AE with fatal outcome (data</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments		
						<p>included deaths after day 28) I: 11/119 (9.2%) C: 16/124 (12.9%)</p> <p>Subjects with any related TEAE with fatal outcome, n/n (%) I: 0/119 (0%) C: 0/124 (0%)</p> <p>Subjects with any TEAE that required permanent treatment discontinuation, n/n (%) I: 0/119 (0%) C: 0/124 (0%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>			
8. Supplements									
8.1. Vitamin C									
Majidi (2021)	<p><u>Type of study:</u> Double-blind, randomized clinical trial.</p> <p><u>Setting:</u> Razi Hospital, Rasht, May to July 2020</p> <p><u>Country:</u> Iran.</p> <p><u>Source of funding:</u> The funding for this study was provided by Sabzevar University of</p>	<p><u>Critically ill patients infected with SARS-CoV-2.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age between 35 and 75; • Diagnosed as COVID-19 positive; • Patients likely to be in the intensive care unit for at least 48h; • An indication for enteral nutrition. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • No completion of the study because of death; • Contraindication to enteral nutrition or intolerance to enteral nutrition so that 	Vitamin C	One capsule of 500 mg of vitamin C daily by adding the supplement to their enteral feeding	Control	The same nutritional support using the same route, although no vitamin C was added to their enteral formula.	<p><u>Length of follow-up:</u> 14 days.</p> <p><u>Loss-to-follow-up:</u> Intervention: N = 9 Reasons: death (N=3) and no indication for enteral feeding/vitamin C (N=6)</p> <p>Control: N = 11 Reasons: death (N=4) and no indication for enteral feeding/vitamin C (N=7)</p>	<p>Clinical outcomes <u>Survival rate on day 14</u> I: 5/31 (16.1%) C: 2/69 (2.9%) (p = 0.028)</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u> Not reported.</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> The results of this study indicated a significant negative correlation between vitamin C supplementation with the level of serum K in patients with COVID-19. Daily supplementation of 500 mg vitamin C resulted in an increase in the survival duration of the patients. Our results further indicated that vitamin C supplementation had no effect on kidney function, ABG parameters, GCS, CBC, and other serum electrolytes such</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Medical Sciences, Sabzevar, Iran (code 99213)</p> <p><u>Conflicts of interest:</u> The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.</p>	<p>supplementation with vitamin C was not possible;</p> <ul style="list-style-type: none"> Contraindications to vitamin C supplementation due to different reasons (such as interaction with drugs) before 14 days of the baseline sampling. <p><u>N total at baseline:</u> N = 120 Intervention: 40 Control: 80</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 59.42 y (15.07) C: 63.82 y (14.58)</p> <p>Sex, n/N (%) male: I: 19/31 (61%) C: 41/69 (58%)</p> <p>Disease severity: not reported.</p> <p>Groups comparable at baseline? Yes.</p>				<p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	<p>as Na, Ca, and P. Further clinical studies are needed to confirm the effect of vitamin C and on COVID-19.</p>
Zhang, 2021	<p><u>Type of study:</u> RCT; multicenter</p> <p><u>Setting:</u> ICU's of Zhongnan Hospital of Wuhan University, Leishenshan Hospital, and Taihe Hospital; Feb 14, 2020, to March 29, 2020.</p> <p><u>Country:</u> China</p>	<p>Hospitalized, critically ill COVID-19 patients</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age \geq 18 and $<$ 80 years RT-PCR positive SARS-CoV-2 pneumonia confirmed by chest imaging admission to the ICU; PaO₂/ FiO₂ (P/F) $<$ 300 mmHg <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> allergy to vitamin C pregnancy or breastfeeding, 	<p>Vitamin C</p> <p>High-dose intraven. vitamin C:</p> <p>24 g vitamin C per day. Patients were infused with 12 g vitamin C diluted in 50 ml of bacteriostatic water every 12 h at a rate of 12 ml/hour by infusion pump for 7 days; Infused via central vein catheterization controlled by a pump.</p>	<p>Placebo</p> <p>50 ml of bacteriostatic water infused every 12 h at the same rate.</p>	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: 0/27 C: 0/29</p>	<p>Clinical outcomes <u>Mortality, 28-day</u>, n, % I: 6(22.2) C: 10(34.5) HR 0.5(0.2 to 1.8), p 0.31 Mortality patients SOFA \geq 3, n, % I: 5(21.7) C: 10(47.6) HR 0.3 (0.1 to 1.1), p 0.07 <u>ICU mortality</u>, n, % I: 6(22.2) C: 11(37.9) HR 0.5(0.2 to 1.5), p 0.20 ICU mortality patients SOFA \geq3, n, %</p>	<p><u>Remarks:</u></p> <ul style="list-style-type: none"> Unclear how many patients received respiratory support or were intubated at baseline Outcomes and timing differ from study protocol <p><u>Authors conclusion:</u> "[...] this pilot trial showed that HDIVC (= High-dose intraven. vitamin C) did not improve the primary endpoint, IMVFD28 (= Invasive mechanical ventilation (IMV)-free days in 28 days), but</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> This work was funded by the Science and Technology Department of Hubei Province (2020FCA024, 2020FCA020), and the Fundamental Research Funds for the Central Universities (2042020kfxg18, 2042020kfxg13).</p>	<ul style="list-style-type: none"> • expected survival duration < 24 h • previous history of glucose-6-phosphate dehydrogenase deficiency or end-stage pulmonary disease • already enrolled in other clinical trials <p><u>N total at baseline:</u> N = 56 Intervention: 27 Control: 29</p> <p><u>Important characteristics:</u> Age, mean ± SD: I: 66.3 ± 11.2 y C: 67.0 ± 14.3 y Sex, n/N (%) male: I: 15/27 (55.6%) C: 22/29 (75.9%) Median duration of symptoms before therapy, days I: 22.0 [IQR 11.0–33.0] C: 15.0 [IQR 11.0–22.0] Respiratory support at baseline: I, C: Unclear</p> <p>APACHE II score All: 13.5[10.3–15.8] I: 14.0[11.0–16.0] C: 13.0[9.5–15.0], p 0.24 GCS score All: 15.0[14.5–15.0] I: 15.0[13.0–15.0] C: 15.0[15.0–15.0], p 0.75</p> <p>Other treatments during 7 days therapy: Corticosteroid use, n, % I: 8/27 (36.4%) C: 10/29 (38.5%) Antibiotic, n, %</p>				<p>I: 5 (21.7) C: 11(52.4) HR 0.2(0.1 to 0.9), p 0.04</p> <p><u>Duration of hospitalization</u> Length of ICU stay, days I: 22.9 ± 14.8 C: 17.8 ± 13.3 Diff coeff 5.0(– 2.5 to 12.7), p 0.20 Length of hospital stay, days I: 35.0 ± 17.0 C: 32.8 ± 17.0 Diff coeff 2.2(– 7.5 to 11.8), p 0.65</p> <p><u>Symptom resolution</u> <u>Patient condition improvement rate;</u> defined as the patient requiring ECMO or IMV on day 1 and switching to HFNC, NIV, or discharged from the ICU after 7 days of treatment, n, % I: 5 (19.2) C: 6 (21.4) Diff coeff. 0.9 (0.2 to 3.3), p 0.84</p> <p><u>Patient condition deterioration rate;</u> defined as the patient requiring HFNC or NIV on day 1 and requiring ECMO or IMV, or dying, after 7 days of treatment, n, %: I: 3 (11.5) C: 6 (24.0) Diff coeff. 0.4 (0.1 to 1.7), p 0.19</p>	demonstrated a potential signal of benefit for critically ill COVID-19, with an improvement in P/F ratio.”

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 24/27 (92.3%) C: 27/29 (96.4%)</p> <p>Groups comparable at baseline.</p>				<p><u>Advanced life support, n, %</u> CRRT Day 1: I: 1(3.8) C: 3(10.7) OR 0.3(0.0 to 3.5), p 0.61 Day 7: I: 3(12.5) C: 1(3.8) OR 3.57(0.4 to 36.9), p 0.34 ECMO Day 1: I: 1(3.8) C: 2(7.1) OR 0.5(0.0 to 6.0), p 1.00 Day 7: I: 7 0(0.0) C: 2(9.1) OR 0.5(0.4 to 0.7), p 0.50</p> <p><u>Sequential organ failure assessment (SOFA) score</u> Day 1 I: 3.5 [3–6.8] C: 2.0 [3.0–5.0] Diff coeff 0.7 (– 0.9 to 2.3), p 0.37 Day 3 I: 4.0 [2.0–8.0] C: 4.0 [3.0–7.0] – 0.3 (– 2.6 to 1.9), p 0.50 Day 7 I: 3.0 [2.0–5.8] C: 6.0 [2.50–8.0] Diff coeff – 1.14 (– 3.1 to 0.8), p 0.24 Δ 7 I: 0.0 [–2.75–1.0] C: 0.0 [–1.0–3.5] Diff coeff – 1.35 (–3.04–0.34), p 0.25</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Also reported: lowest PaO₂/FiO₂, lowest MAP (mean arterial pressure), indicators and inflammation biomarkers</p> <p><u>Need for respiratory support</u> Invasive mechanical ventilation (IMV)-free days in 28 days, <i>defined as the number of days a patient was extubated after recruitment to day 28; if the patient died with MV, a value of zero was assigned; median [IQR]:</i> I: 26.0 [9.0–28.0] C: 22.0 [8.5–28.0] Diff coeff. 1.3 (– 4.7 to 7.2) IMV days to day 28, days I: 1.5 [0.0–19.0] C: 6.0 [0.0–16.0] Diff coeff. – 0.8 (– 6.4 to 4.9) High flow nasal cannula (HFNC) days to day 28, days I: 0.5 [0.0–8.3] C: 2.0 [0.0–7.0] Diff coeff. 0.2 (– 2.9 to 3.3) Non-invasive mechanical ventilation (NIV) days to day 28, days I: 0.0 [0.0–3.3] C: 0.0 [0.0–1.8] Diff coeff. 1.2 (– 1.2 to 3.7)</p> <p>Oxygen-support category HFNC</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Day 1: I: 7(25.9) C 11(37.9) OR 0.6(0.2 to 1.8), p 0.40</p> <p>Day 7: I: 11(47.8) C: 9(39.1) OR 14.3(0.4 to 4.6), p 0.77</p> <p>NIV</p> <p>Day 1: I: 7(25.9) C: 7(24.1) OR 1.1(0.3 to 3.7), p 1.00</p> <p>Day 7 : I: 7(30.4) C: 2(8.7) OR 4.6(0.8 to 25.2), p 0.14</p> <p>IMV</p> <p>Day 1: I: 11(40.7) C: 12(41.3) OR 1.0(0.3 to 2.9), p 1.00</p> <p>Day 7: I: 10(43.5) C: 11(47.8) OR 0.8(0.3 to 2.7), p 1.00</p> <p>Safety <u>Adverse events</u> Serum creatinine during 7-day infusion period: I: Day 1: 64.20[46.58–85.45] Day 7: 57.50[39.95–71] umol/L C: Day 1: 64.20[52.00 - 81.70] Day 7: 63.50[51.70–104.50] umol/L <i>“There were no changes in total bilirubin from day 1 to day 7 in HDIVC, while there was a slight increase</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>from day 1 to day 7 in placebo.”</p> <p>Study related AE's I: 0; C: 0 SAE's requiring stop study participation I: 0; C: 0</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	
Thomas, 2021	<p>Type of study: Prospective randomized clinical open-label trial</p> <p>Setting: Multiple hospitals within a single health system.</p> <p>Country: Ohio and Florida, USA.</p> <p>Source of funding: Thomas, Kumar, Desai.</p> <p>Conflict of Interest: Dr McWilliams reported receiving consulting fees from Gilead Sciences outside the submitted work. Dr Desai reported receiving grants from Myokardia outside the submitted work and being</p>	<p>Adult patients diagnosed with SARS-CoV-2 infection with a polymerase chain reaction-based assay</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients aged 18 years and older; • Patients who had a new diagnosis in an outpatient setting; • Woman of childbearing potential who had a confirmed menstrual period within the past 30 days previous sterilization; • Woman who were perimenopausal required a negative pregnancy test. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Hospitalized patients; • Patients who resided outside of Ohio or Florida; • Pregnant woman; • Actively lactating woman; • Patients with advanced chronic kidney disease; • Patients with liver disease awaiting transplantation; 	<p>Intervention 1: 8000 mg of ascorbic acid (to be divided over 2-3 times per day with meals)</p> <p>Intervention 2: 50 mg of zinc gluconate at bedtime</p> <p>Intervention 3: Both therapies.</p>	Control: Usual care without any study medications.	<p>Length of follow up: 10 days</p> <p>Loss to follow-up: Intervention 1: - N=14 did not complete follow up; - N=7 was lost to follow-up; - N=7 discontinued intervention - N=1 hospitalized - N=4 other</p> <p>Intervention 2: - N=20 did not complete follow-up; - N=11 was lost to follow-up; - N=9 discontinued intervention; - N=4 hospitalized; - N=2 experienced adverse effect; - N=3 other</p> <p>Intervention 3: - N=11 did not complete follow-up; - N=3 was lost to follow-up;</p>	<p>Clinical outcomes</p> <p>Mortality, n/N (%): I1: 1/48 (2.1%) I2: 0/58 (0%) I3: 2/58 (3.4%) C: 0/50 (0%) Total: 3/214 (1.4%)</p> <p>Hospitalization, n/N (%) I1: 2/48 (4.2%) I2: 5/58 (8.6%) I3: 7/58 (12.1%) C: 3/50 (6.0%) Total: 17/214 (7.9%) P=0.50</p> <p>4-symptom scale <u>Patients meeting 50% reduction, n/N (%):</u> I1: 46/48 (95.8%) I2: 51/58 (87.9%) I3: 50/58 (86.2%) C: 44/50 (88.0%) Total: 191/214 (89.3%) P=0.41</p> <p><u>Time to 50% reduction (days), mean (SD):</u> I1: 5.5 (3.7) I2: 5.9 (4.9)</p>	<p>Definitions: -</p> <p>Remarks: -</p> <p>Authors conclusion: In this randomized clinical trial, ambulatory patients diagnosed with SARS-CoV-2, treatment were treated with high doses of zinc gluconate, ascorbic acid, or a combination of zinc gluconate and ascorbic acid. These interventions did not significantly shorten the duration of symptoms associated with the virus compared with usual care.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	supported by the Haslam Family Endowed Chair in Cardiovascular Medicine. No other disclosures were reported.	<ul style="list-style-type: none"> Patients with a history of calcium oxalate kidney stones. <p><u>N total at baseline:</u> N = 214 Intervention 1: N=48 Intervention 2: N=58 Intervention 3: N=58 Control: N=50</p> <p><u>Important characteristics:</u> Age, mean (SD): I1: 45.6 (15.0) years I2: 44.1 (14.8) years I3: 48.7 (14.3) years C: 42.0 (14.6) years</p> <p>Sex, n/N (%) female: I1: 33/48 (68.8%) I2: 37/58 (63.8%) I3: 31/58 (53.4%) C: 31/50 (62.0%)</p> <p><i>Disease severity: Defined by baseline composite COVID-19 symptom score, average points, median (IQR):</i> <u>4-component score</u> I1: 4.0 (3.0 to 6.0) I2: 4.0 (3.0 to 5.0) I3: 4.0 (3.0 to 6.0) C: 4.0 (3.0 to 5.0) Total: 4.0 (3.0 to 5.0)</p> <p><u>12-component score</u> I1: 12.5 (7.0 to 18.0) I2: 8.0 (6.0 to 13.0) I3: 11.0 (7.0 to 14.0) C: 11.0 (7.0 to 15.0) Total: 11.0 (7.0 to 15.0)</p> <p>Groups comparable at baseline? Yes</p>			<ul style="list-style-type: none"> N=8 discontinued intervention; N=3 hospitalized; N=3 experienced adverse effect; N=2 other 	<p>I3: 5.5 (3.4) C: 6.7 (4.4) Total: 5.9 (4.1) P=0.38 (derived from non-parametric test)</p> <p><u>Differene in days (95% CI):</u> I1: -1.18 (95% CI= -2.88 to 0.51) I2: -0.86 (95% CI= -2.76 to 1.03) I3: -1.3 (95% CI= -2.86 to 0.32) C: reference Total: NA. P= NA</p> <p>12-symptom scale <u>Patients meeting 50% reduction, n/N (%):</u> I1: 14/14 (100%) I2: 21/21 (100%) I3: 21/21 (100%) C: 18/19 (94.7%) Total: 74/75 (98.7%) P=0.44</p> <p><u>Time to 50% reduction (days), mean (SD):</u> I1: 6.6 (3.7) I2: 6.6 (3.7) I3: 6.2 (3.2) C: 6.2 (2.9) Total: 6.4 (3.3) P=0.97</p> <p><u>Difference in days (95% CI):</u> I1: 0.40 (95% CI= -1.99 to 2.80) I2: 0.40 (95% CI= -1.77 to 2.58)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I3: 0.07 (95% CI= -1.94 to 2.09) C: reference Total: NA P= NA</p> <p>Time until 4-symptom composite score is 0 <u>Time in days, mean (SD):</u> I1: 12.1 (6.9) I2: 10.8 (6.8) I3: 9.7 (5.7) C: 9.9 (4.4) Total: 10.6 (6.1) P=0.29</p> <p><u>Difference in days (95% CI):</u> I1: 2.22 (95% CI= -0.58 to 5.02) I2: 0.85 (95% CI= -1.91 to 3.62) I3: -0.24 (95% CI= -2.67 to 2.19) C: reference Total: NA P= NA</p> <p>Composite 4-symptom score at day 5 <u>Score, mean (SD):</u> I1: 3.3 (2.1) I2: 3.2 (2.2) I3: 3.3 (2.3) C: 3.1 (2.3) Total: 3.2 (2.2) P=0.94</p> <p><u>Difference in days (95% CI):</u> I1: 0.27 (95% CI= -0.64 to 1.18)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I2: 0.11 (95% CI= -0.78 to 1.00) I3: 0.20 (95% CI= -0.72 to 1.12) C: reference Total: NA P= NA	
JamaliMoghadamSiahkali, 2021	<p><u>Type of study:</u> Open-label, randomized, and controlled trial</p> <p><u>Setting:</u> Ziaeian Hospital</p> <p><u>Country:</u> Tehran, Iran</p> <p><u>Source of funding:</u> This study was supported by the Tehran University of Medical Sciences (TUMS) with grant number 99-1-101-47277.</p>	<p><u>Patients with compelling clinical symptoms for diagnosis of COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age older than 18 years; Positive COVID-19 polymerase chain reaction (PCR) test or COVID-19 suspicion based on clinical findings (mainly fever, dyspnea, dry cough), imaging findings of COVID-19 on spiral chest computer tomography (CT) or high-resolution CT imagings validated by a trained radiologist; Clinical manifestations of ARDS or myocarditis; Oxygen saturation lower than 93% from admission or after 48 hours from the first COVID-19 treatment. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Receiving anti-retroviral therapy or immune system booster medications in the last 3 months; No proven and confirmed COVID-19 disease based on the inclusion criteria; Patients with glucose-6-phosphate dehydrogenase deficiency; 	<p><u>1.5 g vitamin C IV every 6 h for 5 days</u></p> <p>*All of the participants were also treated with oral lopinavir/ritonavir 400/100 mg twice daily and single stat dose of oral hydroxychloroquine (400 mg) on the first day of hospitalization according to the Iranian COVID-19 treatment protocol at time of this study.</p>	<p><u>No vitamin C</u></p> <p>*All of the participants were also treated with oral lopinavir/ritonavir 400/100 mg twice daily and single stat dose of oral hydroxychloroquine (400 mg) on the first day of hospitalization according to the Iranian COVID-19 treatment protocol at time of this study.</p>	<p><u>Length of follow up:</u> 3 days</p> <p><u>Loss to follow-up:</u> I: 0/30 (0%) Reasons: -</p> <p>C: 0/30 (0%) Reasons: -</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality, n/N (%):</u> I: 3/30 (10%) C: 3/30 (10%) P>0.05</p> <p><u>ICU length of stay (days), median (IQR):</u> I: 5.50 (5.0 to 10.0) C: 5.0 (5.0 to 7.0) P=0.381</p> <p><u>Hospital length of stay (days), median (IQR):</u> I: 8.50 (7.0 to 12.0) C: 6.50 (4.0 to 12.) P=0.028</p> <p><u>SPO₂ upon admission (%), median (IQR):</u> I: 86.0% (82.0% to 88.0%) C: 87.5% (85.0% to 88.0%) P=0.148</p> <p><u>SPO₂ at discharge (%), median (IQR):</u> I: 93.5% (91.0% to 95.0%) C: 92.5 (92.0% to 94.0%) P=0.406</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u></p> <p><u>Authors conclusion:</u> In this study, we found that there were improvements in peripheral oxygen saturation and body temperature in both groups during the time of admission, but we did not find significantly better outcomes in the group who were treated with high-dose vitamin C in addition to the main treatment regimen at discharge.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Patients with end-stage renal disease; • Pregnancy. <p><u>N total at baseline:</u> N = 60 Intervention: 30 Control: 30</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 57.53 y (18.27) C: 61 y (15.90) P=0.436</p> <p>Sex, n/N (%) male: I: 15/30 (50%) C: 15/30 (50%) P>0.90</p> <p>Severity score, mean (/10) (SD): <i>Calculated based on the scoring system suggested by Altschul for prediction of inpatient mortality in COVID-19 patients.</i> I: 3.57 (1.357) C: 3.40 (1.476) P=0.651</p> <p>Groups comparable at baseline?</p> <p>Yes, all clinical findings except for fever (23.33% vs. 63.33% in case and control groups, respectively, p=0.002) and myalgia (13.33% vs. 60.0% in case and control groups, respectively, p<0.001) were not significantly different between the two groups.</p>					
Darban, 2021	<u>Type of study:</u> RCT, open-label, pilot	<p>Hospitalized adults with severe COVID-19, admitted to the ICU</p> <p><u>Inclusion criteria:</u></p>	Vitamin C, melatonin and oral zinc sulfate for 10 days + standard care	Standard care Azithromycin (250	<u>Length of follow-up:</u> 10 days after start of the treatment	Clinical outcomes <u>Mortality (28-30 day)</u> Not reported	<u>Definitions:</u> It is not clear how the outcome deterioration of the disease was defined.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> Single-center, period of enrolment is not reported</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> Grant from the vice-chancellor of the research of Semnan University of Medical Sciences.</p> <p><u>Conflicts of interest:</u> The authors declare that they have no conflict of interest.</p>	<ul style="list-style-type: none"> aged 18-65 years confirmed COVID-19 (real-time PCR test) confirmed pneumonia, SaO₂ <94% and PaO₂/FiO₂ <200mmHg admitted to ICU <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> history of nephrolithiasis allergy to study drugs pregnancy hepatic diseases with aminotransferase > 5 times the upper limit of normal range use of fluvoxamine, sodium oxybate and alcohol history of copper deficiency renal failure (eGFR < 30 ml/min) Patients were excluded from the study for these reasons: safety, loss of follow-up, and voluntary reluctance. <p><u>N total at baseline:</u> N = 20 Intervention: 10 Control: 10</p> <p><u>Important characteristics:</u> Age, mean (SD): I: NR C: NR Total: 59 (19)</p> <p>Sex, n/N (%) male: I: NR C: NR Total: 65% male</p> <p>Disease severity, mean (SD): I: NR</p>	<p>Vitamin C: IV 2g, 6qhr Oral melatonin: 6mg, q6hr Oral zinc sulfate: 220 mg containing 50 mg elemental zinc</p>	<p>mg/day), Lopinavir/ritonavir (100mg/25mg/day), glucocorticoids and necessary oxygen</p> <p>(Patients did not receive remdesivir or tocilizumab)</p>	<p><u>Loss-to-follow-up:</u> Intervention: 0 (0%) Reasons: NA</p> <p>Control: 0 (0%) Reasons: NA</p> <p><u>Incomplete outcome data:</u> Intervention: NR Reasons: NA</p> <p>Control: NR Reasons: NA</p>	<p><u>Duration of hospitalization</u> <u>Duration of ICU admission (days ± SD)</u> I: 15±3.3 C: 14.1±4.2 Effect (95%CI): NR P=0.3</p> <p><u>Time to symptom resolution</u> <u>Deterioration of the disease (%)</u> I: 20 C: 30 Effect (95%CI): NR P=NR</p> <p><u>Respiratory support</u> Not reported</p> <p>Safety <u>Adverse events</u> The study was stopped before the completion of treatment in 1 patient due to hypersensitivity to treatments.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p> <p>Other outcomes <u>PaO₂/FiO₂ (mmHg±SD)</u> <u>Day 0</u> I: 178±57 C: 189±40 <u>Day 5</u> I: 211.0±29.3 C: 204.1±31.9 <u>Day 10</u> I: 230.1±59.1* C: 222.2±65</p>	<p><u>Remarks:</u> The study was stopped before the completion of treatment in 1 patient due to hypersensitivity to treatments. It is not clear whether data of this patient were included in the analysis.</p> <p>It is not possible to assess comparability between the treatment groups at baseline. Important factors like disease severity were not reported and data were not stratified by treatment group.</p> <p>It is a short communication paper.</p> <p>This study was a pilot study to define a sample size.</p> <p><u>Authors conclusion:</u> Adding high-dose vitamin C, high-dose melatonin, and zinc to standard care is not associated with considerable improvement in the clinical status of patients with severe Covid-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: NR Total: NR</p> <p>Groups comparable at baseline? Authors reported no significant between group differences. However, the number of included patients is very low. Furthermore, important factors like disease severity were not reported and data were not stratified by treatment group.</p>				<p>Effect (95%CI): NR P= 0.2 *P<0.05 vs day 0</p> <p><u>SaO2 (%±SD)</u> <i>Day 0</i> I: 90±3 C: 90±1 <i>Day 5</i> I: 94.2±1 C: 93.3±1 <i>Day 10</i> I: 95±1.1 C: 95.1±2 Effect (95%CI): NR P= 0.6</p> <p>Also available: LDH, ESR, CRP, Ferritin, WBC count, Lymphocyte and Neutrophil/lymphocyte</p>	
8.2. Vitamin D							
Cannata-Andía, 2022	<p><u>Type of study:</u> Multicentre, international, randomised, open label, clinical trial</p> <p><u>Setting:</u> 12 centres between April 04, 2020 to April 22, 2021</p> <p><u>Country:</u> Spain, Argentina, Guatemala, Chile</p> <p><u>Source of funding:</u> The study was not supported by any pharmaceutical company. Several</p>	<p>Hospitalized patients with moderate or severe COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients aged ≤18 years • Hospitalized patients with confirmed moderate or severe COVID-19 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with dementia or not able to communicate • Tested negative for SARS-CoV-2 despite clinical findings compatible with COVID-19 • Pregnant and lactating women • Patients who received any form of Vitamin D in the previous 3 months • Allergic to vitamin D 	<p>A single oral bolus of 100,000 IU of cholecalciferol, (cholecalciferol group)</p> <p>All patients received other therapies according to local protocols (not specified)</p> <p>Patients received Enoxaparin, Ceftriaxone, Methylprednisolone, Azithromycin, Dexamethasone</p>	<p>All patients received other therapies according to local protocols (not specified)</p> <p>Patients received Enoxaparin, Ceftriaxone, Methylprednisolone, Azithromycin, Dexamethasone</p>	<p><u>Length of follow-up:</u> Not defined</p> <p>Patients were followed from admission to discharge or death</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention, n/N (%): 3/277 (1.08%) Reason: incomplete data</p> <p>Control, n/N (%): 2/271 (0.74%) Reason: incomplete data</p>	<p><u>Clinical outcomes</u> <u>Mortality at 28 days</u> I: 22/274 (8.0%) C: 15/269 (5.6%)</p> <p><u>Duration of hospitalization</u> <i>Length of hospital stay, median (95%CI)</i> I: 10 (9.0-10.5) C: 9.5 (9.0-10.5)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Invasive respiratory support</u> Not reported.</p> <p><u>Non-invasive respiratory support</u></p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Length of hospitalisation • Admission to ICU • Mortality <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • In the cohort analyses, the relationship between serum calcidiol at admission with (a) pulmonary involvement and (b) with the same three outcomes of the trial was assessed <p><u>Definitions:</u></p> <ul style="list-style-type: none"> • Pulmonary involvement was defined as: bilateral multifocal ground-glass opacities > 50%), and/or moderate-severe flu-like syndrome having oxygen saturation lower than 94% breathing room air

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>fundings are reported from different research grants.</p> <p><u>Conflicts of interest:</u> Transparently reported.</p>	<p><u>N total at baseline:</u> N = 548 Intervention: N = 277 Control: N = 271</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 59 y (49-70) C: 57 y (45-67)</p> <p>Sex, n/N (%) male: I: 181/274 (66.1%) C: 172/269 (63.9%)</p> <p>Disease severity, defined as pulmonary involvement, n/N (%) I: 234/274 (85.4%) C: 217/269 (80.7%)</p> <p>Groups comparable at baseline: In the cholecalciferol group, serum calcidiol was higher compared with the control group 29.0 vs. 16.4ng/mL, p=0.000</p>				<p>Not reported.</p> <p>Safety <u>Serious adverse events</u> Not reported.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	<p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Open-label trial • Standard care was not defined by the authors <p><u>Authors conclusion:</u> The randomised clinical trial showed the administration of an oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve the outcomes of the COVID-19 disease. A cohort analysis showed that serum calcidiol at hospital admission was associated with outcomes.</p>
Elamir, 2021	<p><u>Type of study:</u> open label, randomized clinical trial</p> <p><u>Setting:</u> Mount Sinai Beth Israel, Mount Sinai Morningside, and Mount Sinai West Hospitals, between September 2020 and December 2020</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u></p>	<p>hospitalized patients with COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18y • hospitalized with COVID-19 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • admitted directly to the intensive care unit (ICU) • hypercalcemia and/or hyperphosphatemia on admission blood tests • untreated disorders of calcium metabolism including hyperparathyroidism, hypoparathyroidism, chronic renal insufficiency with 	calcitriol 0.5 µg daily for 14 days or hospital discharge	no treatment (1:1) at time of enrollment	<p><u>Length of follow-up:</u> 10 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention: N = 0</p> <p>Control: N = 0</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> I: 0/25 (0.0%) C: 3/25 (12.0%) P= 0.23</p> <p><u>Duration of hospitalisation</u> <u>Length of hospital stay</u> Days, mean (SD) I: 5.5 (3.9%) C: 9.2 (9.4%) P=0.14</p> <p><u>ICU admission</u> I: 5/25 (20.0%) C: 8/25 (32.0%) P=0.33</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> Limitations of our trial include lack of a placebo and lack of blinding. 25-hydroxyvitamin D levels were not measured in our study. Sample size was another limitation.</p> <p><u>Authors conclusion:</u> This pilot study illustrates improvement in oxygenation among hospitalized patients with COVID-19 treated with calcitriol and suggests the need for a larger randomized trial.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>No funding.</p> <p><u>Conflicts of interest:</u> None to declare.</p>	<p>glomerular filtration rate < 30 ml/min, or</p> <ul style="list-style-type: none"> prescribed calcitriol for any reason outside of the study declined to participate prior to enrollment <p><u>N total at baseline:</u></p> <p>Intervention: = 25 Control: N = 25</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 69 y (18.0) C: 64 y (16)</p> <p>Sex, n/N (%) male: I: 12/25 (48.0%) C: 13/25 (52%)</p> <p>Groups were comparable at baseline.</p>				<p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u></p> <p><u>Endotracheal intubation</u></p> <p>I: 0/25 (0.0 %) C: 2/25 (8.0%) P=0.48</p> <p><u>Other</u></p> <p><u>Readmission within 30 days</u> I: 2/25 (8.0 %) C: 4/25 (16.0%) P=0.67</p> <p><u>Safety adverse effects</u> Reduction in glomerular filtration rate by >10% Readmission within 30 days I: 0/25 (8.0 %) C: 4/25 (16.0%) P=0.1</p> <p><u>Virological outcomes</u> Not reported</p>	
Lakkireddy, 2021	<p>Type of study: RCT, open-label</p> <p>Setting and country: Single centre, India</p> <p>Funding and conflicts of interest:</p>	<p><u>COVID-19 patients, (hospitalized, mild/moderate disease)</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> confirmed COVID-19 age > 18 years Hypovitaminosis D (vit.D level < 30 ng/ml) mild to moderate illness (SpO2 > 90%) 	<p>Vitamin D (pulse therapy) + standard of care</p> <p>Adjunctive Pulse D therapy (60,000 IUs of vit.D in the form of aqueol nano solution (Deksel) per day for 8 days for subjects with BMI 18–25 and 10 days for subjects with BMI > 25).</p>	<p>Standard of care</p> <p>(not described)</p>	<p><u>Length of follow-up:</u> Until end of hospital discharge (?)</p> <p><u>Loss-to-follow-up:</u> Intervention: n=21 Reasons: Discharged at request before the analysis of inflammatory</p>	<p><u>Mortality (28-30 day) - crucial</u> Uitwerken of 'not reported'</p> <p><u>In-hospital mortality, n</u> I: 2 C: 5 Effect (95%CI): NR P=NR</p>	<p><u>Definitions:</u> NR</p> <p><u>Remarks:</u> Pulse pharmaceutical funded the study. This organisation was however not involved in any phase of the study. Therefore it is unlikely that this sponsoring induced risk of bias.</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Pulse Pharmaceutical. Funding source has no involvement in study design, collection, analysis, interpretation of data, writing the report or decision to submit the article for publication. The authors declare no competing interests.</p>	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • severe illness • patients who have taken high dose vit.D (60,000 IUs) in the last 3 months, • patients with active malignancy, chronic renal disease and HIV • pregnant and breastfeeding mothers <p><u>N total at baseline:</u> 130 (87 completed study) Intervention: 65 (44 completed) Control: 65 (43 completed)</p> <p><u>Important prognostic factors²:</u></p> <p><u>age ± SD:</u> I: NR C: NR Total: NR</p> <p><u>Sex:</u> I: NR C: NR Total: 75% M</p> <p><u>Disease severity:</u> I: NR C: NR Total: NR</p> <p><u>Vitamin D (ng/ml) ±SD</u> I: 16±6 C: 17±6</p> <p><u>C-reactive protein (mg/l) mean±SD/median (IQR)</u> I: 81±66 C:11 (3-43)</p> <p>Groups comparable at baseline?</p>	Standard of care: see control group.		<p>biomarkers (n=17); died (n=2); discontinued intervention (n=2))</p> <p>Control: n=22 Reasons: Discharged at request before the analysis of inflammatory biomarkers (n=18), died (n=4).</p> <p><u>Incomplete outcome data:</u> Intervention: NR Reasons: NA</p> <p>Control: NR Reasons: NA</p>	<p><u>Respiratory support - mechanical respiratory support, optiflow) - crucial</u> Not reported</p> <p><u>Duration of hospitalization – important</u> <u>Hospital stay, mean days±SD</u> I: 13±5 C:14±5 Effect (95%CI): NR P= 0.9</p> <p><u>ICU admission, n/N (%)</u> I: 4 C: 5 Effect (95%CI): NR P=NR</p> <p><u>Time to symptom resolution - important</u> Not reported</p> <p><u>Respiratory support - non-invasive respiratory support - important</u> Not reported</p> <p><u>Adverse events - important</u> No adverse reactions attributable to vitamin D toxicity were noted in any of the patients studied. Serum calcium level in VD group after treatment was within normal limits (9 ± 0.5 mg/dl).</p>	Immune dysregulation in COVID-19 is marked by increased inflammatory biomarkers such as N/L ratio, CRP, LDH, IL6 and Ferritin. Vitamin D is a potential immunomodulator and its adjunctive role in the treatment of COVID-19 is established by this study. Improvement of serum vit.D level to 80–100 ng/ml has significantly reduced the inflammatory markers without any side effects. Hence, adjunctive Pulse D therapy can be added safely to the existing treatment protocols of COVID-19

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Unclear, since baseline characteristics are not reported for the different treatment groups.				Viral clearance - important Not reported	
Murai, 2020	<p>Type of study: RCT; multicenter, double-blind, randomized, placebo-controlled</p> <p>Setting: 2 sites in Sao Paulo; enrollment from June 2, 2020, to Aug 27, 2020; final follow-up on Oct 7, 2020.</p> <p>Country: Brazil</p> <p>Source of funding: This study was supported by FAPESP (grants 20/05752-4; 19/24782-4; 20/11102-2; 16/00006-7; 17/13552-2; 15/26937-4; 19/18039-7) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (305556/2017-7); The funders had no role in the design and conduct of the study; collection,</p>	<p>Hospitalized patients with moderate to severe COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> age ≥18 years; diagnosis of COVID-19 via PCR testing for SARS-CoV-2 from nasopharyngeal swabs or CT scan findings compatible with the disease (bilateral multifocal ground-glass opacities ≥50%); diagnosis of flu syndrome with institutional criteria for hospitalization on hospital admission, moderate to severe COVID-19: respiratory rate > 24/min, saturation < 93% while breathing room air, or risk factors for complications (eg, heart disease, diabetes, systemic arterial hypertension, neoplasms, immunosuppression, pulmonary tuberculosis, obesity) followed by COVID-19 confirmation. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> unable to read and sign the written consent form, already admitted + receiving invasive mech. ventilation, previous vitamin D3 supplementation (>1000 IU/d), kidney failure requiring dialysis or creatinine of at least 2.0 mg/dL, 	<p>Single oral dose of 200 000 IU of vitamin D3</p> <p>[single, oral dose of 200 000 IU of vitamin D3 dissolved in a 10-mL peanut oil solution.]</p>	<p>Placebo</p> <p>[10 mL of a peanut oil solution]</p>	<p>Length of follow up: Unclear; “[Time Frame: From date of randomization until the date of hospital discharge or death, which is usually less than 1 month]”</p> <p>Loss to follow-up: I: 1/120 (0.8%) C: 2/120 (1.7%) Reasons: withdrew consent</p>	<p>Clinical outcomes In-hospital mortality; <i>defined as the number of patients who died during hospitalization</i> I: 7.6 % (3.5 to 13.9) C: 5.1 % (1.9 to 10.7) Difference 2.5% (95% CI – 4.1% to 9.2%)</p> <p>Subgroup: Patients with 25-hydroxyvitamin D deficiency (<20 ng/mL) n = 57 n = 58 I: 7.0% (1.9 to 17.0) C: 1.7% (0.04 to 9.2) Difference 5.3% (–3.3 to 15.1)</p> <p>Duration of hospitalization Hospital length of stay; median [IQR] I: 7.0 [4.0-10.0] days C: 7.0 [5.0-13.0] days unadj. HR 1.07 (95% CI 0.82-1.39) adj. HR, 0.99 (95% CI 0.71 - 1.37)</p> <p>Admission to the intensive care unit; I: 16.0 % (9.9 to 22.5) C: 21.2 % (14.2 to 29.7) Difference –5.2% (95% CI – 15.1% to 4.7%)</p> <p>Subgroup: Patients with 25-hydroxyvitamin D</p>	<p>Definitions:</p> <ul style="list-style-type: none"> Hospital length of stay: defined as the total number of days that patients remained hospitalized from the date of randomization until the date of hospital discharge; The criteria used for patient discharge were no need for supplemental oxygen in the past 48 hours, no fever in the past 72 hours, and oxygen saturation greater than 93% without supplemental oxygen and without respiratory distress <p>Remarks: -Predefined length of follow-up unclear -Patients were given a dose of vitamin D3 after a relatively long time from symptom onset to randomization (ie, mean of 10.3 days).</p> <p>Authors conclusion: Among hospitalized patients with COVID-19, a single high dose of vitamin D3, compared with placebo, did not significantly reduce hospital length of stay. The findings do not support the use of vitamin D3 for treatment of moderate to severe COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.	<ul style="list-style-type: none"> hypercalcemia (total calcium >10.5 mg/dL), pregnant or lactating, expected hospital discharge < 24 hours <p><u>N total at baseline:</u> N = 237 (randomized 240) Intervention: 119 (random. 120) Control: 118 (random. 120)</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 56.5 (13.8) C: 56.0 (15.0) Sex, n/N (%) male: I: 70 (58.8) C: 63 (53.4) Time from symptom onset to enrollment, mean (SD), d I: 10.2 (3.9) C: 10.4 (4.7) Time from hospital admission to enrollment, mean (SD), d I: 1.3 (0.9) C: 1.4 (0.9) Oxygen supplementation, No. (%) No oxygen therapy I: 16 (13.4) C: 9 (7.6) Oxygen therapy I: 86 (72.3) C: 95 (80.5) Noninvasive ventilation I: 17 (14.3) C: 14 (11.9)</p> <p>Also described: Race, BMI, acute covid-19 symptoms, coexisting diseases, concomitant medications, ground-glass opacities on CT, laboratory values.</p>				<p>deficiency (<20 ng/mL) n = 57 n = 58 I: 19.3% (10.0 to 31.9) C: 15.5% (7.4 to 27.4) Difference 3.8% (-10.3 to 17.8)</p> <p><u>Symptom resolution</u> not reported</p> <p><u>Need for respiratory support</u> Need for mechanical ventilation: I: 7.6 % (3.5 to 13.9) C: 14.4 % (8.6 to 22.1) difference -6.8% (95% CI -15.1% to 1.2%) Duration of mechanical ventilation, mean: I: 15.0 C: 12.8 days difference 2.2 (95% CI -8.4 to 12.8)</p> <p><i>Subgroup:</i> Patients with 25-hydroxyvitamin D deficiency (<20 ng/mL) n = 57 n = 58 I: 7.0% (1.9 to 17.0) C: 8.6% (2.9 to 19.0) Difference -1.6% (-12.5 to 9.2)</p> <p><u>Also reported:</u></p> <ul style="list-style-type: none"> serum levels of 25-hydroxyvitamin D (assessed by a chemiluminescent immunoassay), total calcium (assessed by a 5-nitro-5'-methyl-[1,2-bis[o- 	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline.				aminophenoxy]ethan-N,N,N',N'-tetraacetic acid method), • creatinine (assessed by a colorimetric assay based on the kinetic Jaffe reaction), • and C-reactive protein (assessed by an immunoturbidimetric assay) Safety <u>Adverse events</u> Serious adverse events I: 0 C: 0 Adverse events I: 1 (vomiting after vitamin d3 administration) C: 0 Virological outcomes <u>Viral clearance</u> Not reported	
Rastogi, 2020	<u>Type of study:</u> RCT Randomised, placebo-controlled. <u>Setting:</u> tertiary care hospital <u>Country:</u> North India <u>Source of funding:</u> The authors have not declared a specific grant for	Consecutive individuals with SARS-CoV-2 infection who were mildly symptomatic or asymptomatic with or without comorbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) admitted to tertiary care hospital. <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Patients with vitamin D deficiency defined as 25 (OH)D level<20 ng/ml 	daily 60000 IU of cholecalciferol (5 ml oral solution in nano droplet form)for 7 days with the aim to achieve 25 (OH)D level>50 ng/ml.	placebo (5 ml distilled water) for 7 days	<u>Length of follow up:</u> 21 days or virus negativity <u>Loss to follow-up:</u> None.	Change in the levels of serum inflammatory markers during follow-up Δ Vitamin D (ng/ml) I: 42.4 (39 to 48.8) C: 5.1 (0 to 12.3) P<0.001* Δ D-dimer (g/L) I: -80.0 (-308.0 to 13.2) C: -31.2 (-202 to 0) P=0.241 Δ Fibrinogen (ng/mL) I: -0.9 (-2.0 to -1.0) C: -0.04 (-1.02 to 0.0)	<u>Definitions:</u> - <u>Remarks:</u> - <u>Authors conclusion:</u> In conclusion, a high dose, oral vitamin D supplementation to augment 25(OH)D >50 ng/ml helped to achieve SARS-CoV-2 RNA negativity in greater proportion of asymptomatic vitamin D-deficient individuals with SARS-CoV-2 infection along with a significant

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	this research from any funding agency in the public, commercial or not-for-profit sectors.	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients requiring invasive ventilation; Patients with significant comorbidities like uncontrolled hyperglycaemia or hypertension. <p><u>N total at baseline:</u> N = 40 Intervention: N = 16 Control: N = 24</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 50.0 y (36 to 51) C: 47.5 y (39.3 to 49.2)</p> <p>Sex, n/N (%) male: I: 6/16 (37.5%) C: 14/24 (58.3%)</p> <p>Disease severity: not reported</p> <p>25 (OH) D3 (ng/ml)(median;IQR) I: 8.6 (7.1 to 13.1) C: 9.54 (8.1 to 12.5) P=0.730</p> <p>Fibronogen (g/L) (median;IQR) I: 4.06 (3.7 to 5.12) C: 3.73 (3.40 to 4.30) P=0.232</p> <p>D-Dimer (ng/ml) (median;IQR) I: 345 (219 to 860) C: 236.7 (224.8 to 384.4) P=0.295</p> <p>Procalcitonin (nl/ml) (median;IQR)</p>				<p>P=0.001*</p> <p>Δ C-reactive protein (ng/ml) I: -0.3 (-1.4 to 0.2) C: 0.0 (-0.9 to 0.3) P=0.507</p> <p>Δ Procalcitonin (mg/L) I: 0.00 (-0.2 to 0.7) C: -0.1 (-0.60 to 0.04) P=0.260</p> <p>Adverse events</p> <p>No episodes of hypercalcaemia were observed in either group.</p> <p>SARS-CoV-2 negativity (n/N) I: 10/16 (62.5%) C: 5/24 (20.8%) P=0.018</p> <p>Mean duration to SARS-CoV-2 negativity (mean;SD) I: 17.6 (6.1) C: 17.6 (6.4)</p>	<p>decrease in inflammatory marker. SARS-CoV-2 RNA negativity by cholecalciferol supplementation may help in reducing transmission rates of the highly contagious SARS-CoV-2 infection. A reassurance for public health workers regarding greater likelihood of SARS CoV-2 RNA negativity in individuals receiving therapeutic cholecalciferol supplementation will be encouraging.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 0.02 (0.02 to 0.03) C: 0.03 (0.02 to 0.09) P=0.411</p> <p>C reactive protein(mg/L) (median;IQR) I: 2.1 (0.8 to 20.4) C: 2.6 (0.7 to 14) P=0.295</p> <p>Calcium (mg/dl) (median;IQR) I: 9.4 (9.2 to 9.7) C: 8.8 (8.0 to 9.2) P=0.042</p> <p>Phosphorus (median;IQR) I: 4.0 (2.1 to 6.2) C: 3.3 (3.1 to 3.8) P=0.121</p>					
Castillo, 2020	<p><u>Type of study:</u> Paralel pilot randozmied open label. double-masked clinical trial</p> <p><u>Setting:</u> University hospital setting (Reina Sofia University Hospital, cordoba)</p> <p><u>Country:</u> Spain</p> <p><u>Source of funding:</u> Not reported.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Hospitalized patients with COVID-19 infection clinical picture of acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB65 severity scale. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients <18 years Pregnant woman. <p><u>N total at baseline:</u> N = 76</p> <p>Intervention: 50 Control: 26</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 53.14y (10.77) C: 52.77 (9.35) 95% CI: -0.34 to 9.60)</p>	Calcifediol in soft capsules (0.532 mg) (added to standard care)	No Calcifediol (standard care)	Until admission to ICU, hospital discharge or death.	<p><u>Need for ICU</u></p> <p><i>Not requiring ICU; n/N (%)</i> I: 49/50 (98%) C: 13/26 (50%)</p> <p><i>Requiring ICU; n/N (%)</i> I: 1/50 (2%) C: 13/26 (50%)</p> <p><u>Death; n/N (%)</u> I: 0/50 (0%) C: 2/26 (7.7%)</p> <p>Note: 13 patients who were not admitted to the ICU, were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged.</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Our pilot study demonstrated that administration of a high dose of Calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D endocrine system, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19. Calcifediol seems to be able to reduce severity of the disease, but larger trials with groups properly matched will be required to show a definitive answer.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		P=0.07 Sex, n/N (%) male: I: 27/50 (54%) male C: 18/26 (69%) male P=0.20					
8.3. Zinc							
Patel, 2021	<p><u>Type of study:</u> RCT; double-blind</p> <p><u>Setting:</u> Single-site; Austin Health, Heidelberg, Victoria, Australia</p> <p><u>Country:</u> Australia</p> <p><u>Source of funding:</u> No funding reported. "The authors declare that there are no conflict of interests."</p>	<p>COVID-19 confirmed hospitalized adults with oxygen saturation (SpO2) of 94% or less while on ambient air</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • adult patients • age ≥18 years old. • Laboratory-confirmed SARS-CoV-2 infection • Hospitalised with an illness of any duration with evidence of pneumonia and severe disease, critical disease or multisystem organ dysfunction at baseline • Ability to provide informed consent signed by study patient or legally acceptable representative • Willingness and ability to comply with study-related procedures/assessments • oxygen saturation (SaO2) of ≤ 94% while breathing ambient air or a ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) (PaO2 : FiO2) ≤ 300mg Hg. • No chronic kidney disease (CKD) defined by stage II or higher using the Kidney Disease Improving Global Outcomes classification <p><u>Exclusion criteria:</u></p>	<p>high-dose intravenous zinc (HDIVZn)</p> <p>Colorless pharmaceutical grade Zinc Chloride (ZnCl2) stock solution obtained from Phebra Pty Ltd was diluted in 250 ml of normal saline and infused via peripheral intravenous access over 3 h at a dose of 0.5 mg/kg/day (elemental zinc concentration, 0.24 mg/kg/day) for a maximum of 7 days, or until hospital discharge or death.</p>	Placebo	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> No loss to FU described</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> not reported</p> <p><u>Duration of hospitalization</u> not reported</p> <p><u>Time to symptom resolution</u> not reported</p> <p><u>Need for respiratory support</u> Eight-level ordinal scale, N (%)</p> <p>Day 14</p> <p>0. Not hospitalized, no infection I: 2 (14.3) C: 2 (11.1)</p> <p>2. Not hospitalized, with limitations I: 5 (35.7) C: 10 (55.6)</p> <p>3. Hospitalized, no supplemental oxygen I: 3 (21.4) C: 2 (11.1)</p> <p>4. Hospitalized, with supplemental oxygen I: 3 (21.4) C: 0 (0.0)</p> <p>5. Hospitalized, NIV, and/or HFNC I: 0 (0.0) C: 1 (5.6)</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -relatively small study; goal to include 160 patients was not met; primary outcomes could not be reported</p> <p><u>Authors conclusion:</u> In summary, our study provides the first evidence showing the safety and feasibility of intravenous zinc treatment and the ability of HDIVZn to reverse the acute phase zinc deficiency associated with COVID-19. These findings support further investigation of this treatment in larger RCTs.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Thomas, 2021	See evidence table of Thomas (2021) by Vitamin C.	<ul style="list-style-type: none"> pregnant or lactating female Allergy to zinc Severe hepatic impairment defined as Child C liver disease. See protocol for additional criteria <p><u>N total at baseline:</u> N = 33 Intervention: 15 Control: 18</p> <p><u>Important characteristics:</u> Age, mean±SD (range): I: 59.8 ± 16.8 (25–84) C: 63.8 ± 16.9 (31–95) Sex, n/N (%) male: I: 11 (73.3%) C: 10 (55.5%) Zinc, µmol/l (range) I: 7.7 ± 1.6 (4.8–10.5) C: 6.9 ± 1.1 (4.6–8.5)</p> <p><i>Also reported: comorbidities; laboratory parameters</i></p> <p>Groups comparable at baseline?</p>				<p>8. Death I: 1 (7.1) C: 3 (16.7) Day 28 0. Not hospitalized, no infection I: 2 (14.3) C: 2 (11.1) 1. Not hospitalized, without limitation I: 1 (7.1) C: 0 (0.0) 2. Not hospitalized, with limitations I: 7 (50.0) C: 12 (66.7) 3. Hospitalized, no supplemental oxygen I: 1 (7.1) C: 1 (5.6) 4. Hospitalized, with supplemental oxygen I: 1 (7.1) C: 0 (0.0) 8. Death I: 2 (14.3) C: 3 (16.7) <i>Also reported for day 1 and 7</i></p> <p>Safety <u>Adverse events</u> I: 0 (among 94 injections) C: 0 Infusion site irritation after HDIVZn: 3 patients; 2 on Day 4, and 1 on Day 6.</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Darban, 2021	See evidence table of Darban (2020) by Vitamin C.						
Abd-Elsalam, 2020b	<p>Type of study: RCT</p> <p>Setting: Conducted at three University hospitals (Assiut, Tanta, and Cairo)</p> <p>Country: Egypt</p> <p>Source of funding: The authors declare that they have no conflicts of interest.</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Patients with a confirmed diagnosis of COVID-19 infection All included patients were classified into mild, moderate, severe, and critical according to the WHO case severity classification for COVID-19 infection. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Patients with hypokalemia or hypomagnesemia, porphyria, neutrophilia, myasthenia gravis, maculopathy or changes in the visual field, heart failure, prolonged QT interval in ECG, liver cirrhosis, psoriasis, epilepsy, anemia form pyruvate kinase and G6PD deficiencies, chronic kidney disease, and pregnant or lactating females were excluded. <p>N total at baseline: N = 191 Intervention: 96 Control: 95</p> <p>Important characteristics:</p> <p>Age, mean (SD): I: 43.48 y (14.62) C: 43.64 y (13.17)</p> <p>Sex, n/N (%) male: I: 52/96 (54.2%) C: 64/95 (67.4%)</p> <p>Clinical severity grading (n/N (%)) I: Mild: 9/96 (9.4%) Moderate: 58/96 (60.4%)</p>	Hydroxychloroquine was given in a dose of 400 mg twice daily on the first day, then 200 mg twice daily for 5 days. Zinc was given in a dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily as many clinical trials did.	Only hydroxychloroquine (see description intervention)	<p>Length of follow up: Not described. The mean duration of hospital stay was 13.51 ± 5.34 days in the intervention group and 14.01 ± 6.26 days in the control group.</p> <p>Loss to follow-up: Not described</p>	<p>Mortality: I: 5 (5.2%) C: 5 (5.3%) P = 0.986</p> <p>Recovery within 28 days: I: 76 patients (79.2%) C: 74 patients (77.9%) P-value = 0.969</p> <p>The need for mechanical ventilation: I: 4 (4.2%) C: 6 (6.3%) P = 0.537</p> <p>No subgroup analyses done.</p> <p>Also available: univariate analyses to risk factors associated with mortality.</p>	<p>Definitions: WHO case severity classification for COVID-19 infection: Mild cases: symptoms for COVID-19 infection but no pneumonia or hypoxia. Moderate cases: patients with mild viral pneumonia and SpO₂>90% on room air. Severe cases: patients with signs of severe pneumonia such as respiratory rate > 30 breaths/min, severe respiratory distress, or SpO₂ <90% on room air. Critical cases: patients with acute respiratory distress syndrome, sepsis and septic shock.</p> <p>Remarks: Both groups received the standard of care treatment for COVID-19 infection, according to the Egyptian Ministry of Health guidelines for 15 days.</p> <p>The two groups were matched for age and gender (p = 0.940 and p = 0.062, respectively).</p> <p>Authors conclusion: In conclusion, zinc supplements did not add value or enhance the clinical efficacy of HCQ. Zinc supplementation may be studied further with other drug regimens for COVID 19, but it did not add any clinical values when added to HCQ.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Severe: 18/96 (18.8%) Critical: 11/96 (11.6%) C: Mild: 12/95 (12.6%) Moderate: 55/95 (57.9%) Severe: 20/95 (18.8%) Critical: 8/95 (8.4%) Groups comparable at baseline? Groups comparable in age, gender, smoking, comorbidities, laboratory investigations, and clinical severity grading.					
9. Antiviral treatment							
9.1. Darunavir (antiretroviral treatment; also in combination with cobicistat)							
Chen, 2020b	<p><u>Type of study:</u> randomized, open-label trial</p> <p><u>Setting:</u> Shanghai Public Health Clinical Center (SPHCC), between January 30, 2020 to February 6, 2020</p> <p><u>Country:</u> China (Shanghai)</p> <p><u>Source of funding:</u> -This work was supported by the Ministry of Science and Technology of China (2017ZX09304027); the Shanghai Science</p>	<p><u>Inclusion criteria:</u> laboratory-confirmed SARS-CoV-2 infection</p> <p><u>Exclusion criteria:</u> -hypersensitivity to darunavir, cobicistat, or any excipients -severe liver injury (Child-Pugh Class C) -patients receiving concomitant medications that are highly dependent on cytochrome P450 3A clearance, and for which the elevated plasma concentrations are associated with serious or life-threatening events - considered to be unable to complete the study (e.g, severely and critically ill patients*) -not suitable for the study by researchers.</p> <p>*Patients who met any of the following criteria were classified as severe cases: respiratory rate</p>	<p><u>darunavir/cobicistat+ standard care</u> 1 pill of DRV/c (a single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat) per day for 5 days</p>	<p><u>standard care</u> interferon alpha 2b and standard of care as per guideline recommendation in China (no oral antiviral drugs).</p>	<p><u>Length of follow-up:</u> 14 days</p> <p><u>Loss to follow-up:</u> All participants completed the study, except 1 patient in the DRV/c group who progressed to critical condition on day 4 and withdraw from the study</p>	<p><u>viral clearance rate at day 7 after randomization</u> Defined as reverse transcriptase polymerase chain reaction (RT-PCR) negative on at least 2 consecutive oropharyngeal swabs collected at least 1–2 days apart. I: 7/15 (46.7%) C: 9/15 (60.0%) P=.72</p> <p><u>viral clearance rate at day 3</u> I: 3/15 (20%) C:3/15 (20%) P-value not reported</p> <p><u>viral clearance rate at day 5</u> I: 4/15 (26.7%) C: 3/15 (20%) P-value not reported</p>	<p><u>Remarks</u> -More patients in the DRV/c group showed bilateral pneumonia (80.0% vs 53.3%) (not statistically significant). -Small sample size -P-values were not reported for several secondary outcome measures.</p> <p><u>Authors' conclusion:</u> Our results do not suggest that 5 days of DRV/c could increase the proportion of negative conversion at day 7 vs standard of care alone, although it was well tolerated.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>and Technology Committee (20411950200); Shanghai Major Projects on Infectious Diseases (shslczdk01102); and the Shanghai "Rising Stars of Medical Talent" Youth Development Program, Specialist Program (No. 2019-72). -All authors declare no reported conflicts of interest.</p>	<p>≥30 times/min, pulse oxygen saturation ≤93% at resting, or ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO₂/ FiO₂) ≤300 mmHg. Critical illness was defined as respiratory failure that needed mechanical ventilation or shock or exacerbation of any comorbidity that required transfer to the intensive care unit.</p> <p><u>N total at baseline:</u> N = 30 Intervention: 15 Control: 15</p> <p><u>Important characteristics:</u> <i>Age, mean±SD</i> I: 51.5 ± 12.2 C: 51.5 ± 12.2</p> <p><i>Sex male, n(%)</i> I: 9 (60) C: 9 (60)</p> <p><i>Chronic comorbidity, n (%)</i> <i>Cardiovascular diseases</i> I: 4 (26.7) C: 4 (26.7) <i>Diabetes</i> I: 0 C: 2 (13.3)</p> <p>Groups comparable at baseline? The clinical characteristics and laboratory findings of the 2 groups were comparable. Despite a difference that was not significant, more patients in the</p>				<p>The median duration from randomization to confirmed negative PCR was 8 days and 7 days, respectively.</p> <p>DRV/c was not associated with faster clearance of SARS-COV-2 on oropharyngeal swab (HR 0.82; 95% CI, 0.36–1.88)</p> <p><u>critical illness at day 14</u> I: 1/15 C: 0/15 P = 1.0</p> <p><u>mortality rate of subjects at day 14</u> I: 0/15 (0%) C: 0/15 (0%)</p> <p><u>treatment-related adverse events</u> <i>Diarrhea</i> I: 3/15 (20%) C: 2/15 (13.3%) <i>Anemia</i> I: 1/15 C: 0/15 <i>Elevated transaminase levels</i> defined as >2-fold of the upper limit of the normal range I: 2/15 (13.3%) C: 4/15 (26.7%) <i>Renal dysfunction</i> defined as estimated glomerular filtration rate <90 mL/min/1.73 m² in</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		DRV/c group showed bilateral pneumonia (80.0% vs 53.3%)				<p>patients without chronic kidney diseases I: 2/15 (13.3%) C: 1/15 (6.7%)</p> <p>All the adverse events were mild. No participants discontinued DRV/c due to these adverse events.</p>	
9.2. Favipiravir							
Ivashchenko, 2021	<p><u>Type of study:</u> Adaptive, multicenter, open-label, randomized, phase II/III clinical trial.</p> <p><u>Setting:</u> Six Russian clinical sites in Moscow, Smolensk, and Nizhniy Novgorod.</p> <p><u>Country:</u> Russia.</p> <p><u>Source of funding:</u> This work was supported by the Russian Direct Investment Fund, the Ministry of Industry and Trade of the Russian Federation and the Skolkovo Innovation Center.</p> <p><u>Conflicts of interest:</u> All other authors report no potential conflicts.</p>	<p><u>Hospitalized patients with moderate COVID-19 pneumonia.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Men and nonpregnant woman of 18 years or older; Patients who signed informed consent; Patients with moderate PCR-confirmed COVID-19 (positive at screening); Patients who were able to administrate the drug orally and willing to use adequate contraception during the study and three months after its completion. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> - <p><u>N total at baseline:</u> N = 60 Intervention 1: N=20 Intervention 2: N=20 Control: N=20</p> <p><u>Important characteristics:</u> <i>Age, mean (SD):</i> Not reported. <i>Sex, n/N (%) male:</i> Not reported.</p>	<p><u>Intervention 1 (I1):</u> AVIFAVIR 1600 mg BID on Day 1, followed by 600 mg BID on Days 2–14 (1600/600 mg).</p> <p><u>Intervention 2 (I2):</u> AVIFAVIR 1800 mg BID on 532 • cid 2021:73 (1 August) • BRIEF REPORT Day 1, followed by 800 mg BID on Days 2–14 (1800/800 mg)</p>	<p><u>Control (C):</u> Standard of care according to the Russian guidelines for treatment of COVID-19.</p>	<p><u>Length of follow-up:</u> 29 days.</p> <p><u>Loss-to-follow-up:</u> None in any of the groups.</p> <p><u>Incomplete outcome data:</u> None in any of the groups.</p>	<p><u>Clinical outcomes</u> <u>Mortality (28-30 day)</u> Two patients on AVIFAVIR 1600/600 mg were moved to intensive care unit, received mechanical ventilation, and later died. Both patients had the increased risk of severe disease, including diabetes mellitus, arterial hypertension, obesity, CRP > 50 mg/L, and supplemental oxygen at baseline.</p> <p><u>Duration of hospitalization</u> <i>Discharged from hospital and/or achieved Score 2 on WHO-OSCI by day 15, n/N (%):</i> I1: 13/20 (65.0%) I2: 17/20 (85.0%) C: 17/20 (85.0%)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety</p>	<p><u>Definitions:</u></p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> The concomitant therapy of COVID-19 in all groups included antibiotics, anticoagulants, and/or immunosuppressants, as well as symptomatic treatment. <p><u>Authors conclusion:</u> Based on the interim results of the Phase II/III clinical trial, the Russian Ministry of Health granted a conditional marketing authorization to AVIFAVIR, which makes it the only approved oral drug for treatment of moderate COVID-19 to date.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Risk factors for severe disease, n/N (%):</i> 28/60 (46.7%)</p> <p><i>On ambient air (Score 3 on WHO-OSCI), n/N (%):</i> 45/60 (75%)</p> <p><i>Required supplemental oxygen via mask or nasal cannula (Score 4 on WHO-OSCI), n/N (%):</i> 15/60 (25%)</p> <p><i>Body temperature >38 degrees celcius, n/N (%):</i> 15/60 (25%)</p> <p><i>C-reactive protein >10 mg/L, n/N (%):</i> 42/60 (70%)</p> <p><i>Mean disease duration at baseline from the start of the symptoms:</i> 6.7 days.</p> <p><i>Mean study drug administration period, mean (SD):</i> I1: 10.9 (2.8) days. I2: 10.9 (2.8) days.</p> <p>*C: hydroxychloroquine or chloroquine was administered to 15/20 (75%) patients, lopinavir/ritonavir was used in 1/20 (5%) patient, and 4/20 (20%) patients did not receive etiotropic treatment.</p> <p>Groups comparable at baseline? Yes.</p>				<p><u>Adverse drug reactions to AVIFAVIR, n/N (%):</u> I: 7/40 (17.5%)</p> <p>*Adverse drugs reactions included diarrhea, nausea, vomiting, chest pain, and an increase in liver transaminase levels. The adverse drug reactions were mild to moderate and caused early discontinuation of the study drug in 2/540 (5%) patients.</p> <p>Virological outcomes <u>Viral clearance on day 5:</u> <u>n/N (%):</u> I: 25/40 (62.5%) C: 6/20 (30.0%) P=0.018</p> <p><u>Viral clearance on day 10:</u> <u>n/N (%):</u> I: 37/40 (92.5%) C: 16/20 (80%) P=0.155</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Zhao, 2021	<p>Type of study: RCT (open-label)</p> <p>Setting: 5 hospitals in mainland China, 27 March to 9 May 2020</p> <p>Country: China</p> <p>Source of funding: Chinese COVID-19 scientific research emergency project, China Mega-Project for Infectious Diseases, China Mega Project for Innovative Drugs</p> <p>Conflicts of interest: No conflict of interest.</p> <p>clinicaltrials.gov nr, NCT04333589</p>	<p>Patients tested re-positive for SARS-CoV-2 RNA after discharge.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age ≥ 18 male and female • Negative SARS-CoV-2 RNA test of respiratory specimens such as sputum or nasopharyngeal swabs, for two consecutive times (sampling time interval of at least 24 h) • Discharged • Positive SARS-CoV-2 RNA test of COVID-19 in any of sputum, nasopharyngeal swabs, blood, feces or other specimens. • Volunteer to participate with signed informed consent form. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Allergic to favipiravir • Pregnant or lactating women • Not suitable to participate decided by researchers. <p>N total at baseline: N = 55 Intervention: 36 Control: 19</p> <p>Important characteristics: Age, mean (SD): I: 55.8 y (14.2) C: 55.5 y (12.6) Sex, n/N (%) male: I: 16/36 (44.4%) C: 6/19 (47.4%)</p> <p>Disease severity, mean (SD): <i>Defined by Clinical type*</i> Mild I: 1 (2.8%) C: 0 (0%)</p>	<p>Favipiravir: 1600 mg (bid) on the first day, and 600 mg (bid) from the 2nd day to the 7th day, orally. Researchers decided whether to continue favipiravir according to the patient's condition, but no more than 14 days of treatment</p>	<p>Drugs other than favipiravir and treatment according to the needs of the disease.</p>	<p>Length of follow up: 30 days</p> <p>Loss to follow-up: I: 0/36 (0%) C: 0/19 (0%)</p>	<p>Secondary outcomes: Changes of blood routine and CRP, the count and proportion of T lymphocyte subsets in peripheral blood, changes of cytokines</p> <p>Clinical outcomes Mortality (28-30 day) Death, 30 days I: 0 C: 0</p> <p>Duration of hospitalization Not reported</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support Not reported</p> <p>Safety Adverse events 19 adverse events I: 12 C: 7 Increased ALT: (I: 4 vs. C: 3) Increased ALT: (I: 3 vs. C: 2) Hyperuricemia: (I: 2 vs. C: 1) Diarrhea: (I: 2 vs. C: 0) Nausea: (I: 1 vs. C:1)</p> <p>Serious adverse effects: I: 0 C:0</p>	<p>Definitions: *Clinical type based on China COVID-19 guidelines (7th Edition):</p> <ul style="list-style-type: none"> • Mild: mild clinical symptoms, no pneumonia was found in imaging. • Moderate: symptoms such as fever and respiratory tract, and pneumonia can be seen on imaging. • Severe: any of the following criteria : (1) Shortness of breath and respiratory rate > 30 beats / min (2) In a resting state, oxygen saturation ≤ 93%. (3) PaO₂ / FiO₂ ≤ 300mmHg (4) Lung imaging showed that the lung lesions progressed significantly (>50%) within 24-48 hours • Critical: any of the following criteria : (1) Respiratory failure occurs and requires mechanical ventilation (2) Shock occurs (3) Patients with other organ failure need ICU monitoring and treatment. <p>Remarks: Open-label trial; no role of sponsor in design and analysis</p> <p>Authors conclusion: Favipiravir was safe and superior to control in shortening the duration of viral shedding in SARS-CoV- 2 RNA recurrent positive after discharge. However, a larger scale and randomized, double-blind, placebo-controlled trial is required to confirm our conclusion.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Moderate I: 34 (94.4%) C: 17 (89.5%) Severe I: 1 (2.8%) C: 2 (10.5%)</p> <p>Groups were comparable at baseline, with the exception of the number of patients who showed the symptom "cough". In the control group, more patients showed this symptom (I: 3 vs. C: 6).</p>				<p>Virological outcomes Viral clearance: Time from start of study treatment to negative nasopharyngeal swab and sputum, median: I: 17 days C: 26 days HR 2.1 [95% CI 1.1–4.0], p =0.038</p> <p>Negative SARS-CoV-2 RNA PCR, day 30 I: 80.6% [29/36] C: 52.6% [10/19] p =0.030</p>	
Udwadia, 2020	<p><u>Type of study:</u> Randomized, open-label, parallel-arm, multicenter, phase 3 trial.</p> <p><u>Setting:</u> Breach Candy Hospital Mumbai, Glenmark Pharmaceuticals Limited Mumbai, Glenmark Pharmaceuticals Ltd, Watford UK. Glenmark Pharmaceuticals, Inc., USA, Mahwah, NJ</p> <p><u>Country:</u> India</p> <p><u>Source of funding:</u> This study was sponsored and funded by</p>	<p><u>Adults with mild-to-moderate COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age 18-75 years; Infection with SARS-CoV-2 virus confirmed by RT-PCR within 48 hours prior to randomization; No participation in any other interventional clinical study; Agreement to use effective contraception during the study and for >7 days following the last treatment; A negative pre-treatment pregnancy test (for female patients). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Severe infection; Oxygen saturation <93% or arterial oxygen partial pressure or fraction of inspired oxygen of <300 mmHg; Requiring ICU care for management of ongoing clinical status; 	<p>Oral favipiravir + supportive care</p> <p>(1800 mg BID loading dose on Day 1; 800 mg BID maintenance dose thereafter) plus standard supportive care (including antipyretics, cough suppressants, antibiotics, and vitamins) for up to a maximum of 14 days</p>	<p>Supportive care alone (including antipyretics, cough suppressants, antibiotics, and vitamins).</p>	<p><u>Length of follow up:</u> Treatment period 1-14 days. Study participation was a maximum of 28 days from the day of randomization.</p> <p><u>Loss to follow-up:</u> 150 patients were enrolled and randomized to favipiravir in addition to supportive care (N = 75) or a control group with standard supportive care alone (N = 75).</p> <p>N = 2 in the intervention group did not receive study drug and were excluded from the safety population.</p>	<p>Viral outcomes</p> <p><u>SARS-CoV-2 oral shedding (primary endpoint), within 28 days</u> <i>Number of events, n/N (%)</i> I: 70/72 (97.2%) C: 68 (90.7%)</p> <p><i>Time to event, median days (95% CI)</i> I: 5.0 (95% CI= 4.0 to 7.0) C: 7.0 (95% CI= 5.0 to 8.0) Log-rank P value= 0.1290 Hazard ratio P value= 1.367 (95% CI= 0.944 to 1.979) Hazard ratio P value= 0.098</p> <p>Clinical outcomes</p> <p><u>Time to Clinical Cure, 72 hours</u> <i>Number of events, n/N (%)</i> I: 51/53 (96.2%) C: 46/49 (93.9%)</p>	<p><u>Definitions:</u> Clinical cure was defined as recovery of fever (axillary temperature $\leq 97.8^{\circ}\text{F}$), respiratory rate of ≤ 20 breaths/minute, oxygen saturation $\geq 98\%$ without oxygen supplementation (which was later revised to align with the discharge criterion of $\geq 95\%$ oxygen saturation issued by the Indian Ministry of Health prior to the start of the study), and cough relief (mild or no cough) maintained for ≥ 72 hours.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, the results of this study suggest that despite failure to achieve statistical significance on the primary endpoint of time to RT-PCR negativity, early administration of oral favipiravir may reduce the duration of clinical signs and symptoms in patients with mild-to-moderate COVID-19, as demonstrated by the significantly decreased time to clinical cure. The</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Glenmark Pharmaceuticals Limited, India.</p> <p><u>Conflict of interest disclosures</u> The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Monika Tandon, Pawan Singh, Hanmant Barkate, Saiprasad Patil, Shabbir Rangwala, Amol Pendse, and Jatin Kadam are full-time employees of Glenmark Pharmaceuticals Limited, India. Wen Wu is a full-time employee of Glenmark Pharmaceuticals Ltd, United Kingdom. Cynthia Caracta is a full-time employee of Glenmark Pharmaceuticals Inc., USA. Zarir F Udawadia received an investigator grant from Glenmark</p>	<ul style="list-style-type: none"> • Inability to take or tolerate oral medications; • Allergy or hypersensitivity to favipiravir, asthma or chronic lung disease; • Severe liver disease; • History of gout or hyperuricemia, prolonged QT; • Severely reduced left ventricular function; • Severe renal impairment; • Having received continuous renal replacement therapy; • Hemodialysis or peritoneal dialysis. <p><u>N total at baseline (ITT population):</u> N = 147 Intervention: N = 72 Control: N = 75</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 43.6 y (12.2) C: 43.0 y (11.2)</p> <p>Sex, n/N (%) male: I: 51/72 (70.8%) C: 57/75 (76.0%)</p> <p><u>Severity of COVID-19, n/N (%)</u> <i>Mild</i> I: 44/72 (61.1%) C: 45/75 (60.0%)</p> <p><i>Moderate</i> I: 28/72 (38.9%) C: 30/75 (40.0%)</p> <p><u>Baseline symptoms (Cough, Fever, Respiratory Rate, SpO2) n/N (%)</u></p>			<p>An additional patient randomized to favipiravir did not have a post-baseline efficacy assessment and was excluded from the ITT population (N = 147).</p> <p>Among patients in the ITT population, 70/72 randomized to favipiravir and 68/75 randomized to control completed the study. The most common reason for study discontinuation was withdrawal of consent (N = 10).</p>	<p><i>Time to event, median days (95% CI)</i> I: 3.0 (95% CI= 3.0 to 4.0) C: 5.0 (95% CI= 4.0 to 6.0) Log-rank P value= 0.0297 Hazard ratio (95% CI)= 1.749 (1.096 to 2.792) Hazard ratio P value= 0.019</p> <p><u>Time to first use of High-Flow Supplemental Oxygen, Ventilation (Non-Invasive or Mechanical), or Extracorporeal Membrane Oxygenation</u> <i>Number of events, n/N (%)</i> I: 7/7 (100%) C: 7/7 (100%)</p> <p><i>Time to event, median days (95% CI)</i> I: 5.0 (95% CI= 1.0 to 6.0) C: 2.0 (95% CI= 1.0 to 4.0) Log-rank P value= 0.0653 Hazard ratio (95% CI)= 0.065 (95% CI= 0.005 to 0.809) Hazard ratio P value= 0.034</p> <p><u>Hospital discharge, within 28 days</u> <i>Number of events, n/N (%)</i> I: 70/72 (97.2%) C: 68/75 (90.7%)</p> <p><i>Time to event, median days (95% CI)</i> I: 9.0 (95% CI= 7.0 to 10.) C: 10.0 ((95% CI= 8.0 to 12.0)</p>	<p>adverse events reported for favipiravir were mild to moderate in severity and transient in nature, consistent with previous experience with the drug. There were no new safety signals. In view of the urgent clinical need for safe and effective treatments for mild-to-moderate COVID-19, orally administered favipiravir appears to be a promising drug candidate. Ongoing studies, including randomized, double-blind, placebo-controlled trials and those in combination with other antiviral therapies, will further clarify the role of favipiravir in COVID-19 patient management.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Pharmaceuticals Limited, India, as a site principal investigator for this study.	I: 53/72 (73.6%) C: 49/75 (65.3%) Groups comparable at baseline? Yes à “Baseline demographic and clinical characteristics were generally similar between favipiravir and control groups”				Log-rank P value= 0.1079 Hazard ratio (95% CI)= 1.406 (95% CI= 0.974 to 2.030) Hazard ratio P value= 0.069 <u>Adverse events by severity</u> <i>Mild, n/N (%)</i> I: 20/73 (27.4%) C: 5/75 (6.7%) <i>Moderate, n/N (%)</i> I: 6/73 (8.2%) C: 0/75 (0%) <i>Severe, n/N (%)</i> I: 0/73 (0%) C: 0/75 (0%) <i>Life threatening, n/N (%)</i> I: 0/73 (0%) C: 0/75 (0%) <i>Death, n/N (%)</i> I: 0/73 (0%) C: 1/75 (1.3%)* * An SAE (acute respiratory distress syndrome) was reported in 1 subject in the control group, and death due to SAE was reported in this same subject, which was considered to be not related to treatment.	
Khamis, 2020	<u>Type of study:</u> RCT, open-label <u>Setting:</u> Royal Hospital, Muscat, Oman,	Hospitalized patients with moderate to severe COVID-19 pneumonia. <u>Inclusion criteria:</u> • age between 18-75 years	<u>Favipiravir combined with inhaled interferon beta-1b</u> -favipiravir 1600mg on day 1 -followed by 600mg	<u>Standard care</u> -per “National COVID-19 Clinical Management Protocol,	<u>Length of follow up:</u> Not reported, but probably 14 days because 14-day mortality was reported.	<u>Clinical outcomes</u> <u>Length of hospital stay in day, median (IQR)</u> I: 7 (4-12) C: 7 (3-11) P=0.948	<u>Remarks:</u> • A total 190 patients was needed (95 on each arm) to have 90% power. Due to logistical and financial constraints, only a total of 89 COVID-19 patients were enrolled into the study.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>from June 22nd 2020 to August 13th 2020.</p> <p><u>Country:</u> Oman</p> <p><u>Source of funding:</u> -No funding was received for this study -The authors have no conflicts of interest to declare</p>	<ul style="list-style-type: none"> confirmed SARS-CoV-2 infection by RT-PCR test on respiratory tract specimens moderate to severe COVID-19 pneumonia according to the WHO interim guidelines case definitions (WHO/2019 nCoV/ Surveillance Case Definition /2020.1) the interval between symptoms onset and randomization is no >10 days female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pretreatment serum or urine pregnancy test eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment not participating in any other interventional drug clinical study before completion of the present one. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> age above 75 refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of favipiravir 	<p>twice a day for a maximum of 10 days</p> <p>- interferon beta-1b at a dose* of 8 million IU (0.25?g) twice a day was given for 5 days through a vibrating mesh aerogen nebulizer (Aerogen Solo)</p> <p>*In case the patient experienced an adverse event related to liver injury of grade ≥ 3 (common terminology criteria for adverse events (CTCAE) v5.0, 2017), the dose was reduced to 800 mg on the day 1 then 400 mg twice a day. The treatment was discontinued if the patient experienced any adverse event related to liver injury of grade ≥ 3 after dose reduction.</p>	<p>Ministry of Health, Oman- version 1" for adult patients with moderate to severe COVID-19 pneumonia</p> <p>-hydroxychloroquine (HCQ) 400 mg twice per day on the day 1, then 200 mg twice per day for 7 days.</p>	<p><u>Loss to follow-up:</u> I: 0/44 (0%) Reasons: not applicable C: 0/45 (0%) Reasons: not applicable</p>	<p><u>Transfer to ICU, n/N (%)</u> I: 8/44 (18.2%) C: 8/45 (17.8%) P=0.960</p> <p><u>Discharged home, n/N (%)</u> I: 29/44 (65.9%) C: 31/45 (68.9%) P=0.764</p> <p><u>Oxygen saturation at discharge, median (IQR)</u> I: 94 (93-96) C: 95 (93-96) P=0.324</p> <p><u>Overall 14-day mortality, n/N (%)</u> I: 5/44 (11.4%) C: 6/45 (13.3%) P=0.778</p> <p><u>Also available: inflammatory markers at hospital discharge</u></p>	<ul style="list-style-type: none"> The findings represent an interim analysis. Limitation: time to viral clearance was not measured as repeating nasopharyngeal swabs was not done due to limited resources, nor the radiological imaging to assess improvement A potential reason for lack of clinical response could be the timing of administration of favipiravir in relation to the course of the illness, in particular during early phases of the disease. A randomized double-blind placebo-controlled trial to determine the safety and efficacy of inhaled IFN-$\beta 1a$ (SNG001for nebulisation) for patients infected with SARS-CoV-2 is ongoing (ClinicalTrials.gov Identifier: NCT04385095) <p><u>Authors conclusion:</u> Favipiravir was not significantly different compared to HCQ with regards to overall length of hospital stay, ICU transfers, discharges, oxygen saturation at discharge, overall mortality as well as changes in the inflammatory cytokine storm biomarkers at discharge in adults hospitalized with moderate to severe COVID19 pneumonia.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the upper limit normal • gout or history of gout or hyperuricemia • known severe renal impairment with creatinine clearance (CrCl) of <30 mL/min or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis • known allergy or hypersensitivity to favipiravir • pregnant or lactating women. • <p><u>N total at baseline:</u> N =89 Intervention: 44 Control: 45</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 54 y (15) C: 56 y (16) Sex, n/N (%) male: I: 28/44 (64%) C: 24/45 (53%) Co-morbidity: diabetes mellitus, n/N (%) I: 17/44 (39%) C: 23/45 (51%) Co-morbidity: hypertension, n/N (%) I: 24/44 (55%) C: 24/45 (53%) Co-morbidity: heart disease, n/N (%)</p>					

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 7/44 (16%) C: 6/45 (13%) Co-morbidity: lung disease, n/N (%) I: 3/44 (6.8%) C: 2/45 (2.4%)</p> <p>Groups comparable at baseline? There were no significant differences among the groups regarding the demographic and clinical characteristics; however, those on favipiravir were more likely to be associated with severe and end stage chronic kidney disease (CKD) compared to those on standard treatment regimens (p = 0.009).</p>					
Lou, 2020	<p>Type of study: Exploratory single center, open-label, randomized, controlled trial (1:1:1)</p> <p>Setting: Hospitalized COVID-19 patients were randomized in the clinical trial and was initiated on February 3, 2020 in the First Affiliated Hospital, Zhejiang University School of Medicine.</p> <p>Country: Zhejiang, China</p> <p>Source of funding: Not reported.</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adults 18 – 85 years Confirmed COVID-19 (by real time RT-PCR) No difficulty in swallowing oral drugs <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Known allergies Critical illness : respiratory failure and mechanical ventilation; shock; other organ failure requiring ICU monitoring and treatment; Renal insufficiency Abnormal ALT or AST levels <p>N total at baseline: N = 29 Baloxavir: n=10 Favipiravir: n=9 Control: n=10</p> <p>Important characteristics:</p> <ul style="list-style-type: none"> Baloxavir group 	<p>Baloxavir marboxil: 80 mg once a day orally on Day 1 and Day 4; for patients who are still positive in virological test, they can be given again on Day 7.</p> <p>+ existing antiviral treatment</p> <p>Favipiravir:</p> <ul style="list-style-type: none"> The first dose was 1600 mg or 2200mg orally, followed by 600 mg each time, three times a day, and the duration of administration was not more than 14 days <p>+ existing antiviral treatment</p>	<p>Control:</p> <ul style="list-style-type: none"> The existing antiviral treatment included lopinavir/ritonavir (400mg/100 mg, bid, po.) or darunavir/cobicistat (800mg/150 mg, qd, po.) and arbidol (200mg, tid, po.) All of them were used in combination with interferon-α inhalation (100,000 iu, tid or qid) 	<p>Length of follow-up: 14 days after the initiation of the trial</p> <p>Loss-to-follow-up: One patient in the favipiravir group was subsequently excluded from the final analysis because of his personal refusal to continue to use favipiravir after Day 1.</p> <p>One patient in the baloxavir marboxil group, and two patients in the favipiravir group were transferred to ICU within seven days after trial initiation.</p>	<p>Viral negative in Day 14 – n/N (%): Total group: 24/29 (82.8%) Baloxavir marboxil: 7/10 (70%) Favipiravir: 7/9 (77%) Control: 10/10 (100%)</p> <p>Time to clinical improvement – median no. of days (IQR): Total group: 14 (6-49) Baloxavir marboxil: 14 (6-49) Favipiravir: 14 (6-38) Control: 15 (6-24)</p> <p>Incidence of mechanical ventilation – n/N (%): Total group: 1/29 (3%) Baloxavir marboxil: 1/10 (10%) Favipiravir: 0/9 Control: 0/10</p>	<p>Comments:</p> <ul style="list-style-type: none"> The number of patients were rather limited. The treatment scheme and medication time before the initiation of the trial was different among the patients, which makes their progression of the disease at the beginning of the trial quite different Viral negative in Day 7 n/N (%), transfer to ICU in Day 14 n/N (%), changes of Ct value compared with Day1 – median (IQR) at day 14 and day 7 <p>Definitions:</p> <ul style="list-style-type: none"> Clinical improvement was defined as a decline of two categories on the modified seven-category ordinal scale of clinical status, or hospital discharge. The seven-category ordinal scale consisted of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized,

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Mean age: 53.5 ± 12.5 Male gender: 7/10 (70%)</p> <ul style="list-style-type: none"> Favipiravir group Mean age: 58.0 ± 8.1 Male gender: 7/9 (77%) Control group Mean age: 46.6 ± 14.1 Male gender: 7/10 (70%) <p><u>Groups comparable at baseline? The demographic characteristics, Ct value, and initial serum biochemistry were balanced in the three groups.</u></p>				<p><u>Time to viral negative- median – no. of days (IQR):</u> Total group: 7 (1-46) Baloxavir marboxil: 6 (1-46) Favipiravir: 9 (2-34) Control: 9 (1-13)</p> <p><u>Clinical improvement (day 14) – n/N (%)</u> Total group: 16/29 (55%) Baloxavir marboxil: 6/10 (60%) Favipiravir: 5/9 (55%) Control: 5/10 (50%)</p> <p><u>Clinical improvement (day 7) – n/N (%)</u> Total group: 4/29 (14%) Baloxavir marboxil: 1/10 (10%) Favipiravir: 2/9 (22%) Control: 1/10 (10%)</p> <p><u>Oxygen support -days (IQR):</u> Total group: 12 (3-41) Baloxavir marboxil: 13 (3-41) Favipiravir: 13 (3-37) Control: 12 (5-23)</p> <p><u>Score on seven-category scale at day 14 – n/N (%)</u> 2: Not hospitalized, but unable to resume normal activities Total group: 14/29 (48%) Baloxavir marboxil: 6/10 (60%) Favipiravir: 4/9 (44%) Control: 4/10 (40%)</p>	<p>but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 7, death.</p> <p><u>Author's conclusion:</u> Our findings could not prove a benefit of addition of either baloxavir marboxil or favipiravir under the trial dosages to the existing standard treatment.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>3: Hospitalization, not requiring supplemental oxygen Total group: 4/29 (14%) Baloxavir marboxil: 0/10 (0%) Favipiravir: 2/9 (22%) Control: 2/10 (20%)</p> <p>4: Hospitalization, requiring supplemental oxygen Total group: 10/29 (34%) Baloxavir marboxil: 3/10 (30%) Favipiravir: 3/9 (33%) Control: 4/10 (40%)</p> <p>5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation Total group: 0/29 (0%) Baloxavir marboxil: 0/10 (0%) Favipiravir: 0/9 (0%) Control: 0/10 (0%)</p> <p>6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both Total group: 0/29 (0%) Baloxavir marboxil: 1/10 (10%) Favipiravir: 0/9 (0%) Control: 0/10 (0%)</p>	
9.3. Lopinavir and ritonavir (brand name = Kaletra; fixed dose combination of antiretroviral treatment)							
Arabi, 2021	See evidence table of Arabi (2021) by hydroxychloroquine.						
Ader, 2021	See evidence table of Ader (2021) by hydroxychloroquine.						
Reis, 2021	See evidence table of Reis (2021) by hydroxychloroquine.						
Purwati, 2021	See evidence table of Purwati (2021) by hydroxychloroquine.						
Pan, 2020	<u>Type of study:</u>	<u>N total at baseline:</u> N = 11,330	Lopinavir	Standard of care	<u>Length of follow up:</u>	Clinical outcomes	<u>Definitions/information:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>RCT (open-label, non-blinded)</p> <p><u>Setting & country:</u> 405 hospitals in 30 countries; WHO Solidarity Trial</p> <p><u>Source of funding:</u> Funded by the World Health Organization;</p> <p>ISRCTN Registry nr, ISRCTN83971151; ClinicalTrials.gov nr, NCT04315948.)</p>	<p><i>Lopinavir arm</i> I: 1399 C: 1372</p> <p><u>Important characteristics:</u> <u>Age, n/N (%)</u>: I: <50y: 511/1399 (36.5%) 50-69y: 597/1399 (42.7%) ≥70y: 291/1399 (20.8%) C: <50y: 501/1372 (36.5%) 50-69y: 596/1372 (43.4%) ≥70y: 275/1372 (20.0%) <u>Sex, n/N (%) male</u>: I: 851/1399 (60.8%) C: 802/1372 (58.5%) <u>Respiratory support</u> I: No suppl. Oxygen at entry: 528/1399 (37.7%) Suppl. Oxygen at entry 759/1399 (54.3%) Already receiving ventilation 112/1399 (8.0%) C: No suppl. Oxygen at entry: 539/1372 (39.3%) Suppl. Oxygen at entry 719/1372 (52.4%) Already receiving ventilation 114/1372 (8.3%) <u>Previous days in hospital</u> I: 0 days: 423/1399 (30.2%) 1 day: 442/1399 (31.6%) ≥2 days: 534/1399 (38.2%) C: 0 days: 403/1372 (29.4%) 1 day: 445/1372 (32.4%) ≥2 days: 524/1372 (38.2%)</p>	<p>Oral; 2 tablets twice daily for 14 days. Each tablet contained 200 mg of lopinavir (plus 50 mg of ritonavir, to slow hepatic lopinavir clearance). No other formulations, so patients did not receive study drug during mechanical ventilation</p> <p><i>Discontinued for futility on July 4, 2020</i></p> <p><u>Taking trial drug midway through scheduled duration*</u>: 94% C: 2%</p> <p><u>Use of non-study drug, n/N (%)s</u>: Corticosteroids I: 316 (22.6%) C: 328 (23.9%) Convalescent plasma I: 24 (1.7%) C: 15 (1.1%) Anti-IL-6 drug I: 42 (3.0%) C: 42 (3.1%) Non-trial interferon I: 4 (0.3%) C: 0 (0.0%) Non-trial antiviral I: 86 (6.2%) C: 90 (6.6%)</p>		<p>28 days, or up to discharge</p> <p><u>Loss to follow-up</u>: I: 12/1411 (0.9%) Reasons: no or unknown consent C: 8/1380 (0.6%) Reasons: no or unknown consent</p>	<p><u>All-cause in-hospital mortality, regardless of whether death occurred before or after day 28</u>: I: 148/1399 (9.7%) C: 146/1372 (10.3%) RR 0.99 (95% CI 0.80 to 1.23)</p> <p>HR=1.00 (0.79-1.25) Adjusted** HR=0.94 (0.76-1.16)</p> <p><u>All-cause in-hospital mortality, stratified by ventilation at randomization</u>: Ventilated: HR 1.08 (95% CI 0.67-1.74) Not ventilated: HR 0.97 (95% CI 0.75-1.26)</p> <p><u>Initiation of mechanical ventilation, in those not receiving ventilation at baseline</u>: I: 126/1287 (9.9%) C: 121/1258 (9.6%) RR 1.02 (95% CI 0.80, 1.29)</p> <p><u>Composite death or initiation ventilation</u>: I: 222/1399 (15.9%) C: 223/1372 (16.3%) RR 0.98 (95% CI 0.82 to 1.16) Publication: RR 0.98 [0.80-1.18]</p> <p><u>Hospitalized, not discharged</u>: <i>Percentage of patients (rather than number of</i></p>	<p><u>Taking trial drug midway through scheduled duration</u>, %, calculated only among patients who died or were discharged alive, % patients who were taking the trial drug midway through the time from entry to death or discharge, if this was shorter). <u>*Adjusted model all-cause mortality</u>: some overlap between the 4 control groups; an exploratory sensitivity analysis used multivariate Cox regression to fit all 4 treatment effects simultaneously; adjusted for several prognostic factors (age, sex, diabetes, bilateral lung lesions at entry (no, yes, not imaged at entry), and respiratory support at entry (no oxygen, oxygen but no ventilation, ventilation). <u>Authors conclusion</u>: These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>patients) ever reported as discharged who were still in the hospital:</p> <p>Day 7 I: 68% C: 59%</p> <p>Day 14 I: 31% C: 22%</p> <p>Day 21 I: 12% C: 11%</p>	
Horby, 2020c	<p>Type of study: Randomised, controlled, open-label. platform trial.</p> <p>Setting: 176 hospitals</p> <p>Country: United Kingdom</p> <p>Source of funding: Medical Research Council and National Institute for Health Research</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Patients with severe hepatic insufficiency or who were using medicinal products that are highly dependent on cytochrome P450 3A4 for clearance and for whom elevated plasma concentrations would be associated with serious or life-threatening events were excluded. <p>N total at baseline: N = 5040 Intervention: 1616 Control: 3424</p> <p>Important characteristics:</p>	lopinavir 400 mg plus ritonavir 100 mg by mouth every 12 h for 10 days or until discharge, if sooner plus usual standard of care	Usual standard of care	28 days	<p>1. 28-day mortality; n/N (%)</p> <p>I: N = 374/1616 (23%) C: N = 767/3424 (22%) P=0.60</p> <p>2. Discharged from hospital within 28 days; n/N (%)</p> <p>I: N = 1113/1616 (69%) C: N = 2382/3424 (70%) P=0.53</p> <p>3. Receipt of invasive mechanical ventilation or death; n/N (%)</p> <p>I: N = 449/1556 (29%) C: N = 871/3280 (27%) P=0.092</p> <p>3.1 Invasive mechanical ventilation</p> <p>I: N = 152/1556 (10%) C: N = 279/3280 (9%) P=0.15</p> <p>3.2 Death</p>	<p>Remarks:</p> <ul style="list-style-type: none"> Follow-up information was complete for 5018 (>99%) of 5040 patients (1606 [99%] of 1616 patients in the lopinavir-ritonavir group and 3412 [99%] of 3424 patients in the usual care group). <p>Authors conclusion: The results from the RECOVERY trial show that lopinavir-ritonavir monotherapy is not an effective treatment for patients admitted to hospital with COVID-19. Treatment of COVID-19 with lopinavir-ritonavir has been recommended as a first-line or second-line in many countries. Since our preliminary results were made public on June 29, 2020, WHO has halted the lopinavir-ritonavir monotherapy and the lopinavir-ritonavir plus interferon beta combination groups of the SOLIDARITY trial because the interim results are in line with those presented here—lopinavir-ritonavir does not improve clinical outcomes for patients admitted to hospital with COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Age, mean (SD): I: 66.0 (16.0) C: 66.4 (15.8) Sex, n/N (%) male: I: 973/1616 (60%) male C: 2104/3424 (61%) male				I: N = 350/1556 (22%) C: N = 712/3280 (22%) P=0.54	
Huang, 2020	<u>Type of study:</u> Randomized, open-labeled, prospective clinical trial <u>Setting:</u> Single centre <u>Country:</u> China <u>Source of funding:</u> This work was supported by the National Science and Technology Major Project of China During the 13th Five-year Plan Period (2018ZX10302104) ; and the Chongqing Special Research Project for Prevention and Control of Novel Coronavirus Pneumonia (No. cstc2020jscxfyzX0005); and the Novel Coronavirus Infection and Prevention	<u>Inclusion criteria:</u> - 18–65 years of age; - diagnosed as mild to moderate COVID-19; and - willing to sign informed consent. <u>Exclusion criteria:</u> - were pregnant or breastfeeding women; -had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5× upper normal limit, creatinine clearance <50 ml/min (Lu and Dong, 2019); -were allergic or intolerant to therapeutic drugs; - were HIV-positive patients; - had severe heart disease, brain disease, lung disease, kidney disease, neoplastic disease, or other systemic diseases, which may have had the potential to influence patients' adherence to the prescribed antiviral regimens; and - withheld informed consent. - patients who did not require supplemental oxygen during hospitalization <u>N total at baseline:</u> N = 101 RBV + IFN-a: 33	<u>RBV + IFN-a</u> <u>LPV/r + IFN-a</u> <u>RBV + LPV/r + IFN-a</u> RBV was given by intravenous injection at a loading dose of 2 g, followed by oral doses of 400–600 mg every 8 h depending on patients' body weight, for 14 d LPV/r was given orally at a dose of 400 mg/100 mg per dose twice per day for 14 d IFN-a was given by atomizing inhalation at a dose of 5 million U or 50 mg per dose twice a day for 14 d.	-	28 days	<u>1. interval from baseline to SARS-CoV-2 nucleic acid Negativity, median days:</u> RBV + IFN-a: 13 LPV/r + IFN-a: 12 RBV + LPV/r + IFN-a: 15 <u>2. proportion of patients with SARS-CoV-2 nucleic acid negativity:</u> RBV + IFN-a: 51.5% LPV/r + IFN-a: 61.1% RBV + LPV/r + IFN-a: 46.9%	<u>Remarks:</u> - <u>Authors conclusion:</u> Our results indicate that there are no significant differences among the three regimens in terms of antiviral effectiveness in patients with mild to moderate COVID-19. Furthermore, the combination of RBV and LPV/r is associated with a significant increase in gastrointestinal adverse events, suggesting that RBV and LPV/r should not be co-administered to COVID-19 patients simultaneously.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Emergency Research Project of Chongqing Municipal Education Commission (KYYJ202001).	<p>LPV/r + IFN-a: 36 RBV + LPV/r + IFN-a : 32</p> <p><u>Important characteristics:</u> Age, mean years (± SD): RBV + IFN-a: 40.3 (12.5) LPV/r + IFN-a: 43.3 (10.4) RBV + LPV/r + IFN-a : 43.8 (11.7)</p> <p>Sex, n/N (%) male: RBV + IFN-a: 18 (55%) LPV/r + IFN-a: 19 (53%) RBV + LPV/r + IFN-a: 9 (28%)</p> <p>Time from symptom onset to enrolment, median days (IQR): RBV + IFN-a: 4.5 (2.3, 7.0) LPV/r + IFN-a: 3.0 (1.3, 6.8) RBV + LPV/r + IFN-a: 4.0 (2.0,7.0)</p> <p>Oxygen saturation (%), mean (± SD): RBV + IFN-a: 97.2 (1.1) LPV/r + IFN-a: 97.2 (1.4) RBV + LPV/r + IFN-a : 97.4 (1.5)</p> <p>Respiratory rate median days breath/min (IQR): RBV + IFN-a: 20.0 (19.0, 21.0) LPV/r + IFN-a: 20.0 (19.0, 22.6) RBV + LPV/r + IFN-a: 20.0 (18.1, 21.9)</p> <p>Groups comparable at baseline? Yes</p>					
Li, 2020a	<p><u>Type of study:</u> Exploratory randomized controlled trial (2:2:1)</p> <p><u>Setting:</u></p>	<p><u>Inclusion criteria:</u></p> <p>1) age between 18 and 80 years old 2) SARS-CoV-2 infection confirmed by real-time PCR (RT-PCR) from pharyngeal swab</p>	In group A 34 patients were administered lopinavir (200mg) boosted by ritonavir (50mg) (orally administered, twice daily, 500 mg, each time for 7-14 days)	In group C (control group), 17 patients were not given any antiviral therapy.	<p><u>Length of follow-up:</u> 21 day period</p> <p><u>Loss-to-follow-up:</u> All patients were followed for 21 days.</p>	<p>At 7 days after initiating treatment: Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)</p>	<p><u>Authors conclusion:</u> LPV/r or arbidol monotherapy present little benefit for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 over supportive care.</p> <p><u>Own noted limitations:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>In Guangzhou Eighth People Hospital, 86 patients with Mild/Moderate COVID-19 were assigned to 3 groups</p> <p><u>Country:</u> China, Guangzhou</p> <p><u>Source of funding:</u> <u>This study was supported by project 2018ZX10302103-002, 2017ZX10202102-003-004, and Infectious Disease Specialty of Guangzhou High-level Clinical Key Specialty (2019-2021).</u></p>	<p>3) mild clinical status, defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging [5]</p> <p>4) the following lab findings: creatinine $\leq 110 \mu\text{mol/L}$, creatinine clearance rate (eGFR) $\geq 60 \text{ ml/min/1.73m}^2$, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 5 \times \text{ULN}$, and total bilirubin (TBIL) $\leq 2 \times \text{ULN}$</p> <p>5) willing to participate the study and sign the informed consent.</p> <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1) known or suspected to be allergic to LPV/r or arbidol; 2) having severe nausea, vomiting, diarrhea or other complaints affecting oral intake or absorption in the digestive tract; 3) taking other drugs that may interact with LPV/r or arbidol; 4) having serious underlying diseases, including but not limited to heart, lung, or kidney disease, liver malfunction, or mental diseases affecting treatment compliance; 5) complicating with pancreatitis or hemophilia prior to the trial; 6) Pregnant or lactating women; 7) having the suspected or confirmed history of alcohol or substance use disorder 8) having participated in other drug trials in the past month 	<p>- In group B (arbidol group), 35 patients were given arbidol (100mg) (orally administered, 200mg three times daily for 7-14 days).</p>			<p>LPV/r: 12/34 (35.3%) Arbidol: 13/35 (37.1%) Control: 7/17 (41.2%) P-value = 0.966</p> <p>At 14 days after initiating treatment:</p> <p>Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%) LPV/r: 29/34(85.3%) Arbidol: 32/35(91.4%) Control: 13/17(76.5%) P-value = 0.352</p> <p>Time to positive-to-negative conversion of SARS-CoV-2 nucleic acid in pharyngeal swab, in days (mean/SD, 95%CI) LPV/r: 9.0(5.00),(7.2,10.8) Arbidol: 9.1(4.4),(7.6,10.6) Control: 9.3(5.2),(6.7,11.9)</p> <p>Conversion rate from moderate to severe/critical clinical status (%) LPV/r: 8/34 (23.5%) Arbidol: 3/35(8.6%) Control: 2/17(11.8%) P-value = 0.206</p> <p>Antipyresis rate (%) LPV/r: 20/27(74.1%) Arbidol: 18/22(81.8%) Control: 8/9(88.9%) P-value = 0.579</p>	<p>- "sample size was small"</p> <p>- "the study did not enroll severely or critically ill patients, or patients with many comorbidities who are at increased risk of poor outcome and was conducted in only one center."</p> <p>- "the study was not completely blinded, so it is possible to influence the outcome."</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>9) deemed otherwise unsuitable for the study by the researchers.</p> <p><u>N total at baseline:</u> N = 86</p> <p>LPV/r: 34 Arbidol: 35 Control: 17</p> <p><u>Important characteristics:</u> LPV/r: Male gender (n, %): 17(50.0%) Age, in years (mean, SD, range): 50.7(15.4;19-79)</p> <p>Arbidol: Male gender (n, %): 16(45.7%) Age, in years (mean, SD, range): 50.5(14.6;20-74)</p> <p>Control: Male gender (n, %): 7(41.2%) Age, in years (mean, SD, range): 44.3(13.1;27-62)</p> <p>Groups comparable at baseline? Yes → <i>No significant differences were observed between the two groups.</i></p>				<p>Rate of cough alleviation (%) LPV/r: 9/21 (42.9%) Arbidol: 7/25(28.0%) Control: 2/9(22.2%) P-value = 0.432</p> <p>Rate of improvement on chest CT (%) LPV/r: 11/28(39.3%) Arbidol: 13/33(39.4%) Control: 6/14 (42.9%) P-value = 0.971</p> <p>Antipyresis rate (%) LPV/r: 24/27 (88.9%) Arbidol: 21/22 (95.5%) Control: 9/9 (100%) P-value = 0.343</p> <p>Rate of cough alleviation (%) LPV/r: 16/21 (76.2%) Arbidol: 14/25 (56.0%) Control: 4/9 (44.4%) P-value = 0.180</p> <p>Rate of improvement on chest CT (%) LPV/r: 21/28(75.0%) Arbidol: 23/33(69.7%) Control: 13/14 (92.9%) P-value = 0.089</p>	
Cao, 2020a	<p><u>Type of study:</u> Open-label individually randomized controlled trial, from Jan 18, 2020, to Feb 3, 2020</p> <p><u>Setting:</u></p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Male / non-pregnant female • Age ≥18y • Diagnostic specimen positive for SARS-CoV-2 on RT-PCR • pneumonia confirmed by chest imaging • oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio 	<p>14 days Lopinavir–ritonavir (400 mg and 100 mg, orally) twice a day</p> <p>plus standard care (for details, see description control group)</p>	<p>14 days Standard care alone</p> <p><i>Standard care: As necessary, supplemental oxygen, non-invasive and invasive</i></p>	<p>7, 14 and 28 days</p> <p>Results based on intention-to-treat analysis.</p> <p>3 patients in the intervention group died between randomization and</p>	<p>Results are provided as median [IQR] unless stated otherwise</p> <p>Clinical improvement</p> <p><u>Time to clinical improvement</u>(days); defined as 2-point improvement on 7-</p>	<p><u>Authors conclusion:</u></p> <ul style="list-style-type: none"> • Lopinavir–ritonavir treatment added to standard supportive care was not associated with clinical improvement or mortality. • The modified analysis showed modest favour of the treatment group.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Jin Yin-Tan Hospital, Wuhan, Hubei Province</p> <p><u>Country:</u> China</p> <p><u>Source of funding:</u> Major Projects of National Science and Technology on New Drug Creation and Development (2020ZX09201001) + (2020ZX09201012); the Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 (2020HY320001); and a National Science Grant for Distinguished Young Scholars (81425001/H0104)</p>	<p>of the partial pressure of oxygen (Pao₂) to the fraction of inspired oxygen (Fio₂) (Pao₂:Fio₂) at or below 300 mg Hg.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> physician decision that involvement in the trial was not in the patient's best interest presence of any condition that would not allow the protocol to be followed safely known allergy or hypersensitivity to lopinavir–ritonavir known severe liver disease (e.g., cirrhosis, with an alanine aminotransferase level >5× the upper limit of the normal range or an aspartate aminotransferase level >5× the upper limit of the normal range) use of medications that are contra-indicated with lopinavir–ritonavir and that could not be replaced or stopped during the trial period (details in appendix at NEJM.org); pregnancy or breast-feeding, or known HIV infection (concerns about development of resistance to lopinavir–ritonavir if used without combining with other antiretrovirals) Patients who were unable to swallow received lopinavir–ritonavir through a nasogastric tube. <p><u>N total at baseline:</u> N = 199 Intervention: 99</p>		<p>ventilation, anti-biotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO).</p>	<p>start of the intervention. Relevant findings from the modified intention-to-treat analysis excluding these 3 patients (intervention, N=96), is placed in the most right column.</p>	<p>category scale, or discharge from hospital; see most right column for 7 categories): I: 16 [13-17] C: 16 [15-18] <i>hazard ratio: 1.31 [95% CI 0.95 to 1.85]; P = 0.09, no difference</i></p> <p><u>Clinical improvement</u>, n (%) defined as 2-point improvement on 7-point scale Day 7 I: 6/99 (6%) C: 2/100 (2%) <i>no difference</i> Day 14 I: 45/99 (46%) C: 30/100 (30%) <i>difference, 15.5 percentage points; 95% CI, 2.2 to 28.8 = in favour of INT group</i> Day 28 I: 78/99 (79%) C: 70/100 (70%) <i>no difference</i></p> <p><u>Clinical deterioration</u> Defined as 1-point increase in 7-point scale HR 1.01 (0.76, 1.34) <i>no difference between groups</i></p> <p>Mortality</p> <p><u>Mortality at 28-days</u>, n/N (%) I: 19/99 (19%) C: 25/100 (25%)</p>	<ul style="list-style-type: none"> The mortality rate (22.1%) indicates that the study population consists of severely ill patients. <p><u>Modified intention-to-treat analysis:</u> excluding 3 patients in intervention group, with early death after randomization but before start intervention <u>Time to clinical improvement in days</u> (median [IQR]); I: 15 [13-17] C: 16 [15-18] <i>hazard ratio, 1.39; 95% CI, 1.00 to 1.91 = in favour of intervention group</i></p> <p><u>Sub-group analysis: randomization ≤12 days vs. 12 days after onset illness</u> Time to clinical improvement in both groups not associated with lopinavir–ritonavir treatment, <i>see manuscript for details</i></p> <p><u>Seven-category ordinal scale:</u> 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6, hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7, death.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Control: 100</p> <p><u>Important characteristics:</u> Intervention group: Age (median [IQR]): 58 [50-68] Male: 61 (62%)</p> <p>Control group: Age (median [IQR]): 58 [48-68] Male: 59 (59%)</p> <p><i>At baseline:</i> There were no important between-group differences in demographics, baseline laboratory test results, distribution of ordinal scale scores, or NEWS2 scores at enrolment.</p> <p><i>During trial:</i> systemic glucocorticoids were administered in 33.0% of patients in the intervention group and in 35.7% of patients in the control group.</p>				<p><i>difference, -5.8 percentage points; 95% CI, -17.3 to 5.7 = in favour of INT group</i></p> <p>Earlier (≤ 12d after onset symptoms): I: 8/99 (19%) C: 13/100 (27%)</p> <p>Later (≥ 12d after onset symptoms): I: 11/99 (19%) C: 12/100 (23%)</p> <p><u>Time from randomization to death</u> (days) I: 9 [6-13] C: 12 [6-15] <i>no difference</i></p> <p>Adverse events n/N (%) Any adverse events, any grade I: 46/95 (48%) C: 49/99 (50%) <i>No difference</i> Any adverse event, grade 3 / 4 I: 20/95 (21%) C: 11/99 (11%) <i>More often in intervention</i> Serious adverse events, grade 3-4 I: 17/95 (18%) C: 31/99 (31%) <i>More often in controls</i></p> <p>Other</p> <p><u>ICU length of stay</u> (days) I: 6 [2-11] C: 11 [7-17] <i>difference, -5 days; 95% CI,</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>-9 to 0 = in favour of INT group</p> <p>Survivors I: 9 [5-44] C: 11 [9-14]</p> <p>Non-survivors I: 6 [2-11] C: 12 [7-17]</p> <p><u>Duration invasive mechanical ventilation</u> (days) I: 4 [3-7] C: 5 [3-9] <i>no difference</i></p> <p><u>Oxygen support</u> (days) I: 12 [9-16] C: 13 [6-16] <i>no difference</i></p> <p><u>Hospital stay</u> (days) I: 14 [12-17] C: 16 [13-18] <i>no difference</i></p> <p><u>Time from randomization to discharge</u> (days) I: 12 [10-16] C: 14 [11-16] <i>difference, 1 day; 95% CI, 0 to 3 = in favour of INT group</i></p> <p><u>Mechanical ventilation for respiratory failure during study period, n/N (%)</u></p> <p><i>Non-invasive</i> I: 10/99 (10%) C: 19/100 (19%)</p> <p><i>Invasive</i> I: 14/99 (14%) C: 18/100 (18%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>More in control group</i></p> <p>Viral loads/clearance: <u>Viral RNA loads over time</u> <i>No difference between groups; see manuscript for details</i></p> <p><u>Percentage of patients with detectable viral RNA for SARS-CoV-2</u> <i>No difference between groups on any sampling day; see manuscript for details</i></p>	
9.4. Molnupiravir							
Jayk Bernal, 2022	<p><u>Type of study:</u> A phase 3, double-blind, randomized, placebo-controlled trial</p> <p><u>Setting:</u> >170 sites, between May 06, 2021 and November 04, 2021 (MOVE-OUT)</p> <p><u>Country:</u> Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Mexico, Philippines, Poland, Russia, South Africa, Spain, Sweden, Taiwan, Ukraine, the United Kingdom</p>	<p>Non-hospitalized patients with mild or moderate disease, determined on the basis of definitions adapted from FDA and WHO guidance.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection no more than 5 days earlier, onset of signs or symptoms no more than 5 days earlier At least one sign or symptom of COVID-19 At least one risk factor for development of severe illness from COVID-19 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Need for hospitalization within the next 48 h Dialysis or estimated GF rate <30ml per minute per 1.73m² Pregnancy Unwillingness to use contraception during the intervention period 	<p>molnupiravir 800 mg delivered as four 200-mg capsules administered orally twice daily for 5 days</p> <p>+</p> <p>Standard care</p> <p>Standard-of-care treatment with antipyretic agents, antiinflammatory agents, glucocorticoids, or a combination was permitted; use of therapies intended as Covid-19 treatments (including any monoclonal antibodies and remdesivir) was prohibited through day 29</p>	<p>Identical placebo administered orally twice daily for 5 days</p> <p>+</p> <p>Standard care</p> <p>Standard-of-care treatment with antipyretic agents, antiinflammatory agents, glucocorticoids, or a combination was permitted; use of therapies intended as Covid-19 treatments (including</p>	<p><u>Length of follow-up:</u> 29 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: N=7 (0.98%) Reasons: Was hospitalized before dose 1 (N=1), did not receive molnupiravir (N=6)</p> <p>680/716 (95%) completed 29-day trial</p> <p>709 included in the modified intention-to-treat analysis</p> <p>Control: N=18 (2.58%) Reason: Were hospitalized before dose 1 (n=2), did not receive placebo (n=16)</p>	<p>Clinical outcomes <u>Mortality (29 day):</u> Mortality, n/N (%): I: 1/709 (0.1%) C: 9/699 (1.3%)</p> <p><u>Duration of hospitalization</u> Not reported</p> <p>Hospitalization I: 48/709 (6.8%) C: 68/699 (9.7%)</p> <p><u>Time to symptom resolution</u> Hazard ratio of time to sustained improvement or resolution of self-reported Covid-19 signs/symptoms through day 29 (all-randomized MITT population) are provided in the supplementary file</p> <p><u>Invasive respiratory support</u></p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> Hospitalization or death at day 29 Incidence of adverse events <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> Changes in WHO Clinical Progression Scale and in patient-reported symptoms of COVID-19 Exploratory end points included mean changes in SARS-CoV-2 viral load from baseline. <p><u>Definitions:</u></p> <ul style="list-style-type: none"> The time to sustained resolution or abatement of signs or symptoms was defined as the number of days from randomization to the first of 3 consecutive days of resolution or alleviation (without subsequent relapse by day 29) and the time to progression of signs or symptoms as the number of days from randomization to the first of 2 consecutive days of worsening. <p><u>Remarks:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>and the United States.</p> <p><u>Source of funding:</u> Funded by Merck Sharp and Dohme</p> <p><u>Conflicts of interest:</u> The trial was designed by representatives of the sponsor. Safety oversight was performed by the sponsor and an independent data monitoring committee. Data were collected by the investigators and site personnel, analyzed by statisticians employed by the sponsor, and interpreted by the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.</p> <p>Disclosure forms are provided</p>	<ul style="list-style-type: none"> Severe neutropenia, Platelet count below 100,000 per microliter SARS-CoV-2 vaccination <p><u>N total at baseline:</u> N = 1433 Intervention: N=716 Control: N=717</p> <p><u>Important characteristics:</u> Age, median (range): I: 42.0 y (18-90) C: 44.0 y (18-88)</p> <p>Sex, n/N (%) male: I: 332/716 (46.4%) C: 366/717 (51.0%)</p> <p>Disease severity: (<i>Definition not clear</i>) <i>Mild:</i> I: 395/716 (55.2%) C: 390/717 (54.4%)</p> <p><i>Moderate:</i> I: 315/716 (44.0%) C: 323/717 (45.0%)</p> <p>Groups are comparable at baseline</p>		any monoclonal antibodies and remdesivir) was prohibited through day 29	699 included in the modified intention-to-treat analysis	<p>Not reported</p> <p>Safety <u>Serious adverse events, n/N (%)</u> I: 5/710 (0.7%) C: 13/701 (1.9%)</p> <p>Virological outcomes <u>Viral clearance</u> SARS-CoV-2 RNA titer (log₁₀ copies/ml,) at day 29, mean change (SD) I: -3.91 (1.656) C: -3.99 (1.712)</p>	- <u>Authors conclusion:</u> These data from the MOVE-OUT phase 3 trial in nonhospitalized at-risk adults with Covid-19 indicate that molnupiravir, initiated within 5 days after the onset of symptoms, reduces the risk of hospitalization for any cause or death through day 29.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Fischer, 2021	<p>Type of study: Phase 2a randomized, double-blind, placebo-controlled trial</p> <p>Setting: Non hospital-based, between June 19, 2020 and January 21, 2021</p> <p>Country: 10 centers in the United States</p> <p>Source of funding: Ridgeback Biotherapeutics and Merck are jointly developing Molnupiravir. Since licensed by Ridgeback Biotherapeutics, all funds used for the development of Molnupiravir by Ridgeback Biotherapeutics have been provided by Wayne and Wendy Holman and Merck.</p> <p>Conflicts of interest: Conflicts of interest were transparently and</p>	<p>Non-hospitalized patients with recently diagnosed COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age ≥ 18 y • unvaccinated • diagnosed with COVID-19 infection through an approved testing method within 96 h and an onset of symptoms of COVID-19 <7 days at the time of treatment • non-hospitalized <p>Exclusion criteria: Not specified in the article. Detailed information is available at clinicaltrials.gov</p> <p>N total at baseline: Randomized: N = 202</p> <p>Intervention I: N = 23 Intervention II: N = 59 Intervention III: N = 52 Control: N = 61</p> <p>Important characteristics: Age, median (range): I (I): 32 y (19-65) I (II): 42.5 y (19-82) I (III): 42 y (18-68) C: 39 y (19-71)</p> <p>Sex, n/N (%) male: I (I): 12/23 (52.2%) I (II): 30/62 (48.4%) I (III): 28/55 (50.9%)</p> <p>C: 28/62 (45.2%)</p>	<p>Intervention I: Molnupiravir (orally BID) 200 mg for 5 days</p> <p>Intervention II: Molnupiravir (orally BID) 400 mg for 5 days</p> <p>Intervention III: Molnupiravir (orally BID) 800 mg for 5 days</p>	Placebo (dry filled capsules)	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up or incomplete data: C: 1/61 (1.6%) I (I): 0/23 (0%) I (II): 2/59 (3.4%) I (III): 2/52 (3.8%)</p> <p>Reasons for loss-to-follow-up or incomplete data is reported</p>	<p>Clinical outcomes</p> <p>Mortality Not reported</p> <p>Duration of hospitalisation Not reported</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support Not reported</p> <p>Safety Experiencing an adverse event C: 18/62 (29.0%) I (I): 11/23 (47.8%) I (II): 20/62 (32.3%) I (III): 11/55 (20%)</p> <p>Virological outcomes</p> <p>Time to viral RNA clearance (median (95% CI), days)* C: 15 (15.0 – 27), reference I (I): 22 (15.0 – 28), p=0.56 I (II): 27 (15.0 – 28), p=0.73 I (III): 22 (13.0 – 14), p=0.013</p> <p>Positive for infectious SARS-CoV-2 Virus, Day 1 (n/N (%)) C: 25/53 (47.2%) I (I): 11/22 (50%) I (II): 18/44 (41.9%) I (III): 20/52 (38.5%)</p> <p>Day 3 (n/N (%))</p>	<p>Definitions: * Time to viral RNA clearance was defined as the first of two timepoints where viral RNA was below the limit of quantitation (<1,018 copies/mL). If the first negative test occurred on the last on-study assessment, it was considered to have achieved viral RNA clearance on the last assessment.</p> <p>Remarks: Differences in virus isolation and viral load reduction on day 5 of the study remained significant when analysis was limited to comparisons between 800 mg molnupiravir and concurrently enrolled placebo participants</p> <p>Authors conclusion: This phase 2a trial provides strong biological evidence supporting development of molnupiravir as an oral agent to reduce infectious virus replication and interrupt progression of COVID-19 during early stages of disease</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	extensively reported.	An imbalance in the randomization occurred, with a greater proportion of seropositive individuals and a lower viral load at baseline among those randomized to receive 800 mg molnupiravir compared to placebo.				C: 9/54 (16.7%), reference I (I): 4/22 (18.2%), p<0.99 I (II): 5/43 (11.6%), p=0.57 I (III): 1/53 (1.9%), p=0.016 <u>Day 5 (n/N (%))</u> C: 6/54 (11.1%), reference I (I): 1/22 (4.5%), p=0.67 I (II): 0/42 (0%), p=0.034 I (III): 0/53 (0%), p=0.027	
9.5. Nitazoxanide (brand name = Alinia; antiparasitic & broad-spectrum antiviral medication)							
Rocco, 2020	<u>Type of study:</u> A double-blind, placebo-controlled trial. <u>Setting:</u> Five freestanding urgent care centers and 2 hospitals. <u>Country:</u> Brazil <u>Source of funding:</u> Supported by the Brazilian Council for Scientific and Technological Development (CNPq), Brazilian Ministry of Science, Technology, and Innovation for Virus Network; Brasília, Brazil, number: 403485/2020-7 and Funding Authority for Studies and	<u>Inclusion criteria:</u> • Patients aged 18 years or older; • Clinical symptoms of COVID-19 (such as dry cough, fever, and/or fatigue) of no longer than 3 days. <u>Exclusion criteria:</u> • negative reverse-transcriptase quantitative real-time polymerase chain reaction (RTPCR) test for SARS-CoV-2 on an nasopharyngeal swab specimen; • inability to swallow; • pre-existing conditions precluding the safe conduct of study procedures, including severe renal, heart, respiratory, liver, or autoimmune diseases, cancer in the last 5 years, or known allergy or hypersensitivity to nitazoxanide; • therapy with nitazoxanide in the 30 days before presentation; • clinical suspicion of bacterial pneumonia or tuberculosis.	Nitazoxanide (500 mg oral solution, 20 mg/mL [25 mL], three times daily for 5 days), dispensed by the pharmacy of each study site	Placebo	<u>Length of follow up:</u> 5 days <u>Loss to follow-up:</u> I: N = 32 Reasons: discontinued intervention (n=21); adverse events (n=6); hospitalized (n=5). Remaining number of participants: N = 206. Total number of participants in the analysis: N = 194. C: N = 24 Reasons: discontinued intervention (n=18); adverse events (n=1); hospitalized (n=5). Remaining number of participants: N = 213. Total number of participants in the analysis: N = 198.	Clinical outcomes <u>Mortality</u> No deaths were reported in either arm. <u>Safety</u> No life-threatening adverse events were reported in either arm. <i>At least one adverse events</i> I: 60/194 (30.9%) C: 60/198 (30.4%) P=0.913 <i>Two adverse events</i> I: 22/ 194 (11.3%) C: 18/198 (9.1%) P=0.507 <i>Three or more adverse events</i> I: 16/194 (8.2%) C: 12/198 (6.1%) P=0.438 <i>Severe adverse events, n/N (%)</i> I: 1/194 (0.5%) C: 1/198 (0.5%)	<u>Definitions:</u> - <u>Remarks:</u> - <u>Authors conclusion:</u> In summary, in patients with mild Covid-19 enrolled within 3 days of symptom onset, nitazoxanide as compared with placebo was not an effective therapy in terms of accelerating symptom resolution after 5 days of therapy, and did not modify clinically relevant secondary outcomes. However, nitazoxanide was safe, significantly decreased viral load, and increased the proportion of patients who tested negative for SARS-CoV2 after completion of therapy

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Projects, Brasília, Brazil, number: 01.20.0003.00.</p> <p><u>Conflict of interest:</u> Dr. Rocco reports personal fees from SANOFI as a DSMB member. The other authors declare no competing interests.</p>	<p><u>N total at baseline:</u> N = 392 Intervention: 194 Control: 198</p> <p><u>Important characteristics:</u> Age, n/N (%): <i>18 to 39 years</i> I: 115/194 (59%) C: 113/198 (57%)</p> <p><i>40 to 59 years</i> I: 68/194 (35%) C: 74/198 (37%)</p> <p><i>60 to 77 years</i> I: 11/194 (6%) C: 11/198 (6%)</p> <p>Overall P=0.891</p> <p>Sex, n/N (%) male: I: 101/194 (52%) C: 83/198 (42%) P=0.054</p> <p>SpO₂ mean (SD): I: 97.3 (1.4) C: 97.4 (1.3) P=0.835</p> <p>Groups comparable at baseline? Yes → <i>No significant differences were observed between the two groups.</i></p>				<p>P=0.999</p> <p><u>Viral outcomes</u> <i>Nasopharyngeal swab RT-PCR viral load (Log₁₀ copies/mL), median (IQR) / (%)</i> I: 3.63 (0 to 5.03) C: 4.13 (2.88 to 5.31) P=0.006</p> <p><i>Reduction in viral load</i> I: 55% C: 45% P=0.013</p> <p><i>Negative for SARS-CoV-2 on RT-PCR</i> I: 29.9% C: 18.2% P=0.009</p>	
9.6. Novaferon (broad-spectrum antiviral drug)							
Zheng, 2020	<p><u>Type of study:</u> Randomized, open-label, parallel group trial</p> <p><u>Setting:</u></p>	<p><u>Inclusion criteria:</u> - Hospitalized COVID-19 patients with confirmed SARS-CoV-2 detection, clinically</p>	40 µg of Novaferon were administered to patients twice per day by the oxygen-driven aerosolized inhalation for 15 minutes	Lopinavir/Ritonavir (200mg of Lopinavir and 50mg of Ritonavir, 2 tablets were	9 days	<p><u>1. Clearance rate at day 3, n (%):</u> Novaferon: 5 (16.7) Novaferon + Lopinavir/Ritonavir: 11 (36.7)</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Single centre</p> <p><u>Country:</u> China</p> <p><u>Source of funding:</u> Not reported</p>	<p>classified as moderate or severe, at the age over 18 years, and without comorbidity of severe heart, lung, brain diseases.</p> <p><u>Exclusion criteria:</u> - patients with co-existing severe cardiac, kidney or liver diseases - steroids treatment</p> <p><u>N total at baseline:</u> N = 89 Novaferon: 30 Novaferon + Lopinavir/Ritonavir: 30 Lopinavir/Ritonavir: 29</p> <p><u>Important characteristics:</u> Age, median (IQR): Novaferon: 46.5(40.0-63.8) Novaferon + Lopinavir/Ritonavir: 50.0(37.8-62.8) Lopinavir/Ritonavir: 37.0(26.0-54.0)</p> <p>Sex, n/N (%) male: Novaferon: 17(56.7%) Novaferon + Lopinavir/Ritonavir: 13(43.3%) Lopinavir/Ritonavir: 12 (41.4%)</p> <p>Median time from symptoms to therapy, days (IQR) : Novaferon: 4.0 (3.0-6.5) Novaferon + Lopinavir/Ritonavir: 7.0 (3.3-11.3) Lopinavir/Ritonavir: 4.0 (3.0-6.0)</p> <p>Moderate Cases, n(%) Novaferon: 28 (93.3%)</p>	<p>of 20 µg of Novaferon (2 x 1 ml vials) diluted with saline.)</p> <p>40 µg of Novaferon were administered to patients twice per day by the oxygen-driven aerosolized inhalation for 15 minutes of 20 µg of Novaferon (2 x 1 ml vials) diluted with saline.) plus Lopinavir/Ritonavir (200mg of Lopinavir and 50mg of Ritonavir, 2 tablets were orally taken twice per day)</p>	orally taken twice per day)		<p>Lopinavir/Ritonavir: 3 (10.3)</p> <p><u>2. Clearance rate at day 6, n (%):</u> Novaferon: 15 (50) Novaferon + Lopinavir/Ritonavir: 18 (60) Lopinavir/Ritonavir: 7 (24.1)</p> <p><u>3. Clearance rate at day 9, n (%):</u> Novaferon: 17 (56.7) Novaferon + Lopinavir/Ritonavir: 21 (70) Lopinavir/Ritonavir: 15 (51.7)</p> <p><u>4. Time to clearance, mean (days):</u> Novaferon: 7.0 Novaferon + Lopinavir/Ritonavir: 6.1 Lopinavir/Ritonavir: 8</p> <p><u>5. Any adverse event, n (%):</u> Novaferon: 25 (83.3) Novaferon + Lopinavir/Ritonavir: 25 (83.3) Lopinavir/Ritonavir: 26 (89.6)</p>	<p>Novaferon exhibited anti-SARS-CoV-2 effects at cellular level and in patients with COVID-19. Data obtained from this randomized, open-label, parallel group trial preliminarily demonstrated the anti-SARS-CoV-2 effects of Novaferon for COVID-19, and justified large-scale clinical studies to verify the efficacy of Novaferon as a potential antiviral drug for COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Novaferon + Lopinavir/Ritonavir: 28 (93.3%) Lopinavir/Ritonavir: 28 (96.6%) Severe cases, n(%) Novaferon: 2 (6.7%) Novaferon + Lopinavir/Ritonavir: 2 (6.7%) Lopinavir/Ritonavir: 1 (3.4%) Comorbidity, n(%) Novaferon: 7 (23.33) Novaferon + Lopinavir/Ritonavir: 6 (20.00) Lopinavir/Ritonavir: 5 (17.24) Groups comparable at baseline? Yes					
9.7. Osetamivir (brand name = Tamiflu)							
NA	NA	NA	NA	NA	NA	NA	NA
9.8. Paxlovid							
NA	NA	NA	NA	NA	NA	NA	NA
9.9. Ribavirine (also known as tribavirin)							
Huang, 2020	See evidence table of Huang (2020) by lopinavir and ritonavir.						
Hung, 2020	<u>Type of study:</u> multicentre, prospective, open-label, randomised, phase 2 trial <u>Setting:</u> Feb 10 and March 20, 2020; in 6 major hospitals <u>Country:</u> Hong Kong <u>Source of funding:</u> The Shaw-Foundation, Richard and Carol Yu, May	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> patients admitted to hospital age ≥18 years virologically confirmed COVID-19 <u>Exclusion criteria:</u> Not described, but patients excluded due to: 2 nd and 3 rd degree cardiac arrhythmia, severe depression, and pregnancy <u>N total at baseline:</u> 127 Intervention: 86 Control: 41	Combination treatment: Recruited and treated <7 days from symptom onset: <ul style="list-style-type: none"> 14 days of oral lopinavir–ritonavir (400 mg/100 mg) every 12 h ribavirin 400 mg every 12 h subcutaneous injection interferon beta-1b 1 mL (8 million international units [IU]) on alternate days depending on day of drug commencement from symptom onset: 	Lopinavir–ritonavir 14 days of oral lopinavir–ritonavir (400 mg/100 mg) every 12 h	<u>Follow up period:</u> 30 days after discharge <u>Lost to follow-up:</u> No losses	<u>Virological endpoints:</u> <u>Time to negative RT-PCR result in nasopharyngeal swab, median [IQR]:</u> I: 7 days [5–11]) C: 12 days [8–15] HR 4.37 [95% CI 1.86–10.24] <u>Time to negative RT-PCR result in all swabs:</u> I: 8 days [6–12] C: 13 days [8–15] <u>Disease severity, median [IQR]</u> <u>NEWS2 of 0 maintained for 24h</u> I: 4 days [3–8] C: 8 days [7–9]	<u>Remarks:</u> This was an open label trial, without placebo group. <u>Authors conclusion:</u> Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Tam Mak Mei Yin, and Sanming Project of Medicine	<p><u>Important characteristics:</u> Age, median (IQR): I: 51.0y [31.0-61.3] C: 52.0y [33.5-62.5] Sex, n/N (%) male: I: 45/86 (52%) C: 23/41 (44%) Time from onset to start treatment, days: I: 5 (4-7) C: 4 (3-8)</p> <p>Groups comparable at baseline.</p>	<p>day 1–2: 3 doses of interferon beta-1b day 3–4,; 2 doses day 5–6,; 1 dose.</p> <p>Recruited and treated 7-14 days from symptom onset: interferon beta-1b injection was omitted</p>			<p>HR 3.92 [95% CI 1.66–9.23] <u>SOFA of 0:</u> I: 3 days [1-8] C: 8 days [6.5-9] Length of hospital stay: I: 9 days [7–13] C: 14.5 days [9.3–16] HR 2.72 [1.2–6.13] <u>30-day mortality, n/N (%):</u> I: 0/84 (0%) C: 0/41 (0%)</p> <p>Safety <u>Serious adverse events</u> I: 0/84 (0%) C: 1/41 (2%) <u>Duration of nausea:</u> I: median 2 days [IQR 1-2] C: median 2 days [IQR 1-2] <u>Duration of diarrhoea</u> I: median 3 days [IQR 3-3] C: median 3 days [IQR 3-3]</p>	
9.10. Sofosbuvir (brand name = Sovaldi; has role as a prodrug, an antiviral drug and a hepatitis C protease inhibitor; only recommended with some combination of ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir)							
9.10.1. Sofosbuvir i.c.m. Daclatasvir (brand name = Daklinza; used in combination with sofosbuvir, ribavirin, and interferon)							
Roosbeh, 2020	<p><u>Type of study:</u> Double-blind, randomized, parallel-group, actively-controlled clinical trial.</p> <p><u>Setting:</u> Conducted between 8 April 2020 and 19 May 2020. Patients were recruited from the Miandrood Outpatient Medical Clinic.</p>	<p>Outpatients with mild COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adults, with: Confirmed CT scan findings for COVID-19; Typical COVID-19 clinical symptoms including fever, cough and fatigue; Positive CRP test. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Oxygen saturation less than 93%; Pregnancy; Amiodarone use; Renal failure; 	sofosbuvir/daclatasvir (fixed-dose combination, Sovodak (400/60mg)) + hydroxychloroquine and standard care	hydroxychloroquine alone + standard care	<p><u>Length of follow up:</u> 30 days</p> <p><u>Loss to follow-up:</u> I: 2/30 (7%) C: 3/30 (10%)</p>	<p>Clinical outcomes <u>Mortality</u> Not reported</p> <p><u>Duration of hospitalization</u> Not reported</p> <p><u>Hospital admission</u> I: 1 (4%) C: 4 (14%) p =0.352</p> <p><u>Symptom resolution</u> Calculated across fever, sore throat, headache, stiff neck, myalgia, cough or olfactory loss</p>	<p><u>Definitions:</u></p> <ul style="list-style-type: none"> Ground glass opacity: outcome measure lung CT-scan. A higher percentage reflects more attenuation of the lungs. <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Precision of the results is very low, due to the small sample size and wide confidence intervals. <p><u>Authors conclusion:</u> Sofosbuvir/daclatasvir did not significantly alleviate symptoms after 7 days of treatment compared with control. Although fewer hospitalizations were observed in the</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> This study was supported by the Vice-Chancellor for Research at Mazandaran University of Medical Sciences.</p> <p>The authors state that the 5th author received travel grants from and is a stockholder of Fanavaran Rojan Mohaghegh Daru Co, the pharmaceutical company that provides sofosbuvir/daclatasvir.</p>	<ul style="list-style-type: none"> Cardiovascular diseases. <p><u>N total at baseline:</u> N = 60</p> <p>Intervention: 30 Control: 30</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 43 y (37-52) C: 47.5 y (37-53) Sex, n/N (%) male: I: 12/27 (44%) C: 14/28 (50%)</p> <p>Comorbidity I: 13 (48%)/27 C: 8 (27%)/28</p> <p>Disease severity: <i>Defined by oxygen saturation and ground glass opacity*:</i> Oxygen saturation, median (IQR) I: 98 (97-97) C: 98 (97-99)</p> <p>Ground glass opacity lung CT scan 5%: I: 3 (11%)/27 C: 6 (21%)/28 25%: I: 7 (26)/27 C: 6(21)/28 50%: I: 16(59)/27 C: 16(57)/28 75%: I: 1(4)/27 C: 0(0)/28</p> <p>Groups were comparable at baseline.</p>				<p>Day 1, n(%) / N I: 27 (100%) / 27 C: 26 (93%) / 28</p> <p>Day 3 I: 16 (59%) / 27 C: 15 (54%) / 28</p> <p>Day 5 I: 12 (44%) / 27 C: 12 (43%) / 28</p> <p>Day 7 I: 7 (26%) / 27 C: 7 (28%) / 28</p> <p><i>No statistically significant group differences.</i></p> <p><u>Fatigue at day 30, n(%) / N</u> I: 2 (7%) / 27 C: 16 (57%) / 28 p < 0.0001</p> <p><u>Dyspnoea at day 30, n(%) / N</u> I: 4 (15%) / 27 C: 11 (39%) / 28 p = 0.035</p> <p><u>Anosmia at day 30, n(%) / N</u> I: 0 (0%) / 27 C: 3 (12%) / 28 p = 0.111</p> <p><u>Need for respiratory support</u> Not reported</p> <p>Safety <u>Adverse events</u> Not reported</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<p>sofosbuvir/daclatasvir arm, this was not statistically significant.</p> <p>Sofosbuvir/daclatasvir significantly reduced the number of patients with fatigue and dyspnoea after 1 month. Larger, well-designed trials are warranted.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Sadeghi, 2020	<p><u>Type of study:</u> RCT, open-label</p> <p><u>Setting:</u> Multi-center; 26 March and 26 April 2020; university hospitals in Shariati, Baharloo, Sina (Tehran city) and Sayyad Shirazi (Gorgan city).</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> internal funding of the Digestive Disease Research Institute of Tehran University of Medical Sciences.</p>	<p>Moderate to severe COVID-19 patients, admitted to hospital (patients requiring mechanical ventilation at screening excluded)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age ≥18y • admitted with suspected COVID-19 infection • positive qualitative RT-PCR on nasopharyngeal swab • chest CT scan compatible with moderate / severe COVID-19 infection • signs of severity of disease defined as fever (oral temperature ≥37.8°C at any one time prior to enrolment) and at least one of respiratory rate >24/min, O2 saturation <94% or PaO2/FiO2 ratio <300 mgHg • Onset of symptoms ≤ 8 days <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • known allergy to intervention drugs • pregnant or breastfeeding, • any prior experimental treatment for COVID-19 • heart rate <60 bpm, • taking amiodarone • evidence of multiorgan failure • requiring invasive mechanical ventilation at screening • estimated glomerular filtration rate (eGFR) <50mL/1.73 m2/min. <p><u>N total at baseline:</u></p>	<p>Sofosbuvir + daclatasvir and standard care</p> <p>Single daily oral tablet containing 400mg sofosbuvir and 60mg daclatasvir (Sovodak, Rojan Pharma, Tehran, Iran) in addition to standard care for 14days.</p> <p>Sofosbuvir/daclatasvir was started only after confirmation of COVID-19 by PCR and CT, randomization and consent, which was 24–48 h later.</p>	<p>Standard care</p> <p>At the time of study standard care was hydroxychloroquine 200mg twice daily with or without lopinavir/ritonavir 200mg/50mg twice daily.</p> <p>Standard care was started as soon as patients were admitted</p>	<p><u>Length of follow up:</u> 14 days for primary outcome (clinical recovery). Patients were contacted 1 month after hospital discharge and were asked about COVID-related complications or re-admissions.</p> <p><u>Loss to follow-up:</u> I: 2/35 (%) Reasons: n=1: estimated glomerular filtration rate <50mL; n=1: >8days symptoms and received other trial medications</p> <p>C: 2/35 (%) Reasons: n=1: estimated glomerular filtration rate <50mL; n=1: >8days symptoms and received other trial medications</p>	<p>I, N=33 C, N=33</p> <p>Clinical outcomes</p> <p><u>All-cause mortality</u> I: 3/33 (9%) C: 5/33 (15%)</p> <p><u>Clinical recovery within 14 days</u> I: 29/33 (88%) C: 22/33 (67%)</p> <p><u>Duration of hospitalization, median:</u> I: 6 (IQR 4–8) days C: 8 (IQR 5–13) days</p> <p><u>Time to hospital discharge, median:</u> I: 6 days (IQR 4–10) C: 11 days (IQR 6–17)</p> <p><u>Need for respiratory support:</u> <u>Requirement for invasive mechanical ventilation</u> I: 3/33 (9%) C: 7/33 (21%)</p> <p><u>Concomitant administration</u> Hydroxychloroquine: all patients received hydroxychloroquine, lopinavir/ritonavir I: 33% C: 64% Corticosteroids / antibiotics</p>	<p><u>Definitions:</u> <i>Clinical recovery</i> - defined as normalization of fever (≤37.2_C), respiratory rate (≤24/min) and oxygen saturation (≥94%) without supplementary oxygen therapy sustained for at least 24 h. If patients maintained these criteria for over 24h they were safely discharged from hospital.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Open-label • Relatively small study • Definitions of outcomes inconsistent (recovery vs. discharge used intertwined for same results, but discharge is 24h later than stable clinical recovery) • All patients received hydroxychloroquine; lopinavir/ritonavir was administered to 1/3 of the intervention group and 2/3 of the control group. <p><u>Authors conclusion:</u> The addition of sofosbuvir and daclatasvir to standard care significantly reduced the duration of hospital stay compared with standard care alone. Although fewer deaths were observed in the treatment arm, this was not statistically significant. Conducting larger scale trials seems prudent.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>N = 70 Intervention: 35 Control: 35</p> <p><u>Important characteristics:</u> Age, median (IQR) I: 58 (38–65) C: 62 (49–70) Sex, n/N (% male): I: 20/33 (61%) C: 14/33 (42%) Days from admission to enrolment, median (IQR) I: 1 (1–2) C: 1 (1–1) Comorbidities, n (%) Chronic pulmonary disease I: 6/33 (18%) C: 9/33 (27%) Asthma I: 1/33 (3%) C: 1/33 (3%) Diabetes I: 17/33 (52%) C: 11/33 (33%) Heart failure I: 3/33 (9%) C: 7/33 (21%) Hypertension I: 12/33 (36%) C: 11/33 (33%) Malignancy I: 1 (3%) C: 2 (6%) Obesity (BMI ≥ 30 kg/m²) I: 7 (23%) C: 10 (33%)</p> <p>Groups comparable at baseline.</p> <p>Use ACE inhibitors, symptoms and signs, vitals on admission,</p>				<p>balanced between groups.</p> <p><u>Safety:</u> <u>Drug-related serious adverse events</u> I: 0/33 C: 0/33</p> <p><u>Complications / readmissions, 1 month follow-up:</u> I: 0/33 C: 0/33</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		laboratory findings and CT findings reported in Table 1.					
9.10.2. Sofosbuvir i.c.m. Ledipasvir (brand name = Harvoni; antiviral for hepatitis C-virus)							
Nourian, 2021	<p><u>Type of study:</u> Randomized, open-label clinical trial</p> <p><u>Setting:</u> Imam Khomeini Hospital Complex, a referral tertiary teaching hospital affiliated to Tehran University of Medical Sciences</p> <p><u>Country:</u> Tehran, India</p> <p><u>Source of funding:</u> The authors did not receive any fund for this work. SOF/LDP was a generous donation from Zistdaru Dane sh Co.</p> <p><u>Declaration of interest:</u> There is no conflict of interest for authors to declare.</p>	<p>Patients with mild to moderate COVID-19. Mild and moderate COVID-19 were defined as:</p> <p>- Mild disease: mild symptoms such as fever, rhinorrhoea, mild cough, sore throat, malaise, headache, muscle pain, or malaise, but with no shortness of breath AND no signs of a more serious lower airway disease AND RR<20, HR<90, oxygen saturation >93 on room air.</p> <p>- Moderate disease: more significant lower respiratory symptoms, other than symptoms of mild disease including shortness of breath OR signs of moderate pneumonia, including RR>20, oxygen saturation 88% on room air AND lung involvement less than 50 percent in chest X-ray or CT-scan.</p> <p><u>Inclusion criteria:</u></p> <p>- Adult patients (18 years and older);</p> <p>- Highly suspected (according to the clinical signs/symptoms and imaging findings) or confirmed COVID-19 (a positive PCR of pharyngeal or nasopharyngeal samples)</p> <p><u>Exclusion criteria:</u></p> <p>- History of drug allergy;</p> <p>- Decompensated cirrhosis;</p> <p>- Severe COVID-19;</p> <p>- Patients under haemodialysis;</p> <p>- Pregnant and lactating woman.</p>	<p>SOF/LDP 400/90 daily for <u>10 days plus standard of care.</u></p> <p>*Standard of care included hydroxychloroquine (HCQ 400 mg BD at first day then 200 mg BD for 7 days) plus atazanavir/ritonavir 300/100 mg daily for 7 days.</p>	<p>Standard of <u>care only.</u></p> <p>*Standard of care included hydroxychloroquine (HCQ 400 mg BD at first day then 200 mg BD for 7 days) plus atazanavir/ritonavir 300/100 mg daily for 7 days.</p>	<p><u>Length of follow up:</u> 14 days</p> <p><u>Loss to follow-up:</u> I: 3/45 (6.7%) Reasons: candidates to receive other interventions.</p> <p>C: 5/45 (20%) Reasons: early hospital discharge (N=1), candidates to receive other intervention (N=2), willingness to exclude from study (N=2)</p>	<p>Clinical outcomes</p> <p><u>Mortality (14 days), n/N (%):</u> I: 3/42 (8.82%) C: 3/40 (10%). P=0.60</p> <p><u>Clinical response at 14 days follow-up, n/N (%):</u> I: 38/42 (90.48%) C: 37/40 (92.5%) P=0.65</p> <p><u>Time to clinical response, median (IQR):</u> I: 2 (1 to 3.75) days C: 4 (2 to 5) days P=0.02</p> <p><u>Duration of hospital stay, median (IQR):</u> I: 4 (2 to 9.5) days C: 5 (3.25 to 7) days P=0.98</p> <p><u>Duration of ICU stay:</u> I: 6 (4 to 11) days C: 9 (6 to 12) days P=0.23</p> <p><u>Safety: Drug adverse events</u></p> <p><u>Cardiovascular, n/N (%):</u> I: 2/42 (4.76%) C: 3/40 (7.5%) P=0.48</p> <p><u>Kidney injury</u></p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> To the best of our knowledge, this was the first study that evaluated efficacy and safety of SOF/LDP in the treatment of mild to moderate COVID-19. Added to the standard of care, SOF/LDP accelerated time to the clinical response. However, rate of clinical response, duration of hospital or ICU stay and 14-day mortality were not different. No significant adverse event was detected. More randomized clinical trials with larger sample sizes are needed to confirm efficacy and safety of SOF/LDP in the treatment of COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>N total at baseline:</u> N = 82 Intervention: 42 Control: 40</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 61.5 y (46.5 to 74.25) C: 63.0 y (53.25 to 70.75)</p> <p>Groups comparable at baseline? Yes</p>				<p>I: 3/42 (7.14%) C: 0/40 (0%) P=0.48</p> <p><i>Hyperbilirubinemia</i> I: 3/42 (7.14%) C: 0/40 (0%) P=0.08</p> <p><i>Gastrointestinal</i> I: 6/42 (14.28%) C: 7/40 (17.5%) P=0.46</p> <p><i>Headache</i> I: 1/42 (2.38%) C: 1/40 (2.5%) P=0.74</p>	
9.10.3. Sofosbuvir i.c.m. Velpatasvir (NS5A inhibitor (by Gilead); fixed-dose combination medication with sofosbuvir for the treatment of hepatitis C)							
Sayad, 2021	<p><u>Type of study:</u> Single-centre, randomized, open-labelled, prospective clinical trial.</p> <p><u>Setting:</u> Farabi Hospital in Kermanshah Province, Iran.</p> <p><u>Country:</u> Iran.</p> <p><u>Source of funding:</u> We express our thanks to the patients who participated in this study and Kermanshah University of Medical Sciences</p>	<p><u>Moderate to severe admitted to Farabi Hospital COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> >18 year old; Oxygen saturation of 93% or less in ambient air and/or an absolute lymphocyte count of $<1.1 \times 10^9$ cells/L. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Pregnancy and breastfeeding; Physician's decision against enrolment; Conditions that did not allow complete implementation of the protocol; Allergy of hypersensitivity to the drugs used in this trial; Severe liver disease; 	Fixed-dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir (Shari Pharmaceutical Industry Co., Tehran, Iran) orally once daily for 10 days plus the national standard of care	The national standard of care including 400 mg hydroxychloroquine as a single dose and lopinavir/ritonavir (400 mg/100 mg) orally twice daily for 10 days as well as supplemental oxygen, non-invasive and invasive ventilation, antimicrobials, vasopressors and corticosteroids, if needed.	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: N=1 Reason: After randomization, one patient in the sofosbuvir/velpatasvir arm died before receiving the sofosbuvir/ velpatasvir treatment</p> <p>C: N=0</p>	<p>Clinical outcomes</p> <p><u>Mortality (28 day)</u> I: 3/40 (7.5%) C: 3/40 (7.5%) P=1.00</p> <p><u>Duration of hospitalization, median (IQR)</u> I: 6 (5 to 8.5) days C: 7 (5 to 13) days P=0.25 HR=1.6 (95% CI 0.9 to 2.5)</p> <p><u>Time from randomization to death (days), median (IQR)</u> I: 6 (2 to 9) days C: 7 (7 to 30) days P=0.38</p> <p><u>Time to symptom resolution</u></p>	<p><u>Definitions:</u> Clinical improvement: defined as a decline of two stages in the six-stage saturation status, or hospital discharge, whichever occurred earlier.</p> <p>Viral clearance: conversion of RT-PCR results from positive to negative from the time of randomization to discharge.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> To summarize the above-mentioned data, adding sofosbuvir/ velpatasvir to the standard of care did not improve the clinical status or reduce mortality in patients with moderate to severe COVID-19. The data of this well-designed trial is of great importance because, as previously mentioned, in a recently published report Simmons et</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>for providing the funding</p> <p><u>Conflicts of interest:</u> The authors declare that they have no competing interests</p>	<ul style="list-style-type: none"> Use of medications that are contraindicated with the drugs used in this trial; Known HIV-infection; Known HCV infection. <p><u>N total at baseline:</u> N = 80 Intervention: N = 40 Control: N = 40</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 53.6 y (16.3) C: 54.6 y (19.4) P=0.81</p> <p>Sex, n/N (%) male: I: 20/40/ (50%) C: 24/40/ (60%) P=0.36</p> <p>Disease severity: not reported</p> <p>Groups comparable at baseline? Yes.</p>				<p><i>Time to clinical improvement, median (IQR)</i> I: 6 (4 to 8) days C: 7 (4 to 11) days HR 1.2 (95% CI 0.6 to 2.2)</p> <p><i>Clinical improvement (day 3), N (%)</i> I: 4/40 (10%) C: 6/40 (15%) P=0.49</p> <p><i>Clinical improvement (day 5)</i> I: 10/40 (10%) C: 12/40 (25%) P=0.61</p> <p><i>Clinical improvement (day 7)</i> I: 23/40 (57.5%) C: 21/40 (52.5%) P=0.65</p> <p><u>Need for respiratory support</u> <i>Need for mechanical ventilation, n (%)</i> I: 1/40 (2.4%) C: 3/40 (8.1%) P=0.61</p> <p><i>Duration of mechanical ventilation, median (IQR) to 3) days</i> C: 1 (1 to 1) days P=0.51</p> <p>Safety <u>Adverse events</u> <i>No adverse drug reaction, n (%)</i></p>	<p>al.19 concluded that sofosbuvir/daclatasvir improves survival and clinical recovery in patients with moderate to severe SARS-CoV-2 infection. However, it is noteworthy that, contrary to our well-designed clinical trial, in the mentioned study:18 (a) the sample size for analysis was relatively small; (b) one of the trials was not randomized; and (c) the designs were not standardized, and the results need to be confirmed in larger randomized controlled trials. We recommend that a change in the route of drug administration (for instance as a rectal formulation), increasing the duration of the intervention or increasing drug dosage (e.g. 800 mg sofosbuvir daily) be considered in future clinical trials.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I: 12/42 (27.9%) C: 14/37 (37.8%) P=0.34</p> <p><i>More than one drug reaction, n (%)</i> I: 17/42 (39.5%) C: 11/37 (29.7%) P=0.16</p> <p><i>Headache, n (%)</i> I: 2/42 (4.7%) C: 3/37 (8.1%) P=0.16</p> <p><i>Nausea and vomiting, n (%)</i> I: 8/42 (18.6%) C: 7/37 (18.9%) P=0.55</p> <p><i>Diarrhea, n (%)</i> I: 4/42 (9.3%) C: 1/37 (2.7%) P<0.001</p> <p><i>Discontinued drug, n (%)</i> I: 0/42 (0%) C: 1/37 (2.7%) P=0.31</p> <p><u>Haematological adverse events</u> <i>Leucopenia (<4 x 10⁹ cells/L), n (%)</i> I: 7/42 (16.3%) C: 3/37 (8.1%) P=0.31</p> <p><i>Lymphopenia (<1.1 x 10⁹ cells/L), n (%)</i> I: 11/42 (29.7%) C: 10/37 (23.3%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>P=0.79</p> <p><i>Thrombocytopenia (<100 x 10⁹cells/L), n (%)</i> I: 4/42 (9.3%) C: 5/37 (13.5%) P=1.00</p> <p><i>Haemoglobin decreased by >1 g/dL, n (%)</i> I: 14/42 (35.0%) C: 19/37 (42.2%) P=0.49</p> <p>Virological outcomes <u>Viral clearance</u> <i>RT-PCR conversion (positive to negative), n (%)</i> I: 6/40 (15%) C: 4/40 (10%) P=0.49</p>	
9.11. Umifenovir (brand name = Arbidol)							
Darazam, 2021	<p><u>Type of study:</u> Single-center, open-label RCT</p> <p><u>Setting:</u> One educational hospital, inclusion period unknown</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> No funding source reported.</p> <p><u>Conflicts of interest:</u></p>	<p>Moderate-to severe confirmed (by RT-PCR or CT-scan) Covid 19 patients</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age > 18 years Presence of at least one of: radiation contactless body temperature ≥ 37.5 °C, cough, shortness of breath, nasal congestion/discharge, myalgia/arthralgia, diarrhea/vomiting, headache or fatigue SpO2 ≤ 93% on pulse oximetry Respiratory frequency ≥ 24/min while breathing ambient air Acute onset of symptoms (≤14 days) 	<p>Umifenovir in combination with lopinavir/ritonavir interferon-beta1a (IFN-β 1a), and hydroxychloroquine</p> <p>The intervention group (Arms1) received lopinavir/ritonavir (400 mg/100 mg bid for 10–14 days) (Kaletra) + hydroxychloroquine (400 mg single dose) + interferon-β1a (subcutaneous injections of 44 µg (12,000 IU) on days 1, 3, 5) (Recigen) + umifenovir</p>	<p>Lopinavir/ritonavir interferon-beta1a (IFN-β 1a), and hydroxychloroquine</p> <p>the control group were treated with lopinavir/ritonavir (400 mg/100 mg bid for 10–14 days) (Kaletra) + hydroxychloroquine (400 mg single dose) + interferon-β1a</p>	<p><u>Length of follow-up:</u> Not reported</p> <p><u>Incomplete outcome data:</u> No incomplete outcome data for outcomes of interest.</p>	<p>Clinical outcomes <u>Mortality (21 day) N (%)</u> I: 17/51 (33.3%) C: 19/50 (38.0%) RR: 0.88 (0.52-1.48) Also available: mortality earlier (presentation ≤7 days of symptom onset); mortality later (presentation >7 days of symptom onset); time from randomization to death</p> <p><u>Duration of hospitalization (median (IQR))</u> I: 7 (5-10) C: 5 (4-9)</p>	<p><u>Definitions:</u> Time to clinical improvement was evaluated based on improvement of two points of the seven-category ordinal scale (recommended by the World Health Organization: Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever comes first.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Groups were not completely comparable, the intervention group seemed to have higher prevalence of comorbidity. No blinding due to open-label design There was no funding reported

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	No conflict of interest.	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> potentially interacting medications with lopinavir/ritonavir or IFN-β1a, pregnancy, breastfeeding history of alcohol use disorder, or any illicit drug dependence in past 5 years blood AST/ALT levels ≥ 5-fold higher relative to maximum limit of normal range on laboratory findings participation refusal who needed invasive ventilation from the beginning <p><u>N total at baseline:</u> N = 101 Intervention: 51 Control: 50</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 62.1 y (15.3) C: 60.2 y (16.5)</p> <p>Sex, n/N (%) male: I: .31/51 (60.8%) C: 27/50 (52.0%)</p> <p>Disease severity, mean (SD): Not reported</p> <p>Intervention group seems to be somewhat older, higher prevalence of asthma, pulmonary disease and high heart rate.</p>	(200 mg TDS for 7 days) (Arbidol)	(subcutaneous injections of 44 µg (12,000 IU) on days 1, 3, 5), (Recigen).]		<p>Also available: time from randomization to discharge</p> <p><u>Time to symptom resolution</u> <i>Time to clinical improvement (based on 7-category scale)</i> I: 9 (5-11) C: 7 (4-10) Also available: ICU admission</p> <p><u>Respiratory support</u> <i>Invasive mechanical ventilation N (%)</i> I: 17/51 (33.3%) C: 14/50 (28.0%) RR: 1.19 (0.66-2.15) <i>Time to ventilation median (IQR)</i> I: 3 (2-4) C: 2 (1-4.25) <i>Time on ventilation median (IQR)</i> I: 4 (2-13) C: 5.5 (1-8)</p> <p>Safety <u>Adverse events</u> <i>Several adverse events are reported, but no summary variable was available.</i></p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<ul style="list-style-type: none"> Follow-up length was not reported, therefore it the loss-to-follow-up was unkwon. The patients with increased LFT (liver function test) stopped receiving of lopinavir/ritonavir (20 patients in control group and 18 patients in treatment group). No patient stopped the treatment because of the adverse events. <p><u>Authors conclusion:</u> The umifenovir trial unveiled that intervention group had not numerically more favorable time to clinical improvement when compared to the control group. Furthermore, the mortality rate in the two groups was not different. Additive umifenovir has not been found to be effective in shortening the duration of SARS-CoV-2 in severe patients and improving the prognosis in non-ICU patients.</p>
Li (2020a)	See evidence table of Li (2020) by lopinavir and ritonavir.						
10. Antibiotic treatment							
10.1. Azithromycin							
Oldenburg, 2021	<u>Type of study:</u>	<u>Self-reported COVID-19 symptoms among outpatients</u>	Oral azithromycin	Placebo	<u>Length of follow-up:</u> 21 days.	<u>Clinical outcomes</u> <u>Mortality (28-30 day)</u>	<u>Definitions:</u> -

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Scalable, telemedicine-based, parallel group simple trial.</p> <p><u>Setting:</u> Outpatients throughout the USA. from May 2020 through March 2021</p> <p><u>Country:</u> United States of America.</p> <p><u>Source of funding</u> This trial was supported by the Bill & Melinda Gates Foundation (grant INV-017026). Azithromycin and matching placebo were donated by Pfizer Inc. Dr Doan was supported in part by a Research to Prevent Blindness Career Development Award.</p> <p><u>Role of the funder:</u> The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Documented positive SARS-CoV-2 test result (nucleic acid amplification or antigen within 7 days before enrolment; • Not currently hospitalized; • Willing and able to receive study drug by mail; • Willing and able to return the internet-based study questionnaires at baseline, day 3, 7, 14, and 21 days via email or over the phone; • No known allergy or other contraindication to macrolides; • No known history of prolongation of the QT-interval (eg. History of Torsades de Pointes, congenital long QT syndrome, bradyarrhythmia); • No recent use of hydroxychloroquine within the past 7 days for participants >55 years of age; • Not currently taking nelfinavir or warfarin (Coumadin); • Age 18 years or older at the time of enrolment; • Not currently pregnant. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Negative or no SARS-CoV-2 test and test results not received within the previous seven days; • Currently hospitalized; • Not willing and able to receive study drug by mail; • Not willing and able to return the internet-based study questionnaires at baseline, 3, 7, 	<p>Patients will receive a single oral dose of azithromycin (1.2 gram) or placebo in the mail directly at their home</p>	<p>Matching placebo.</p>	<p><u>Loss-to-follow-up:</u> <i>Lost to follow-up in adverse event analysis (day 3)</i></p> <p>Intervention: N=23 (13.5%) Reasons not reported.</p> <p>Control: N=14 (15.2%) Reasons not reported.</p> <p><i>Lost to follow-up in primary analysis (day 14)</i></p> <p>Intervention: N=36 (21.1%) Reasons not reported.</p> <p>Control: N=18 (19.6%) Reasons not reported.</p> <p><i>Lost to follow-up in secondary analysis (day 21)</i></p> <p>Intervention: N=46 (26.9%) Reasons not reported.</p> <p>Control: N=20 (21.7%) Reasons not reported.</p> <p><u>Missing outcome data:</u> <i>Missing outcome data in adverse event analysis (day 3)</i></p> <p>Intervention: N=3 (1.8%)</p>	<p>Not reported.</p> <p><u>Hospitalization</u> <i>Participant hospitalized at day 21, n/N (%)</i> I: 5/125 (4%) C: 0/72 (0%) Difference 4% (95% CI -1 to 9) P=0.16</p> <p><i>Participant emergency department or urgent care visit, n/N (%)</i> I: 18/125 (14%) C: 2/72 (3%) Difference 12% (95% CI 3 to 20) P=0.01</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u> <i>≥1 Adverse event, n/N (%)</i> I: 82/145 (57%) C: 19/72 (26%)</p> <p><i>≥2 Adverse events, n/N (%)</i> I: 38/145 (26%) C: 5/72 (7%)</p> <p><i>Diarrhea, n/N (%)</i> I: 60/145 (41%) C: 12/72 (17%)</p> <p><i>Nausea, n/N (%)</i> I: 32/145 (22%)</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Among outpatients with SARS-CoV-2 infection, treatment with a single dose of azithromycin compared with placebo did not result in greater likelihood of being symptom free at day 14. These findings do not support the routine use of azithromycin for outpatient SARS-CoV-2 infection.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.</p> <p><u>Conflicts of interest:</u> Ms Cook reported receipt of grants from the National Institutes of Health. Dr Lietman reported receipt of grants from Pfizer Inc, the National Institutes of Health, and the Bill & Melinda Gates Foundation. Dr Arnold reported receipt of grants from the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases and hotel/airfare reimbursement to attend global health meetings from the Bill & Melinda Gates Foundation. No other disclosures were reported.</p>	<p>14, and 21 days via email or over the phone;</p> <ul style="list-style-type: none"> • Known allergy or contraindication to macrolides; • History of known prolongation of QT interval (e.g., history of torsades de pointes, congenital long QT syndrome, bradyarrhythmia); • Recent use of hydroxychloroquine (past 7 days) for participants >55 years or age; • Currently taking nelfinavir or warfarin; • Younger than 18 years old at the time of enrolment; • Currently pregnant; • No provision of informed consent. <p><u>N total at baseline:</u> N = 263 Intervention: N = 171 Control: N = 92</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 42 y (35 to 49) C: 44 y (35. To 51)</p> <p>Sex, n/N (%) male: I: 51/171 (30%) C: 35/92 (38%)</p> <p>Disease severity, mean (SD): <i>Not reported.</i></p> <p>Groups comparable at baseline? Yes.</p>			<p>Reasons not reported.</p> <p>Control: N=6 (6.5%) Reasons not reported.</p> <p><i>Missing outcome data in primary analysis (day 14)</i></p> <p>Intervention: N=4 (2.3%) Reasons not reported.</p> <p>Control: N=4 (4.3%) Reasons not reported.</p>	<p>C: 7/72 (10%)</p> <p><i>Abdominal pain, n/N (%)</i> I: 25/145 (17%) C: 1/72 (1%)</p> <p><i>Vomiting, n/N (%)</i> I: 5/145 (3%) C: 2/72 (3%)</p> <p><i>Rash, n/N (%)</i> I: 4/145 (3%) C: 2/72 (3%)</p> <p><i>Other, n/N (%)</i> I: 10/145 (7%) C: 3/72 (4%)</p> <p>Virological outcomes Not reported.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Hinks, 2021	<p>Type of study: Prospective, open-label, randomised controlled superiority trial.</p> <p>Setting: 19 hospitals in the United Kingdom.</p> <p>Country: United Kingdom.</p> <p>Source of funding: National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford and Pfizer.</p> <p>Conflicts of interest: TSCH has received grants from Pfizer, University of Oxford, the Wellcome Trust, The Guardians of the Beit Fellowship, and the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre</p>	<p><u>Hospitalized patients with a clinical diagnosis of highly probable or confirmed COVID-19 infection.</u></p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Male or Female, aged at least 18 years • Assessed by the attending clinical team as appropriate for initial ambulatory (outpatient) management • A clinical diagnosis of highly-probable or confirmed COVID-19 infection (diagnosis by the attending clinical team) with onset of first symptoms within the last 14 days • No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial • Able to understand written English (for the information and consent process) and be able to give informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Known hypersensitivity to any Macrolide including Azithromycin, Ketolide antibiotic, or the excipients 	<p>Azithromycin plus standard of care</p> <p>500 mg azithromycin once daily orally plus standard care for 14 days</p>	<p>Standard of care</p> <p>Standard of care according to local guidelines.</p>	<p>Length of follow-up: 28 days.</p> <p>Loss-to-follow-up: Intervention: N = 2 Reasons: withdrew.</p> <p>Control: N = 1 Reasons: withdrew.</p> <p>Incomplete outcome data: None.</p>	<p>Clinical outcomes <u>All-cause mortality (28-30 day), n/N (%)</u> I: 1/145 (1%) C: 1/147 (1%) P=1.00</p> <p><u>Duration of hospitalization Hospitalization or death (ITT), n/N (%)</u> I: 14/145 (10%) C: 17/147 (12%)</p> <p>Un-adj. OR 0.88 ((5% CI 0.42 to 1.84) P=0.74 RD -1.2 (95% CI -8.4 to 5.9) HR 0.79</p> <p>Adj. OR 0.91 (95% CI 0.43 to 1.92) P=0.80 RD -1.0 (95% CI -8.0 to 6.1) HR 0.95 (95% CI 0.46 to 1.96) P=0.89</p> <p>Fully adj. OR 0.91 (95% CI 0.42 to 1.97) P=0.82. RD -1.2 (95% CI -8.2 to 5.7) HR 0.99 (0.49 to 2.00) P=0.99</p> <p><u>Hospitalization or death (ITT positive), n/N (%)</u> I: 11/75 (15%)</p>	<p>Definitions: - Standard of care not further specified.</p> <p>Remarks: - The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.</p> <p>Authors conclusion: In conclusion, our findings in mild-to-moderate COVID-19 managed in ambulatory care, taken together with trials in early disease in primary care and from trials in patients admitted to hospital with severe disease, suggest that azithromycin does not reduce hospital admissions, respiratory failure, or death compared with standard care, and should not be used in the treatment of COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>(BRC) during the conduct of the study; and personal fees from Astra Zeneca, TEVA, and Peer Voice, outside of the submitted work. MJ has received grants from the University of Oxford and NIHR Oxford Biomedical Research Centre. DR has undertaken paid consultancy for GlaxoSmithKline outside of the submitted work. IDP reports personal fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, GlaxoSmithKline, Genentech, Regeneron, Teva, Chiesi, Sanofi, Circassia, and Knopp; and grants from NIHR, outside of the submitted work. JU has received honoraria for preparation of educational materials and has served on an advisory board for</p>	<p>including an allergy to soya or peanuts.</p> <ul style="list-style-type: none"> • Known fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase- insufficiency • Currently on a Macrolide antibiotic (Clarithromycin, Azithromycin, Erythromycin, Telithromycin, Spiramycin) • Elevated cardiac troponin at initial assessment suggestive of significant myocarditis (if clinically the clinical team have felt it appropriate to check the patient's troponin levels) • Evidence of QTc prolongation: QTc>480ms • Significant electrolyte disturbance (e.g. hypokalaemia K+<3.5 mmol/L) • Clinically relevant bradycardia (P<50 bpm), non-sustained ventricular tachycardia or • unstable severe cardiac insufficiency • Currently on hydroxychloroquine or chloroquine <p><u>N total at baseline:</u> N = 295 Intervention: 147 Control: 148</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 45.5 y (14.2) C: 46.3 y (15.5)</p>				<p>C: 11/75 (15%)</p> <p>Un-adj. OR 1.00 ((5% CI 0.40 to 2.47) P=1.00 RD 0.0 (95% CI -11.3 to 11.3) HR 0.78</p> <p>Adj. OR 1.02 (95% CI 0.40 to 2.57) P=0.97 RD 0.3 (95% CI -10.8 to 11.4) HR 1.17 (95% CI 0.49 to 2.77) P=0.72</p> <p>Fully adj. OR 1.11 (95% CI 0.43 to 2.90) P=0.83. RD 0.8 (95% CI -10.1 to 11.7) HR 0.99 (0.52 to 3.21) P=0.57</p> <p><u>Time to symptom resolution</u> <i>Progression to pneumonia, n/N (%)</i> I: 0/119 (0%) C: 2/114 (2%) P=0.24</p> <p><u>Respiratory support</u> <i>Level 2 or 3 ventilation or death, n/N (%)</i> I: 2/145 (1%) C: 2/147 (1%) P=1.00</p> <p>Safety <u>Serious adverse events</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Gilead Sciences and ViiV Healthcare, outside of the submitted work. All other authors declare no competing interests.	Sex, n/N (%) male: I: 76/147 (52%) C: 76/148 (51%) Disease severity, mean (SD): <i>Defined by severity scale score Ambulatory, no limitation of activities</i> I: 61/147 (41%) C: 66/148 (45%) <i>Limitation of simple activities</i> I: 85/147 (58%) C: 81/148 (55%) <i>Admitted to hospital, mild disease, no oxygen therapy</i> I: 1/147 (1%) C: 1/148 (1%) Groups comparable at baseline? Yes.				I: 0/147 (0%) C: 0/148 (0%) <i>Complications, n/N (%)</i> I: 3/145 (2.1%) C: 4/147 (2.7%) Virological outcomes <u>Viral clearance</u> Not reported.	
Butler, 2021	<u>Type of study:</u> Open-label prospective RCT (part of larger trial in which multiple interventions for COVID-19 were tested) <u>Setting:</u> Conducted between April 2 and November 30, 2020; patients received treatment in their own homes through community care.	Non-hospitalized people aged ≥ 65 y, or ≥ 50 y with at least one comorbidity, who had been unwell ≤ 14 days with suspected or confirmed COVID-19. <u>Inclusion criteria:</u> • Age ≥ 65 y; or: • Age ≥ 50 y + comorbidity (weakened immune system due to serious illness or medication; heart disease or diagnosis of high blood pressure; asthma or lung disease; diabetes; mild hepatic impairment; or stroke or neurological problems); • Confirmed SARS-CoV-2 infection; Ongoing symptoms from PCR-confirmed or suspected COVID-19;	I: Standard care plus azithromycin 500 mg daily for three days	Standard care only	<u>Length of follow up:</u> 28 days <u>Loss to follow-up:</u> I: 26/526 (4.9%) C: 39/862 (4.5%)	Results are presented across confirmed and suspected COVID-19 patients. Subgroup data on patients with confirmed COVID-19 is also available in the article. Clinical outcomes <u>Mortality (n (%) /N) within 28 days</u> I: 0/526 (0%) C: 0/862 (0%) <u>Duration of hospitalization (days), median (IQR)</u> Not reported <u>Hospitalization (n (%) /N) at 28 days</u>	<u>Remarks:</u> • Patients without confirmed COVID-19 were included because this reflects many primary care settings where timely testing might not be available. • PCR tests were self-executed by patients, which may have decreased the reliability. • Sample size varied between the two groups, however it is not expected that this was problematic for interpretation of the results. <u>Authors conclusion:</u> • Azithromycin plus usual care did not substantially shorten the time to first self-reported recovery or decrease the risk of hospitalization. The findings show that azithromycin should not be used routinely to treat

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> UK</p> <p><u>Source of funding:</u> UK Research and Innovation, department of Health and Social Care through National Institute for Health Research (NIHR) Urgent Public Health Priority research funding.</p>	<ul style="list-style-type: none"> Symptoms started within past 14 days. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients who were already receiving acute antibiotics; Contraindication to azithromycin. <p><u>N total at baseline:</u> N = 1415 allocated, 1388 received I or C. Intervention: 540 allocated, 526 received I. Control: 875 allocated, 862 received C.</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 60.9 (7.9) y C: 60.5 (7.8) y</p> <p>60.9 (7.9) 60.5 (7.8)</p> <p>Sex, n/N (%) male: I: 224/526 (43%) C: 375/862 (44%)</p> <p>Patients with positive SARS-CoV-2 PCR result within 28 days, n/N (%): I: 189/526 (36%) C: 245/862 (28%)</p> <p>Comorbidity, n/N (%): I: 463/526 (88%) C: 760/862 (88%)</p> <p>Disease severity: <i>Defined by symptoms*, n (%) / N</i> Fever No problem: <ul style="list-style-type: none"> I: 222 (42%) / 526 </p>				<p>I: 16/500 (3%) C: 28/823 (3%)</p> <p><u>ICU admission</u> I: 3/495 (1%) C: 5/625 (1%)</p> <p><u>(Self-reported) symptom resolution, cumulative n/N (%)</u> <i>0 days:</i> I: 0 (0%)/500 C: 0 (0%)/823 <i>7 days:</i> I: 265 (53%)/500 C: 400 (49%)/823 <i>14 days:</i> I: 355 (71%)/500 C: 534 (65%)/823 <i>21 days:</i> I: 381 (76%)/500 C: 600 (73%)/823 <i>28 days:</i> I: 402 (80%)/500 C: 631 (77%)/823</p> <p><u>Need for respiratory support</u> Oxygen administration, n(%) / N I: 10 (2%) / 497 C: 15 (2%) / 625 Mechanical ventilation, n(%) / N I: 2 (<1%) / 496 C: 5 (1%) / 625</p> <p>Safety <u>Adverse events</u> I: 1 (<1%) / 526 C: 0 (0%) / 862</p>	COVID-19 in the community in older adults, in the absence of additional indications.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • C: 372 (43%) / 862 Minor problem: <ul style="list-style-type: none"> • I: 164 (31%) / 526 • C: 300 (35%) / 862 Moderate problem <ul style="list-style-type: none"> • I: 122 (23%) / 526 • C: 168 (19%) / 862 Major problem: <ul style="list-style-type: none"> • I: 18 (3%) / 526 • C: 22 (3%) / 862 Malaise No problem: <ul style="list-style-type: none"> • I: 31 (6%) / 526 • C: 44 (5%) / 862 Minor problem: <ul style="list-style-type: none"> • I: 211 (40%) / 526 • C: 291 (34%) / 862 Moderate problem <ul style="list-style-type: none"> • I: 206 (39%) / 526 • C: 263 (31%) / 862 Major problem: <ul style="list-style-type: none"> • I: 53 (10%) / 526 • C: 38 (4%) / 862 Missing data: <ul style="list-style-type: none"> • I: 25 (5%) / 526 • C: 226 (26%) / 862 *Note: baseline severity of the following symptoms is also reported in the article: cough, shortness of breath, muscle ache, nausea, and diarrhoea. Groups were comparable at baseline, with the exception of the number of patients per group. The N was higher in the control group (I: 526, C: 862).				Also available: time to first reported recovery, sustained recovery, time to sustained recovery, sustained alleviation of all symptoms, time to sustained alleviation of all symptoms, initial reduction of severity of symptoms, time to initial reduction of severity of symptoms, rating of how well participant feels per week, wellbeing (WHO-5 Well-Being Index score), self-reported contact with one or more health-care services, general practitioner reported contact with one or more health-care services, prescription of antibiotics, hospital assessment without admission.	
Horby, 2021b	<u>Type of study:</u>	patients admitted to hospital with COVID-19	azithromycin 500 mg once per day by mouth or intravenously for 10 days	usual care	<u>Length of follow-up:</u> 28 days	Prespecified subgroup analyses were performed based on age, sex,	<u>Definitions:</u> -

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
(RECOVERY Collaborative Group)	<p>randomized, controlled, open-label platform trial</p> <p><u>Setting:</u> hospital-based, between April 7 and November 27, 2020</p> <p><u>Country:</u> 176 hospitals in the UK</p> <p><u>Source of funding:</u> UK Research and Innovation (Medical Research Council) and National Institute of Health Research. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.</p> <p><u>Conflicts of interest:</u> The authors have no conflict of interest or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> patients admitted to hospital with clinically suspected or laboratory confirmed SARS-CoV-2 infection no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial age \geq 18 years, but from May 9, 2020, the age limit was removed <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> prolonged QTc interval hypersensitivity to a macrolide antibiotic already receiving chloroquine or hydroxychloroquine <p><u>N total at baseline:</u> Randomized: N = 7763</p> <p>Intervention: N = 2582 Control: N = 5181</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 65.4 y (15.6) C: 65.2 y (15.7)</p> <p>Sex, n/N (%) male: I: 1604/2582 (62%) C: 3215/5181 (62%)</p> <p>Groups were comparable at baseline.</p>	or until discharge + usual care		<p><u>Loss-to-follow-up:</u> I: 76/2582 (2.9%) <i>Reasons: not reported</i></p> <p>Control: 127/5181 (2.5%) <i>Reasons: not reported</i></p>	<p>ethnicity, days since symptom onset, respiratory support at randomisation, and use of corticosteroids.</p> <p>Clinical outcomes</p> <p><u>Mortality</u></p> <p><u>28-day mortality</u> I: 561/2582 (22%) C: 1162/5181 (22%) RR 0.97 (95%CI: 0.87-1.07)</p> <p><u>Duration of hospitalization</u></p> <p><u>Time to being discharged alive</u> Days I: 10 (5 to \geq 28) C: 11 (5 to \geq 28)</p> <p><u>Discharged from hospital within 28 days</u> I: 1788/2582 (69%) C: 3525/5181 (68%) RR 1.04 (95%CI: 0.98-1.10)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support*</u></p> <p><u>Invasive mechanical ventilation or death within 28 days</u> I: 603/2430 (25%) C: 1273/4881 (26%) RR 0.95 (95%CI: 0.87-1.03)</p> <p><u>Safety</u></p> <p><u>Serious adverse events</u> There was one report of a serious adverse reaction</p>	<p><u>Remarks:</u> * Among those not on invasive mechanical ventilation at baseline.</p> <p><u>Authors conclusion:</u> In patients admitted to hospital with COVID-19, azithromycin did not improve survival or other prespecified clinical outcomes. Azithromycin use in patients admitted to hospital with COVID-19 should be restricted to patients in whom there is a clear antimicrobial indication.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	produce the manuscript.					<p>believed to be related to azithromycin: a case of pseudomembranous colitis from which the patient recovered with standard treatment.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p> <p>Prespecified subsidiary clinical outcomes included cause-specific mortality, use of haemodialysis or haemofiltration, major card arrhythmia, and receipt and duration of ventilation.</p>	
Furtado, 2020	<p><u>Type of study:</u> RCT, open-label</p> <p><u>Setting:</u> 57 centres,</p> <p><u>Country:</u> Brazil</p> <p><u>Source of funding:</u> This trial was funded by the members of the COALITION COVID-19 Brazil. EMS provided partial funding, the study drugs, and coordinated logistics for the trial, but was not involved in the study conduct, analysis, or</p>	<p>Patients with severe COVID-19 infection</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age ≥ 18 y • admitted to hospital • suspected or confirmed COVID-19 • Symptom onset < 14 days • ≥1 of following severity criteria: use of oxygen supplementation of more than 4 L/min flow; use of high-flow nasal cannula; use of non-invasive positive-pressure ventilation; or use of mechanical ventilation <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • use of hydroxychloroquine, chloroquine, or macrolides for more than 48 h before enrolment and since symptom onset (ie, patients could 	<p>Azithromycin (500 mg via oral, nasogastric, or IV administration once daily for 10 days) plus standard of care</p> <p>Standard of care included hydroxychloroquine (400 mg twice daily for 10 days)</p>	<p>Standard of care without macrolides.</p> <p>Standard of care included hydroxychloroquine (400 mg twice daily for 10 days)</p>	<p><u>Length of follow-up:</u> 29 days</p> <p><u>Loss to follow-up:</u> I: 2 (did not have ordinal scale or vital status ascertained at 29 days because they were lost to follow-up; however, both had clinical status ascertained at 15 days) C: 0</p> <p><u>Excluded after randomisation due to negative PCR result:</u> I: 22/237 (9%) C: 27/210 (13%)</p>	<p>Clinical outcomes <u>Clinical status:</u> score on six-point ordinal scale <i>Day 7:</i> OR 1.60 (95% CI 1.08 to 2.35) <i>Day 15:</i> OR 1.36 (95% CI 0.94 to 1.97) <i>Day 29:</i> OR 1.43 (95% CI 0.96 to 2.12)</p> <p><u>Mortality</u>, at 29 days: I: 90/214 (42%) C: 73/183 (40%) HR 1.08 (95% CI 0.79 to 1.47)</p> <p><u>Ventilator-free days</u>, patients on mechanical ventilation at baseline, median (IQR): I: 0 days (0–14)</p>	<p><u>Remarks:</u> -Hydroxychloroquine was included in standard of care -4% of the control group received a macrolide during the course of the study</p> <p><u>6-point ordinal scale to indicate clinical status:</u> 1: not admitted to hospital 2: admitted to hospital, not requiring supplemental oxygen 3: admitted to hospital, requiring supplemental oxygen 4: admitted to hospital, requiring HFNC or NIPPV 5: admitted to hospital, requiring ECMO, invasive mechanical ventilation, or both 6: death</p> <p><u>Authors conclusion:</u> In conclusion, in patients admitted to hospital with severe COVID-19, adding</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	decision to publish these results	<p>be enrolled if treated for index COVID-19 infection with one of those drugs as long as treatment duration was not longer than 48 h); history of severe ventricular cardiac arrhythmia or ECG with QTc interval of ≥ 480 ms</p> <ul style="list-style-type: none"> known allergy to any of the trial drugs. <p><u>N total at baseline:</u> N = 397 (modified ITT group) Intervention: 214 Control: 183</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 59.4 (49.3–70.0) C: 60.2 (52.0–70.1) Sex, n/N (%) male: I: 140/214 (65%) C: 122/183 (67%)</p> <p>Groups comparable at baseline.</p>				<p>C: 1 day (0–18) MD –3.33 (95% CI –5.89 to –0.77]</p> <p><u>Duration of hospital stay, in survivors, median (IQR):</u> I: 26 days (11–29) C: 18 days (11–29) MD 8.00 (95% CI 0.81 to 15.19)</p> <p><u>Secondary infection</u> I: 87/214 (41%) C: 65/183 (36%) RR 1.11 (95% CI 0.92 to 1.33)</p> <p><u>Safety</u> (I – n=241; C – n=198) <u>Serious adverse events</u> I: 102/241 (42%) C: 75/198 (38%) <u>QTc interval prolongation :</u> I: 47/241(20%) C: 42/198 (21%) Additional SAE's reported also not statistically different between groups.</p>	azithromycin to a standard of care (a regimen that included hydroxychloroquine) did not result in clinical improvement or mortality reduction. These findings do not support the routine use of azithromycin in combination with hydroxychloroquine for this patient population and can inform clinical practice and guidelines.
Sekhavati, 2020	<p><u>Type of study:</u> Open-label randomised trial</p> <p><u>Setting:</u> Ziaeiian Hospital in Tehran</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> This study was supported by the Tehran University</p>	<p><u>Inclusion criteria:</u> Positive RT-PCR test and significant findings compatible with radiographic imaging of COVID-19 pulmonary involvement.</p> <p><u>Exclusion criteria:</u> Age < 18 years, pregnancy or nursing during the time of admission, past history or concurrent cardiac disease, recent history of antiviral therapy, and contraindications for use of HCQ, AZM or LPV/r,</p>	<p>Azithromycin (AZM)</p> <p>Oral AZM 500 mg daily, oral LPV/r 40 0/10 0 mg twice daily and oral HCQ 400 mg daily, for 5 days.</p>	<p>Hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r)</p> <p>Oral LPV/r 40 0/10 0 mg twice daily and oral HCQ 400 mg daily, for 5 days</p>	30 days	<p>Primary endpoints <u>Hospital stay (days)</u> I: 4.61 \pm 2.59 C: 5.96 \pm 3.21 P=0.020</p> <p>Need for ICU admission I: 2 (3.57%) C: 7 (12.73%) P=0.070</p> <p>Death I: 0 (0.00%) C: 1 (1.82%) P=0.50</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Patients in the group receiving the experimental treatment regimen that included AZM had a significantly shorter hospital stay as well as significantly higher SpO2 and lower respiratory rate at discharge. However, a risk scoring system should be utilised before initiating treatment to prevent QTc prolongation, especially for high-risk patients.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	of Medical Sciences research centre [grant no. 47493].	<p>such as retinopathy or glucose-6-phosphate dehydrogenase deficiency, or a history of allergic reactions to these medicines.</p> <p><u>N total at baseline:</u> N = 111 Intervention: 56 Control: 55</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 54.38 ± 15.92 C: 59.89 ± 15.55 P=0.70</p> <p>Sex, n/N (%) male: I: 28/56 (50.00%) C: 23 (41.82%) P=0.39</p> <p><i>Groups comparable at baseline?</i> Myalgia, headache and vomiting were initially reported more by control patients (P = 0.000, 0.005 and 0.031, respectively). Weakness was found significantly more frequently in patients in the case group (P = 0.042).</p>				<p>Secondary endpoints</p> <p><u>Discharge body temperature (°C)</u> I: 36.88 ± 0.33 C: 36.77 ± 0.53 P=0.19</p> <p><u>ICU length of stay (days)</u> I: 5.00 ± 0.01 C: 4.43 ± 2.99 P=0.16</p> <p><u>RR at discharge (breaths/min)</u> I: 15.85 ± 1.99 C: 17.42 ± 2.42 P=0.010</p> <p><u>SpO₂ at discharge (%)</u> I: 93.95 ± 2.14 C: 92.40 ± 4.58 P=0.030</p> <p>Need for intubation I: 0 (0.00%) C: 3 (5.45%)</p> <p>Heart rate No patient in either group experienced cardiac arrhythmia or QTc prolongation.</p>	
Brown, 2020	See evidence table of Brown (2020) by hydroxychloroquine.						
Cavalcanti, 2020	See evidence table of Cavalcanti (2020) by hydroxychloroquine.						
10.2. Doxycycline							
Mahmud, 2021	<p><u>Type of study:</u> RCT; placebo-controlled</p> <p><u>Setting:</u></p>	Outpatients and hospitalized patients with mild to moderate severe COVID-19 (no patients were receiving oxygen therapy at randomization)	<p>Ivemectin + standard of care</p> <p>Single dose of ivermectin 12 mg and doxycycline 100</p>	<p>Placebo + standard of care</p> <p>Standard of care included</p>	<p><u>Length of follow up:</u> Not specified but outcomes announced up to 14 days; time from randomization to</p>	<p>Clinical outcomes <u>Mortality (28-30 day)</u> not reported <u>Mortality</u> I: 0/200 C: 3/200</p>	<p><u>Definitions:</u> Clinical recovery; defined as a normal body temperature of 36.1C to 37.2C maintained for at least 3 days, significantly improved respiratory</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Dhaka Medical College Hospital; Enrolment: 1 June 2020 to 30 August 2020</p> <p><u>Country:</u> Bangladesh</p> <p><u>Source of funding:</u> "This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors"</p> <p><u>Conflicts of interest:</u> "The authors declare that there is no conflict of interest. Popular Pharmaceuticals Limited, Bangladesh provided ivermectin, doxycycline, and placebo. The company was not involved in the planning or design of the study and had no role in the collection, analysis, or interpretation of the data."</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age >18 years positive COVID-19 RT-PCR test within 3 days prior to enrollment mild to moderately severe COVID-19 infection <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> unable to receive oral medications pregnant or breastfeeding, severe COVID-19 symptoms (defined as tachypnea [>30 breaths/ minute] and hypoxia [oxygen saturation (SpO₂) <90%] requiring supplemental oxygen), admitted to intensive care or high-dependency units, known hypersensitivities to ivermectin or doxycycline <p><u>N total at baseline:</u> N = 400 Intervention: 200 Control: 200</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 41 y (14) C: 38 (12) Sex, n/N (%) male: I: 123 (62%) C: 112 (56%) <i>Time between onset of symptoms and enrollment, median (IQR), days a</i> I: 4 (3–5) C: 4 (3–5) <i>Disease severity d</i> <i>Mild</i> I: 141 (71%)</p>	mg, twice daily for 5 days, in addition to standard of care	administration of paracetamol, anti-histamines, cough suppressants, vitamins, oxygen therapy according to indication and need, low molecular weight heparin according to indication, appropriate other broad-spectrum antibiotics, remdesivir injection, other antiviral drugs, and other drugs for associated comorbid conditions	<p>mortality also registered</p> <p><u>Loss to follow-up:</u> I: 17/200 (8.5%) Reasons: not specified and 3/200 (1.5%) excluded from analysis C: 17/200 (8.5%) Reasons: not specified for n=15; discontinued intervention due to adverse drug reaction (n=2)</p>	<p><i>They died 8, 22, and 28 days after randomization of respiratory failure due to COVID-19-related pneumonia.</i></p> <p><u>Duration of hospitalization</u> not reported</p> <p><u>Time to symptom resolution</u> Recovery period, median (IQR) I: 7 (4–10) days C: 9 (5–12) days HR 0.73 (95% CI 0.60 to 0.90) P=0.003</p> <p>Recovery <i>Within 7 days</i> I: 111/183 (60%) C: 80/180 (44%) HR 0.06 (95% CI 0.04 to 0.09), p= <0.001 <i>Between 7 – 11 days</i> I: 47% C: 53% <i>More than 12 days</i> I: 42 (23%) C: 67 (37%) HR 0.04 (95% CI 0.03 to 0.07); p= <0.001</p> <p>Increase in stage of severity, n (%) (worsen to moderate or severe disease) I: 16/183 (8.7%) C: 32/180 (17.8%) HR 0.43 (95% CI 0.38–0.62), p= <0.001</p>	<p>symptoms (respiratory rate <25 breaths/minute, no dyspnea), and oxygen saturation greater than 93% without assisted oxygen inhalation.</p> <p>Disease severity; defined as: Mild disease: symptoms of an upper respiratory tract viral infection, including mild fever, dry cough, sore throat, nasal congestion, headache, muscle pain, anosmia, and malaise. Moderate respiratory symptoms such as cough and shortness of breath were observed without signs of severe pneumonia. Severe disease: included severe dyspnea, tachypnea (>30 breaths/minute), and hypoxia (SpO₂ <90% at room air).</p> <p><u>Remarks:</u> -both outpatients and hospitalized patients included; unclear how many patients were hospitalized in the treatment groups (at randomization or during study) -8.5-10% per treatment group lost to follow-up -inconsistencies in paper (recovery within 7 days, 7-11 day or more than 12 days in total (185, 183)is different from total amount of patients (183, 180)).</p> <p><u>Authors conclusion:</u> Patients with mild-to-moderate COVID-19 infection treated with ivermectin plus doxycycline recovered earlier, were less likely to progress to more serious disease, and were more likely to be COVID-19 negative by RT-PCR on day 14.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: 136 (68%) Moderate I: 59 (30) C: 64 (32)</p> <p>Groups comparable at baseline.</p>				<p><u>Respiratory support</u> not reported</p> <p>Safety I: n=200, C: n=200 <u>Adverse events</u> <u>Adverse drug reaction</u> I: 9 (2.25%) C: 0 <u>Non-ulcer dyspepsia</u> I: 7 (3.8%) C: 0 <u>Erosive esophagitis</u> I: 2 (1.1%) C: 0</p> <p>Virological outcomes <u>Viral clearance</u> Persistent COVID-19 RT-PCR positivity (positive RT-PCR at 14 days; n (%)) I: 14/183 (7.6) C: 36/180 (20) HR 0.61 (95% CI 0.44 to 0.83), p= 0.002</p>	
10.3. Lincomycine							
NA	NA	NA	NA	NA	NA	NA	NA
11. Antifungal treatment							
11.1. Intraconazole							
Liesenborghs, 2021	<p><u>Type of study:</u> RCT (open-label)</p> <p><u>Setting:</u> University Hospitals Leuven, Belgium, March - June 2020</p> <p><u>Country:</u> Belgium</p> <p><u>Source of funding:</u></p>	<p>hospitalized COVID-19 patients</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age ≥ 18 with COVID-19, confirmed by PCR or typical chest CT-scan with at least one of: Radiographic infiltrates, SpO2 94% on room air or requiring supplemental oxygen. <p><u>Exclusion criteria:</u></p>	<p>Itraconazole + Standard of care</p> <p>As capsules or as an oral solution; loading dose of 200 mg three times per day for the first 3 days, followed by 200 mg twice daily.</p>	Standard of care	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> Not reported.</p>	<p>Clinical outcomes <u>Mortality (28 day)</u> I: 0 (0%) C: 0 (0%)</p> <p><u>Duration of hospitalization</u> Hospital stay [days], median (IQR): I: 8 (4 to 17) C: 9 (4 to 16)</p>	<p><u>Definitions:</u> Primary outcome: cumulative clinical status on day 15 based on the 7-point WHO ordinal scale Secondary outcomes: time to sustained clinical improvement or live discharge, time to events (admission to ICU, death, discharge); mortality on day 29, duration of supplemental oxygen, need for and duration of mechanical ventilation, duration of hospitalization, duration of</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Covid-19-Fund KU Leuven / University Hospitals Leuven, the COVID-19 call of the Research Foundation - Flanders (FWO) (grant G0G4820N), the European Union's Horizon 2020 research and innovation program (Grant 101003627, Swift COronavirus therapeutics REsponse project) and the Bill and Melinda Gates Foundation (Grant INV-00636).</p> <p><u>Conflicts of interest:</u> P Verhamme reports grants from KU Leuven during the conduct of the study and grants and personal fees for lectures and consultancy from Bayer Healthcare, Daiichi Sankyo, Pfizer, BMS, Bayer and Boehringer outside the submitted work, and personal fees for consultancy from Boehringer Ingelheim and</p>	<ul style="list-style-type: none"> Elevated liver tests (ALT/AST > 5 times ULN) pregnancy or breast feeding heart failure with severely reduced ejection fraction (30%) concomitant treatment with lopinavir/ritonavir or potent CYP450 inducers <p><u>N total at baseline:</u> N = 65 Intervention: 32 Control: 33</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 62 y (10) C: 63 y (13) Sex, n/N (%) male: I: 21/32 (66%) C: 20/33 (61%)</p> <p>Disease severity: Based on 7-point WHO ordinal scale Groups were comparable at baseline, no major differences in baseline characteristics. (No p values reported)</p>				<p>Estimate (95% CI): 0.92 (0.55 to 1.53)</p> <p>ICU stay [days], median (IQR) : I: 14 (8 to 22) C: 12 (9 to 18) Estimate (95% CI): 0.76 (0.34 to 1.70)</p> <p><u>Time to symptom resolution</u> Time to sustained clinical improvement, median [days] (IQR): I: 10 (5 to 18) C: 9 (5 to 6) Estimate (95% CI): 0.94 (0.56 to 1.60)</p> <p><u>Cumulative status on day 15 mean (SD):</u> I: 49 (20) C: 47 (17) Estimate (95% CI): 1.01 (0.85 to 1.19)</p> <p><u>Clinical Status on day 15 no. (%)</u> 1: I: 10 (31%) C: 7 (23%) 2: I: 12 (38%) C: 14 (45%) 3: I: 1 (3%) C: 3 (10%) 4: I: 4 (13%) C: 3 (10%) 5: I: 1 (3%) 2 (7%) 6: I: 4 (13%) C: 2 (7%)</p> <p><u>Respiratory support</u> Invasive mechanical ventilation, no. (%) I: 6 (19%) C: 5 (15%) ECMO, no. (%): I: 0 (0) C: 0 (0)</p>	<p>intensive care stay, daily National Early Warning Score (NEWS) 7-point WHO ordinal scale : 1) not hospitalized, no limitations on activities; 2) not hospitalized, limitations on activities; 3) hospitalized, not requiring supplemental oxygen; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, on non-invasive ventilation or high flow oxygen devices; 6) hospitalized, requiring extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation; and 7) death.</p> <p><u>Remarks:</u> Open-label trial; The study was put on hold by the DSMB when 68 patients had been randomized in order to evaluate pharmacokinetic data. After reviewing the preliminary pharmacokinetic and the preclinical data, the Steering Committee decided not to restart the study. <u>Authors conclusion:</u> Despite antiviral activity of itraconazole in an in vitro antiviral assay against SARS-CoV-2, itraconazole is unlikely to be of clinical benefit in the treatment of COVID-19. The combined analysis of data from a preclinical hamster COVID-19 model [6,7 and a pilot clinical trial in hospitalized COVID-19 patients led to this conclusion.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Portola, outside the submitted work. The trial was part of the DAWn clinical studies.					Duration of mechanical ventilation, median (IQR): I: 12 (8 to 16) C: 11 (7 to 12) Estimate (95% CI): 0.37 (0.11 to 1.29) Safety No differences in ECG parameters; Adverse events and SAEs were not reported in results. Virological outcomes Viral load at baseline and on day 6 did not differ between study groups.	
12. Antiparasitic treatment							
12.1. Ivermectin (broad spectrum anti-parasitic agent)							
Abbas, 2022	<u>Type of study:</u> Double-blind, randomized, placebo-controlled, trial <u>Setting:</u> Hospitalized patients, between May to August 2021 <u>Country:</u> Shanghai, China <u>Source of funding:</u> Not reported	Patients with mild COVID-19 <u>Inclusion criteria:</u> • Patients with COVID-19 aged 18 to 50 y <u>Exclusion criteria:</u> • History of treatment with steroid drugs during the last week • Concomitant use of anticoagulants, history of any allergies to the studied drugs • History of any allergies to the studied drugs • history of recent bleeding for any reason	ivermectin at a dose of 300 µg per kilogram of body weight for 5 days	Placebo for 5 days	<u>Length of follow-up:</u> 21 days <u>Incomplete outcome data & loss-to-follow-up:</u> 8 patients were discharged according to the exclusion criteria (Unknown to which treatment the patients were allocated)	Clinical outcomes <u>Mortality (unknown timeframe)</u> I: 1/99 (1.0%) C: 1/103 (0.97%) <u>Duration of hospitalization</u> Not reported <u>Time to symptom resolution, days:</u> I: 9 (8-12) C: 13 (10-14) P=0.08 <u>Invasive respiratory support</u> Not reported	Primary outcome: • Time to resolution of symptoms • Symptoms resolved Secondary outcome(s): • Deterioration of 2 or more points • Developing of fever during the study • Escalation of care • Deaths <u>Definitions:</u> - <u>Remarks:</u> Ivermectin was provided by Merck (Ivermectin) South Africa in bottles of 0.6 % solution for oral administration

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> The authors declared no conflict of interest.</p>	<ul style="list-style-type: none"> Patients with chronic diseases such as cardiovascular disease <p>N total at baseline: N = 210 Intervention: N=99 Control: N=103</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 38.3 y (6.8) C: 37.3 y (5.8)</p> <p>Sex, n/N (%) male: I: 47/99 (47.4%) C: 43/103 (42.3%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline? Yes</p>				<p><u>Non-invasive respiratory support</u> Not reported</p> <p>Safety <u>Serious adverse events</u> Respiratory failure I: 2/99 (2%) C: 1/103 (1%)</p> <p>Acute Kidney failure I: 1/99 (1%) C: 2/103 (2%)</p> <p>Multiorgan failure I: 2/99 (2%) C: 3/103 (3%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<p><u>Authors conclusion:</u> Among adults with mild coronavirus disease 2019, a 5 d course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild coronavirus disease 2019.</p>
Reis, 2022	<p><u>Type of study:</u> Double-blind, randomized, placebo-controlled, adaptive platform trial (TOGETHER)</p> <p><u>Setting:</u> Outpatient with SARS-CoV-2 infection, between March 23, 2021, and August 6, 2021</p> <p><u>Country:</u> 12 public health clinics, Brazil</p>	<p>Outpatients with SARS-COV-2 infection</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> ≥18 years presentation to an outpatient care setting with an acute clinical condition consistent with Covid-19 within 7 days after symptom onset Confirmed COVID-19 by PCR or another rapid test Patients over 18 years of age and with at least ONE of the following criteria a. Age 50³ years (do not need any of the other criteria) 	<p>ivermectin at a dose of 400 µg per kilogram of body weight for 3 days</p> <p>+ standard care for COVID-19 provided by health care professionals in Brazil</p>	<p>Placebo for 3 days¹</p> <p>+ standard care for COVID-19 provided by health care professionals in Brazil</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: 679 Were included in the intention to-treat analysis (100%) 674 Were included in the modified intention-to-treat analysis (99.3%) 624 Were included in the per-protocol</p>	<p>Clinical outcomes <u>Mortality (day 28)</u> I: 21/679 (3.1%) C: 24/679 (3.5%) RR: 0.88 (0.49-1.55)</p> <p><u>Duration of hospitalization (for any cause)</u> I: 79/679 (11.6%) C: 95/679 (14%) RR: 0.83 (0.63-1.10)</p> <p><u>Time to symptom resolution</u> Median no. of days to clinical recovery*: I: 14 (11-14) C: 14 (11-14)</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> Composite outcome was hospitalization due to coronavirus disease 2019 (Covid-19) within 28 days after randomization or an emergency department visit due to clinical worsening of Covid-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomization. <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> Viral clearance at day 3 and 7 Hospitalization for any cause Time to hospitalization Duration of hospitalization Time to emergency visit lasting more than 6 hours

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> FastGrants and the Rainwater Charitable Foundation</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported</p>	<p>b. Diabetes mellitus requiring oral medication or insulin</p> <p>c. Hypertension requiring at least 01 oral medication for treatment</p> <p>d. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardopathy under treatment, clinically manifest heart diseases with clinical repercussions)</p> <p>e. Lung disease symptomatic and/or under treatment (emphysema, fibrosing diseases)</p> <p>f. Patients with symptomatic asthma requiring chronic use of agents for symptom control.</p> <p>g. Smoking</p> <p>h. Obesity, defined as BMI > 30 kg/m² on weight and height information provided by the patient;</p> <p>i. Transplant Patients</p> <p>j. Patient with stage IV chronic kidney disease or on dialysis.</p> <p>k. Immunosuppressed patients/in use of corticotherapy (equivalent to at least 10 mg prednisone per day) and/or immunosuppressive therapy)</p> <p>l. Patients with a history of Cancer in the past 05 years or currently undergoing oncological treatment</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients with an acute respiratory condition • Taking serotonin reuptake inhibitors 			<p>analysis (91.9%)</p> <p>Control: 679 Were included in the intention to-treat analysis (100%)</p> <p>675 Were included in the modified intention-to-treat analysis (99.4%)</p> <p>288 Were included in the per-protocol Analysis (42.4%)¹</p>	<p>RR: 1.05 (0.88-1.24)</p> <p><u>Invasive respiratory support</u> I: 19/679 (2.8%) C: 25/679 (3.7%) RR: 0.77 (0.43-1.36)</p> <p><u>Non-invasive respiratory support</u> Not reported</p> <p>Safety <u>Serious adverse events</u> Grade 3 or more I: 79/679 (11.6%) C: 92/679 (13.5%)</p> <p>Virological outcomes <u>Viral clearance</u> Day 3 I: 11/148 (7.4%) C: 17/170 (10.0%) RR: 0.76 (0.36-1.52)</p> <p>Day 7 I: 36/142 (25.4%) C: 42/165 (25.5%) RR: 1.00 (0.68-1.46)</p>	<ul style="list-style-type: none"> • Time to clinical recovery (WHO scale) • Death from any cause • Time to death • Receipt of mechanical ventilation • Number of days with mechanical ventilation • Health-related quality of life • Percentages of patients who adhered to the assigned regimen • Adverse reactions <p><u>Definitions:</u> *Clinical recovery was assessed with the use of the World Health Organization clinical progression scale</p> <p><u>Remarks:</u> Only the results in the 3-day ivermectin group as compared with the concurrent placebo group are reported in this article.</p> <p>¹Participants in the placebo group received placebo for 1, 3, 10, or 14 days, comparable to the active-treatment groups in the trial. Although all the participants who had been assigned to receive any placebo were included in the intention-to-treat population, only those in the 3-day placebo groups were included in the per-protocol population.</p> <p><u>Authors conclusion:</u> Treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of Covid-19 or of prolonged emergency department</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Pregnant/locating • Known allergies to the study drug <p><u>N total at baseline:</u> N = 3515 Intervention: N=679 Control: N=679 <i>2157 participants were assigned to other treatment groups</i></p> <p><u>Important characteristics:</u> Age, median (IQR): I: 49 y (39-57) C: 49 y (37-56)</p> <p>Sex, n/N (%) male: I: 296/679 (43.6%) C: 271/269 (39.9%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline? Yes</p>					observation among outpatients with an early diagnosis of Covid-19.
Gonzalez, 2022	<p><u>Type of study:</u> Double-blind, placebo-controlled, randomized clinical trial</p> <p><u>Setting:</u> Hospitalized, August 2020</p> <p><u>Country:</u> Mexico</p> <p><u>Source of funding:</u></p>	<p>Hospitalized COVID-19 patients without severe respiratory failure.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • 16 years to 90 years • RT-PCR-or antigen test confirmed COVID-19 • Pneumonia, diagnosed by an X-ray or high-resolution chest CT scan • Recently established hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease 	<p>ivermectin, 12 mg or 18 mg, according to patient weight</p> <p>The dose of ivermectin was 12 mg in patients weighing less than 80 kg and 18 mg in those above 80 kg</p>	<p>Placebo: calcium citrate was chosen as a placebo and was administered as 2 tablets every 12 h on the first day, followed by one tablet every 12 h for the following 4 days.</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Not reported</p>	<p>Clinical outcomes</p> <p><u>Mortality:</u> I: 5/36 (13.8%) C: 6/37 (16.2%)</p> <p><u>Duration of hospitalization</u> Median (IQR) I: 6 (4-11) C: 5 (4-7)</p> <p><u>Time to symptom resolution</u> Discharge without respiratory deterioration or death</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Mean days of hospital stay • Rate of respiratory deterioration, requirement of invasive mechanical ventilation or dead • Mean of oxygenation index delta <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Mean time to negative viral PCR <p><u>Definitions:</u> -</p> <p><u>Remarks:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Centenario Hospital Miguel Hidalgo</p> <p><u>Conflicts of interest:</u> The authors declare no conflict of interest</p>	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Requiring high oxygen volumes • Predictors of a poor response to high-flow oxygen nasal prong therapy • Requiring mechanical ventilation <p>N total at baseline: N = 106*</p> <p>Intervention: N=36 Control: N=37</p> <p><u>Important characteristics:</u></p> <p>Age, mean (SD): I: 56 y (16.5) C: 53.8 y (16.9)</p> <p>Sex, n/N (%) male: I: 21/36 (58.3%) C: 23/37 (62.1%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline? Yes</p>	<p>All hospitalized patients received pharmacological thromboprophylaxis with low molecular weight heparin or unfractionated heparin according to local and international guidelines, dexamethasone (based on the RECOVERY trial)</p>	<p>All hospitalized patients received pharmacological thromboprophylaxis with low molecular weight heparin or unfractionated heparin according to local and international guidelines, dexamethasone (based on the RECOVERY trial)</p>		<p>I: 27/36 (75%) C: 27/37 (72.9%)</p> <p><u>Invasive respiratory support</u> Not reported</p> <p><u>Non-invasive respiratory support</u> Not reported</p> <p>Safety <u>Serious adverse events</u> Not reported</p> <p>Virological outcomes <u>Viral clearance</u> They were unable to determine whether the SARS-CoV-2 PCR tests became negative, due to the lack of reactants and the minimal usefulness of proving its negativity from a clinical-practical viewpoint.</p>	<p>*33 patients were allocated to group 1 (hydroxychloroquine). This group is not included in this summary of findings table.</p> <p>Patients were classified as high- or low-risk for the development of QT interval prolongation due to hydroxychloroquine according to their electrocardiogram. The QT interval was measured with Bazett's formula. Patients with an interval of ≥ 500 ms were randomized to ivermectin or placebo, while those with an interval of < 500 ms were randomized to ivermectin, hydroxychloroquine, or placebo.</p> <p><u>Authors conclusion:</u> In non-critically ill, hospitalized patients with pneumonia secondary to COVID-19, the use of hydroxychloroquine or ivermectin did not decrease significantly the number of hospitalization days, respiratory deterioration, or deaths.</p>
Lim, 2022	<p><u>Type of study:</u> Open-label multicenter randomized controlled clinical trial</p> <p><u>Setting:</u> 21 sites, between May 31, 2021 and October 25, 2021</p>	<p>Hospitalized patients with mild or moderate disease at admission</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • SRT-PCR or antigen test confirmed COVID-19 cases • < 50 years with at least 1 comorbidity • Presented with mild to moderate illness (WHO clinical progression scale 2-4) within 7 days from symptom onset 	<p>Ivermectin 0.4mg/kg/day for 5 days</p> <p>+</p> <p>Standard care</p>	<p>The standard of care for patients with mild to moderate disease consisted of symptomatic therapy and monitoring for signs of early deterioration</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: N=9 (3.6%) Reasons: Did not fulfil inclusion criteria (N=2), met exclusion criteria identified after</p>	<p>Clinical outcomes <u>Mortality (28 day):</u> Mortality, n/N (%): I: 3/241 (1.2%) C: 10/249 (4.0%) RR 0.31 (95% CI 0.09-1.11). p=0.09</p> <p><u>Duration of hospitalization</u> ICU stay, mean (SD): I: 7.7 days (4.4) C: 7.3 days (4.3)</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Proportion of patients who progressed to severe COVID-19 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Time to progression to severe disease • 28-day in-hospital all-cause mortality • Mechanical ventilation rate, ICU admission • Length of hospital stay after enrolment

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> Malaysia</p> <p><u>Source of funding:</u> Not reported</p> <p><u>Conflicts of interest:</u> None</p>	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Asymptomatic patients Oxygen required patients SPO₂ <95% at rest Severe hepatic impairment, acute medical or surgical impairment, concomitant viral infection Pregnancy or breastfeeding Warfarin therapy History of taking ivermectin or any antiviral drugs with reported activity against COVID-19 (i.e. favipiravir, hydroxychloroquine etc). <p><u>N total at baseline:</u> N = 500 Intervention: N=250 Control: N=250</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 63.0 y (8.9) C: 62.0 y (8.4)</p> <p>Sex, n/N (%) male: I: 111/241 (46.1%) C: 112/249 (45.0%)</p> <p>Disease severity: <i>Defined by WHO scale 2-4) n/N (%)</i>: <i>Mild</i>: I: 83/241 (34.4%) C: 84/249 (33.7%)</p> <p><i>Moderate</i>: I: 158/241 (65.6%) C: 165/249 (66.3%)</p>		<p>based on clinical findings, laboratory test results, and chest imaging.</p>	<p>randomization (N=1) or withdrew from study (N=6)</p> <p>232/241 (96.3%) completed 5 doses</p> <p>3 withdrew from study owing to adverse events after taking ivermectin</p> <p>241 included in the modified intention-to-treat analysis</p> <p>Control: N=1 (0.4%) Reason: Excluded due to exclusion criteria after randomization</p> <p>249 included in the modified intention-to-treat analysis</p>	<p>P=0.38</p> <p><u>Time to symptom resolution</u> Complete symptom resolution at day 5, n/N (%) I: 122/238 (51.3%) C: 131/247 (4.0%) RR 0.97 (95% CI 82-1.15). p=0.72</p> <p><u>Invasive respiratory support</u> Mechanical ventilation rate, n/N (%) I: 4/241 (1.7%) C: 10/249 (4.0%) RR 0.41 (95% CI 0.13-1.30). p=0.17</p> <p>Safety <u>Serious adverse events, n/N (%)</u> I: 4/241 (1.7%) C: 1/249 (0.4%)</p> <p>A detailed record of all adverse events is reported in the article.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<ul style="list-style-type: none"> Patients were also assessed on day 5 of enrollment for symptom resolution, changes in laboratory test results, and chest radiography findings Adverse events and Serious Adverse Events <p><u>Definitions:</u></p> <ul style="list-style-type: none"> Progression is defined as the hypoxic stage requiring supplemental oxygen to maintain SPO₂ 95% or greater (Malaysian COVID-19 clinical severity stages 4 or 5; WHO clinical progression scale 5-9) Adverse events and serious adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 <p><u>Remarks:</u></p> <ul style="list-style-type: none"> The study was not designed to assess the effects of ivermectin on mortality from COVID-19 Open-label trial <p><u>Authors conclusion:</u> In this randomized clinical trial of high-risk patients with mild to moderate COVID-19, ivermectin treatment during early illness did not prevent progression to severe disease. The study findings do not support the use of ivermectin for patients with COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups are comparable at baseline					
Buonfrate, 2022	<p>Type of study: Phase 2, dose-finding, randomized, double-blind, placebo-controlled trial</p> <p>Setting: Non hospital-based, between July 31, 2020 and May 26, 2021</p> <p>Country: 4 centers in the United States</p> <p>Source of funding: InsudPharma & Mundo Sano donated the study medication. Alpine Lions Cooperation contributed to the study. The study was partly funded by the Italian Ministry of Health "Fondi Ricerca Corrente" to IRCCS Sacro Cuore Don Calabria Hospital.</p> <p>Conflicts of interest: None to declare.</p>	<p>Non-hospitalized patients with recently diagnosed COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age ≥ 18 y • positive RT-PCR test (nasopharyngeal swabs) • COVID-19 Severity Score < 3 • patient able to take oral drugs <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • pregnant or lactating women • suffering from known CNS disease • patient under dialysis • any severe medical condition with a prognosis <6 months • patients under warafin or antiviral treatment • patients under chloroquine phosphate or hydroxychloroquine <p>N total at baseline: Randomized: N = 93</p> <p>Intervention B: N = 29 Intervention C: N = 32 Control A: N = 32</p> <p>Important characteristics: Age, median (range): I (B): 47.0 y (31.0-62.0) I (C): 44.5 y (31.0-55.5) C (A): 50.0 y (26.0-57.0)</p> <p>Sex, n/N (%) female: I (B): 14/29 (48.3%) I (C): 8/32 (25.0%) C (A): 17/32 (53.1%)</p>	<p>Intervention B: Single dose ivermectin 600 µg/kg plus placebo for 5 days</p> <p>Intervention C: Single dose ivermectin 1200 µg/kg for 5 days</p>	<p>Placebo (A): Identical in appearance to ivermectine for 5 days</p>	<p>Length of follow-up: 30 days</p> <p>Loss-to-follow-up or incomplete data: C (A): 2/32 (6.2%) I (B): 3/29 (10.3%) I (C): 13/32 (40.6%)</p>	<p>Clinical outcomes</p> <p>Mortality Not reported</p> <p>Duration of hospitalisation Not reported</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support Not reported</p> <p>Safety Concerning adverse event (hospitalization for worsening of the disease) C (A): 0/32 (0%) I (B): 1/29 (3.4%) I (C): 3/32 (9.4%)</p> <p>No SADR were reported</p> <p>Virological outcomes <u>Differences in viral load decline from baseline to 7 days (Log10) (mean, SD)</u> C (A): 2.9 (1.6) ref I (B): 2.5 (2.2), p=0.122 I (C): 2.0 (2.1), p=-0.099</p>	<p>Remarks: As observed by the researchers, the 4 participants whose disease worsened enough to cause hospitalization were all in the treatment arms, and 3 of these in the high-dose arm</p> <p>The recruitment was stopped, because of a dramatic drop of cases</p> <p>Authors conclusion: High-dose ivermectin demonstrated safe</p> <p>There was no significant difference in viral load reduction between study arms</p> <p>Mild/moderate side effects were more frequent with the highest dose of ivermectin</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		An imbalance in the sex ratio is observed					
Mohan, 2021	<p>Type of study: randomized, double-blind, placebo-controlled, single-centre pilot study</p> <p>Setting: hospital-based, between July 28 2020 and September 29 2020</p> <p>Country: New Delhi, India</p> <p>Source of funding: The trial was supported by the Science and Engineering Research Board, Department of Science and Technology, Government of India. The funder had no role in study design, data collection, data analysis or writing of the report.</p> <p>Conflicts of interest: None to declare.</p>	<p>hospitalized patients with mild-to-moderate COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age ≥ 18 y • diagnosis of nonsevere COVID-19, i.e., SpO₂ > 90%, and with no hypotension or requirement of mechanical ventilation • positive result on RT-PCR or a rapid antigen test <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • no informed consent given • pregnancy or lactation • known hypersensitivity to ivermectin • chronic kidney disease with eGFR < 30 mL/min • transaminase levels > 5 ULN • myocardial infarction or heart failure within 90 days prior to enrolment • corrected QT interval > 450 ms • any other severe comorbidity as per investigator's assessment • enrolment in another clinical trial <p>N total at baseline: Randomized: N = 157 mITT population: N = 125</p> <p>Intervention 1 (24 mg): N = 40 Intervention 2 (12 mg): N = 40 Control: N = 45</p> <p>Important characteristics: Age, mean (SD): I1: 34.3 y (10.45) I2: 36.3 y (10.54)</p>	single oral dose of ivermectin 24 mg (I1) or 12 mg (I2) on the day of randomization	placebo	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up or incomplete data:</p> <p>Intervention 1: N = 12 (23.1%) Reasons</p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 1)</i> • <i>negative RT-PCR at baseline (n = 11)</i> <p>Intervention 2: N = 12 (23.1%) Reasons</p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 3)</i> • <i>negative RT-PCR at baseline (n = 9)</i> <p>Control: N = 8 (15.1%) Reasons</p> <ul style="list-style-type: none"> • <i>withdrew consent (n = 1)</i> • <i>negative RT-PCR at baseline (n = 8)</i> 	<p>Clinical outcomes</p> <p>Mortality Not reported</p> <p>Duration of hospitalisation Discharge by day 14 I1: 38/40 (95.0%) I2: 37/40 (92.5%) C: 39/45 (86.7%) p = 0.42</p> <p>Hospital-free days at day 28 Mean (SD) I1: 17.0 (2.3) I2: 16.7 (2.0) C: 17.0 (2.0) p = 0.79</p> <p>Time to symptom resolution Days to symptom resolution Mean (SD) I1: 4.26 (2.65) I2: 4.76 (2.44) C: 4.58 (2.94) p = 0.77</p> <p>Respiratory support Not reported</p> <p>Other WHO ordinal scale at day 14 I1: I1: 37/40 (92.5%) I2: 37/40 (92.5%) C: 39/45 (86.7%)</p>	<p>Definitions: -</p> <p>Remarks: -</p> <p>Authors conclusion: In patients with mild and moderate COVID-19, a single oral administration of Ivermectin did not significantly increase either the negativity of RT-PCR or decline in viral load at day 5 of enrolment compared with placebo.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>C: 35.3 y (10.52)</p> <p>Sex, n/N (%) male: I1: 37/40 (92.5%) I2: 35/40 (87.5%) C: 39/45 (86.7%)</p> <p>Disease severity: <i>Mild</i> I1: 24/40 (60.0%) I2: 27/40 (67.5%) C: 29/45 (64.4%)</p> <p><i>Moderate</i> I1: 16/40 (40.0%) I2: 13/40 (32.5%) C: 16/45 (35.6%)</p> <p>Groups were comparable at baseline.</p>				<p>2: I1: 1/40 (2.5%) I2: 0/40 (0%) C: 0 /45(0%)</p> <p>3: I1: 2/40 (5.0%) I2: 3/40 (7.5%) C: 6/45 (13.3%) p = 0.40</p> <p><u>Change in WHO ordinal scale between day 1-14</u> <i>No change:</i> I1: 2/40 (5.0%) I2: 3/40 (7.5%) C: 5/45 (11.1%)</p> <p><i>Decrease by 1:</i> I1: 1/40 (2.5%) I2: 0/40 (0%) C: 1/45 (2.2%)</p> <p><i>Decrease by 2:</i> I1: 35/40 (87.5%) I2: 32/40 (80.0%) C: 37/45 (82.2%)</p> <p><i>Decrease by 3:</i> I1: 2/40 (5.0%) I2: 5/40 (12.5%) C: 2/45 (4.4%) p = 0.67</p> <p><u>Any clinical worsening</u> I1: 3/40 (7.5%) I2: 2/40 (5.0%) C: 5/45 (11.1%) p = 0.65</p> <p>Safety <u>Serious adverse events</u> I1: 0/51 (0%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I2: 0/49 (0%) C: 0/52 (0%)</p> <p>Virological outcomes</p> <p><u>Viral load</u></p> <p><i>At enrolment</i> Mean (SD) I1: 5.54 (2.02) I2: 5.79 (1.82) C: 6.12 (0.35) p = 0.35</p> <p><i>Day 3:</i> Mean (SD) - absolute: I1: 3.89 (1.88) I2: 3.85 (2.17) C: 3.96 (2.00) p = 0.97</p> <p>- decrease (day 0-3): I1: 1.65 (1.63) I2: 1.94 (1.86) C: 2.16 (1.74) p = 0.40</p> <p><i>Day 5:</i> Mean (SD) - absolute: I1: 2.49 (2.50) I2: 2.75 (2.30) C: 3.04 (2.44) p = 0.58</p> <p>- decrease (day 0-5): I1: 3.05 (2.29) I2: 3.04 (2.05) C: 3.08 (1.98) p = 0.99</p> <p><i>Day 7:</i> Mean (SD) - absolute:</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I1: 1.95 (1.84) I2: 2.30 (1.99) C: 2.37 (2.20) p = 0.62</p> <p>- decrease (day 0-7): I1: 3.65 (2.51) I2: 3.56 (1.83) C: 3.88 (2.19) p = 0.76</p> <p><u>Negative RT-PCR - mITT population</u> Day 3: I1: 3/40 (7.5%) I2: 7/40 (17.5%) C: 7/45 (15.6%) RR (I1 vs. C): 0.48 (95% CI: 0.14-1.59) RR (I2 vs. C): 1.12 (95% CI: 0.44-2.84)</p> <p>Day 5: I1: 19/40 (47.5%) I2: 14/40 (35.0%) C: 14/45 (31.1%) RR (I1 vs. C): 1.53 (95% CI: 0.89-2.65) RR (I2 vs. C): 1.12 (95% CI: 0.61-2.05)</p> <p>Day 7: I1: 16/36 (44.4%) I2: 13/36 (36.1%) C: 16/42 (38.1%) RR (I1 vs. C): 1.17 (95% CI: 0.68-1.98) RR (I2 vs. C): 0.95 (95% CI: 0.53-1.68)</p> <p><u>Negative RT-PCR - mild disease</u> Day 3:</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I1: 0/24 (0%) I2: 3/27 (11.1%) C: 4/29 (13.8%) RR (I1 vs. C): 0.00 (95% CI: 0.00-1.07) RR (I2 vs. C): 0.80 (95% CI: 0.22-2.96)</p> <p><i>Day 5:</i> I1: 8/24 (33.3%) I2: 6/27 (22.2%) C: 7/29 (24.1%) RR (I1 vs. C): 1.38 (95% CI: 0.60-3.21) RR (I2 vs. C): 0.92 (95% CI: 0.36-2.32)</p> <p><i>Day 7:</i> I1: 10/23 (43.5%) I2: 7/25 (28.0%) C: 9/29 (31.0%) RR (I1 vs. C): 1.40 (95% CI: 0.69-2.86) RR (I2 vs. C): 0.90 (95% CI: 0.39-2.02)</p> <p><u>Negative RT-PCR - moderate disease</u> <i>Day 3:</i> I1: 3/16 (18.8%) I2: 4/13 (30.8%) C: 3/16 (18.8%) RR (I1 vs. C): 1.00 (95% CI: 0.26-3.85) RR (I2 vs. C): 1.64 (95% CI: 0.48-5.71)</p> <p><i>Day 5:</i> I1: 9/16 (56.2%) I2: 8/13 (61.5%) C: 7/16 (43.8%) RR (I1 vs. C): 1.29 (95% CI: 0.64-2.68)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						RR (I2 vs. C): 1.41 (95% CI: 0.69-2.92) <i>Day 7:</i> I1: 6/13 (46.2%) I2: 6/11 (54.5%) C: 7/13 (53.8%) RR (I1 vs. C): 0.86 (95% CI: 0.38-1.86) RR (I2 vs. C): 1.01 (95% CI: 0.46-2.14) <u>Negative RT-PCR - duration of clinical symptoms</u> <i>< 4 days:</i> I1: 8/17 (47.0%) I2: 4/16 (25.0%) C: 6/21 (28.6%) RR (I1 vs. C): 1.65 (95% CI: 0.72-3.84) RR (I2 vs. C): 0.87 (95% CI: 0.30-2.43) <i>> 4 days:</i> I1: 9/16 (56.2%) I2: 8/17 (47.0%) C: 7/20 (35.0%) RR (I1 vs. C): 1.61 (95% CI: 0.78-3.41) RR (I2 vs. C): 1.34 (95% CI: 0.62-2.95) <u>Negative RT-PCR - viral load at baseline</u> <i>CT < 24:</i> I1: 4/18 (22.2%) I2: 5/18 (27.8%) C: 2/21 (9.5%) RR (I1 vs. C): 2.33 (95% CI: 0.56-10.10) RR (I2 vs. C): 2.92 (95% CI: 0.74-12.07)	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						CT > 24: I1: 15/22 (68.2%) I2: 9/22 (40.9%) C: 12/24 (50.0%) RR (I1 vs. C): 1.36 (95% CI: 0.83-2.30) RR (I2 vs. C): 0.82 (95% CI: 0.42-1.54)	
Ravikirti, 2021	<p>Type of study: RCT (double blind)</p> <p>Setting: All India Institute of Medical Sciences (AIIMS), Patna, India. All admissions between 1st August and 31st October 2020.</p> <p>Country: India</p> <p>Source of funding: Not reported</p> <p>Conflicts of interest: None.</p>	<p>Hospitalized patients with mild or moderate disease at admission.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Age ≥ 18 years; diagnosis of COVID-19; mild or moderate disease on admission. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> known allergy or adverse drug reaction with ivermectin; unwillingness or inability to provide consent to participate in the study; prior use of ivermectin during the course of current illness; pregnancy and lactation. <p>N total at baseline: N = 115 Intervention:57 Control: 58</p> <p>Important characteristics: Age, mean (SD): I: 50.7 y (12.7) C: 54.2 y (16.3)</p> <p>Sex, n/N (%) male: I:40/55 (73%) C:41/57 (72%)</p> <p>Disease severity, mean (SD): <i>Defined by</i></p>	<p>Ivermectin</p> <p>Ivermectin 12 mg, on day 1 and 2 after their enrolment</p>	<p>Placebo tables</p> <p>placebo tablets on day 1 and 2 after their enrolment.</p>	<p>Length of follow-up: 10 days</p> <p>Loss-to-follow-up: Intervention: 2 (4%) Reasons: 1 lost to follow-up, 1 was administered unblinded ivermectin tablet by the treating team on day 2, hence excluded.</p> <p>Control: 1 (2%) Reasons: 1 was administered unblinded ivermectin tablet by the treating team on day 2, hence excluded.</p> <p>Incomplete outcome data: Intervention: 23 (40%) Reasons: 23 no or inconclusive report [9 discharged before 6th day; 2 sample not sent for unknown reason; 9 sample lost; 3 report inconclusive</p> <p>Control: 13 (22%) Reasons: 13 no or</p>	<p>Clinical outcomes Mortality (28-30 day) not reported</p> <p>Mortality (in-hospital) I: 0/55 (0%) C: 4/57 (7%)</p> <p>Duration of hospitalization Discharged at day 10 I: 44/55 (80%) C: 42/57 (74%)</p> <p>Time to symptom resolution Symptom free at day 6 I: 46 (84%) C: 51 (90%)</p> <p>Respiratory support Invasive ventilation I: 1/55 (2%) C: 5 /57 (9%)</p> <p>Safety Adverse events No adverse events attributable to ivermectin were reported during this trial.</p> <p>Virological outcomes Viral clearance % negative PCR at day 6 I: 13/55 (24%)</p>	<p>Definitions: Definition severity: Mild: No evidence of breathlessness or hypoxia (normal saturation); Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease (defined by the Ministry of Health and Family Welfare (MOHFW), Government of India (GOI) guidelines)</p> <p>Remarks: Role of pharmaceutical company is unclear (Ivermectin tablets were procured from the learning resource allowance of the principal investigator. Placebo tablets were provided by Sun Pharma Pvt. Ltd.)</p> <p>Authors conclusion: Inclusion of ivermectin in treatment regimen of mild to moderate COVID-19 patients could not be recommended with certainty based on our study results as it had shown only marginal benefit in successful discharge from the hospital with no other observed benefits. Larger, multicentre RCTs should be planned to provide a clearer answer.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		I: 42/55 (76%) mild, 13/55 (24%) moderate disease C: 46/57 (81%) mild, 11/57 (19%) moderate disease Groups comparable at baseline? Yes			inconclusive report: [3 discharged before 6th day ; 1 died; 2 sample not sent for unknown reason; 3 sample lost; 4 report inconclusive]	C: 18/57 (32%)	
Vallejos, 2021	Type of study: Randomized, double-blind, placebo-controlled trial. Setting: Ministry of Public Health of the Province of Corrientes. Country: Argentina. Source of funding: None. Conflicts of interest: The authors declare that they have no competing interests. ClinicalTrials.gov NCT04529525.	Patients with early COVID-19 Inclusion criteria: <ul style="list-style-type: none"> Individuals >18 years of age; Individuals residing in the province of Corrientes at the time of diagnosis with confirmed RT-PCR test for SARS-CoV-2 detection in the last 48 hours; If they are woman of childbearing age, they should be using a contraceptive method of proven efficacy and safety; All individuals were to weigh at the time of inclusion equal to or greater than 48 kg. Exclusion criteria: <ul style="list-style-type: none"> Patients who required current home oxygen; Patients who required hospitalization for COVID-19 at the time of diagnosis; History of hospitalization for COVID-19; Pregnant or breastfeeding woman; Known allergy to ivermectin or the components of ivermectin or placebo tablets; Presence of mal-absorptive syndrome; 	Ivermectin plus standard of care The dose of ivermectin used was the approved dose in Argentina for the treatment of other parasitic diseases, such as parasitic diseases, and it was staggered according to weight. Those weighing up to 80 Kg received 2 tablets of 6 mg (mg) each at inclusion and another 2 tablets of 6 mg each 24 h after the first dose (total 24 mg). Those weighing more than 80 kg and up to 110 kg received 3 tablets of 6 mg each at inclusion and another 3 tablets of 6 mg each 24 h after the first dose (total 36 mg). Those weighing more than 110 kg received 4 tablets of 6 mg each at inclusion and another 4 tablets of 6 mg each 24 h after the first dose (total 48 mg)	Placebo plus standard of care Individuals randomized to placebo received the equivalent number of placebo tablets to the ivermectin weight-based dosage, at baseline and again after 24 h.	Length of follow-up: 30 days after the final visit. Loss-to-follow-up: Intervention: In the ivermectin group, 249 patients had 100% compliance and 1 had 50% compliance. Control: In the placebo group, 248 patients had 100% compliance, 2 patients had 50% compliance and 1 patient had 0% compliance. * Considering that an intention-to-treat analysis was performed, all 501 patients were included for the analysis of primary and secondary outcomes. There were no arm crossovers. Incomplete outcome data: None.	Clinical outcomes (All-cause) mortality (28-30 day) I: 4/250 (1.60%) C: 3/251 (1.20%) OR 1.34 (95% CI 0.30 to 6.07) P=0.70 Requiring hospitalization I: 14/250 (5.60%) C: 21/251 (8.37%) OR 0.65 (95% CI 0.32 to 1.31) P=0.227 Time to hospitalization days (in those who were hospitalized), median (IQR) I: 3.5 (3 to 5) C: 3 (2 to 5) P=0.59 Time to symptom resolution Not reported. Respiratory support Invasive mechanical ventilatory support, n/N (%) I: 4/250 (1.60%) C: 3/251 (1.20%) OR 1.34 (95% CI 0.30 to 6.07) P=0.70	Definitions: <ul style="list-style-type: none"> The standard of care was in accordance with the recommendations of the Argentine Ministry of Health. Remarks: - Authors conclusion: In the IVERCORCOVID19 trial, in patients with a positive COVID-19 nasal swab by RT-PCR technique in the last 48 h, ivermectin in a staggered dose according to the patient's weight for 2 days had no significant effect on preventing hospitalization of patients with COVID19. No significant differences were observed in secondary outcomes such as the time elapsed from study enrollment to hospitalization in those who required it. Additionally, no significant differences were observed in the use of invasive mechanical ventilatory support, the requirement for dialysis, negative nasal swabs at 3 and 12 days after study enrollment, or in all-cause mortality. Patients who received ivermectin required invasive mechanical ventilatory support earlier. The use of ivermectin was not associated with increased adverse events.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Presence of any other concomitant acute infectious disease; • Known history of severe liver disease; • Recent or expected need for dialysis. • Concomitant use of hydroxychloroquine or chloroquine or antiviral drugs due to a viral pathology other than COVID-19 at the time of admission was prohibited as was the use of ivermectin up to 7 days before randomization; • Individuals with participation in a research study that involved the administration of a drug within the last 30 days. <p><u>N total at baseline:</u> N = 501 Intervention: N = 250 Control: N = 251</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 42.58 y (15.29) C: 42.40 y (15.75)</p> <p>Sex, n/N (%) female: I: 111/250 (44.4%) C: 126/251 (50.2%)</p> <p>Disease severity: Not reported: <i>"Lastly, we did not include any scale to determine the severity of the patients who were enrolled."</i></p> <p>Groups comparable at baseline? Yes.</p>				<p>Safety <u>Adverse events</u> I: 45/250 (18.00%) C: 53/251 (21.11%) P=0.60</p> <p>*specific adverse events were reported in the publication.</p> <p>Virological outcomes <u>Viral clearance</u> <i>Negative nasal swab day 3, n/N (%)</i> I: 113/250 (47.08%) C: 120/251 (49.79%) OR 0.90 (95% CI 0.63 to 1.28)</p> <p><i>Negative nasal swab day 12, n/N (%)</i> I: 212/250 (89.08%) C: 221/251 (92.47%) OR 0.76 (95% CI 0.45 to 1.27) P=0.29</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Abd-Elsalam, 2021b	<p>Type of study: RCT Open-label study</p> <p>Setting: Tanta and Assiut University Hospitals (tertiary hospitals), between March 2020 and October 2020.</p> <p>Country: Egypt</p> <p>Source of funding: Not reported in the article.</p> <p>Conflicts of interest: All the authors declare that there are no conflict of interests.</p>	<p>Hospitalized patients, mildly to moderately affected</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> ages 20 to 65 mildly to moderately affected COVID-19 infection confirmed by pharyngeal swab polymerase chain reaction (PCR) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> allergy or contraindication to the drugs used in the study pregnant and lactating mother patients with cardiac problem <p>N total at baseline: N = 164 Intervention: 82 Control: 82</p> <p>Important characteristics: Age, mean (SD): I: 42.38 y (16.02) C: 39.38 y (16.92) Sex, n/N (%) male: I: 37/82 (45.1%) C: 45/82 (54.9%)</p> <p>Groups comparable at baseline? No significant differences between groups on patients' characteristics and clinical presentation.</p>	<p>Ivermectin a single dose of oral ivermectin tablets (12 mg) every day for 3 days added to the standard protocol of treatment according to the Egyptian Ministry of Health (MOH) protocol of COVID-19 treatment. Ivermectin tablets (Iverzine tablets, Unipharma) were used in the study</p>	<p>Standard protocol standard protocol of treatment alone for 14 days.</p> <p>It included paracetamol, oxygen, fluids (according to the condition of the patient), empiric antibiotic, oseltamivir if needed (75 mg/12 h for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO₂ less than 60 mm Hg, O₂ saturation less than 90% despite oxygen or noninvasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock.</p>	<p>Length of follow up: 1 month</p> <p>Loss to follow-up: I: 0/82 (0%) C: 0/82 (0%)</p> <p>All the patients continued the study medications to the end of the duration of treatment and follow-up.</p>	<p>Clinical outcomes All-cause mortality (within 1 month after randomization), n (%) I: 3/82 (3.7%) C: 4/82 (4.9%) P=1.00</p> <p>Duration of hospitalization <i>Length of hospital stay (in days), mean ± SD</i> I: 8.82 ± 4.94 C: 10.97 ± 5.28 P=0.08</p> <p>Time to symptom resolution Not reported.</p> <p>Respiratory support <i>Need for mechanical ventilation, n (%)</i> I: 3/82 (3.7%) C: 3/82 (3.7%) P=1.00</p> <p>Safety Adverse events Not reported.</p> <p>Virological outcomes Viral clearance Not reported.</p>	<p>Authors conclusion: The usage of ivermectin did not achieve significance for any of the endpoints. However; there was an observed trend to reducing hospital stay in the ivermectin-treated group. These findings may suggest using ivermectin as an add-on therapy to protocols used for the treatment of COVID-19. However, these results are needed to be validated in a larger prospective follow-up study.</p>
Samaha, 2021	<p>Type of study: RCT;</p>	Asymptomatic COVID-19 subjects who had a positive PCR screening	Ivermectine	Standard of care	<p>Length of follow up: 10 days</p>	<p>Clinical outcomes Mortality (28-30 day)</p>	<p>Definitions: -</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> Sept – Nov 2020;</p> <p><u>Country:</u> Lebanon</p> <p><u>Source of funding:</u> "This research received no external funding."</p> <p><u>Conflicts of interest:</u> "The authors declare no conflict of interest."</p>	<p>test 5 days after having come in contact with suspected or positive cases</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • adult subjects • weight ≥ 45 kg • SARS-CoV-2-positive based on a PCR result showing a Ct value < 20. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • lactating or pregnant ladies, • history of allergy to a component of the used medication, • end-stage kidney or liver diseases, • pulmonary fibrosis, • advanced COPD, • heart failure NYHA class IV, • recent cardiac intervention (less than two months). <p><u>N total at baseline:</u> N = 100 Intervention: 50 Control: 50</p> <p><u>Important characteristics:</u> Age, mean (SD): I: .31.78 (7.85) C: 31.58 (7.68) Sex, n/N (%) male: I: 25 (50%) C: 25 (50%) Disease severity, mean (SD): Not explicitly reported, but group described as 'asymptomatic' at inclusion.</p>	<p>Single dose; Depending on body weight: 45–64 kg, 65–84 kg, or above 85 kg received (PO) 9 mg, 12 mg, or 150 µg/kg body weight respectively</p>	<p>Zinc (30–50 mg/day) and Vitamin C (500 mg, twice daily) supplements</p>	<p>(symptoms reported after 72h, viral cycle threshold reported at day zero and day three)</p> <p><u>Loss to follow-up:</u> No loss to follow-up reported</p>	<p>not reported</p> <p><u>Duration of hospitalization</u> Hospitalization, within 72h after treatment I: 0 (0%) C: 3 (6%) , p= 0.079</p> <p><u>Time to symptom resolution</u> Symptoms reported after 72h of treatment; n (%)</p> <p>Fever I: 1 (2%), C: 11 (22%), p= 0.002</p> <p>Cough I: 2 (4%) C: 5 (10%), p= 0.240</p> <p>Runny Nose I: 1 (2%) C: 2 (4%) , p= 0.558</p> <p>Headache I: 2 (4%) C: 5 (10%), p= 0.240</p> <p>Anosmia I: 3 (6%) C: 16 (32%) , p= 0.001</p> <p>Myalgia I: 0 (0%) C: 9 (18%) , p= 0.002</p> <p>Loss of Taste I: 3 (6%) C: 12 (24%) , p= 0.012</p> <p>Fatigue I: 0 (0%) C: 3 (6%), p= 0.079</p> <p>Dizziness I: 0 (0%) C: 2 (4%) , p= 0.153</p> <p><u>Respiratory support</u> not reported</p>	<p><u>Remarks:</u> -details of methods (concealment of randomization, procedures, blinding, planned analysis) missing</p> <p><u>Authors conclusion:</u> "Ivermectin appears to be efficacious in providing clinical benefits in a randomized treatment of asymptomatic SARS-CoV-2-positive subjects, effectively resulting in fewer symptoms, lower viral load and reduced hospital admissions. However, larger-scale trials are warranted for this conclusion to be further cemented."</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline, except for comorbidity hyperuricemia (0 (0%) in control group, 3 (6%) in intervention group)				Safety <u>Adverse events</u> not reported Virological outcomes <u>Viral clearance</u> Ct-value; Day zero I: 15.13 (2.07) C: 14.20 (2.48) P= 0.058 Ct-value; Day three I: 30.14 (6.22) C: 18.96 (3.26) P <0.001	
Krolewiecki, 2021	<p>Type of study: Pilot, multicenter, randomized, open label, outcome assessor blinded, controlled study.</p> <p>Setting: The trial was done at 4 hospitals in the metropolitan area of Buenos Aires.</p> <p>Country: Argentina.</p> <p>Source of funding: This work was supported by grant IP-COVID-19-625 from Agencia Nacional de Promocion de la Investigaci on, el Desarrollo Tecnol ogico y la Innovacion, Argentina and</p>	<p>Hospitalized patients with COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Aged 18 to 69 years-old; • RT-PCR confirmed infection; • Hospitalized and not requiring intensive care; • COVID-19 symptoms onset 5 days at recruitment; • Absence of use of drugs with potential activity against SARS-CoV-2 (hydroxychloroquine, lopinavir, remdesivir and azithromycin); and those drugs were not permitted during the first week of the trial. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • The use of immunomodulators within 30 days of recruitment; • Pregnancy; • Breast feeding; • Poorly controlled comorbidities. • Patients of child-bearing age (men and women) were eligible if agreed to take effective 	<p>Oral Ivermectin</p> <p>Patients in the IVM group received oral treatment for 5 consecutive days with either breakfast or lunch at approximately 24 h intervals. IVM 6 mg ranurated tablets (IVER P, Laboratorios Elea/ Phoenix, Argentina) were used in all cases at a dose of 600 mg/kg/day based on baseline weight rounding to the lower full (6 mg) and half (3 mg) dose.</p>	<p>No treatment</p> <p>All patients in both groups received standard of care which at that moment in the study area included hospitalization of all symptomatic cases → not further specified.</p>	<p>Length of follow-up: 30 days</p> <p>Loss-to-follow-up: Intervention: N=1 (3.7%) Reasons: missed visit on day-30.</p> <p>N=2 withdrew consent (excluded from efficacy analysis).</p> <p>Control: N=1 (6.7%) Reasons: discontinued on day-5 (administration of medication not allowed) (included in the efficacy analysis).</p> <p>Incomplete outcome data: Intervention: None.</p>	<p>Clinical outcomes <u>Mortality (28-30 day)</u> 0</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u> not reported</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Patients with adverse events</u> I:13/30 (43%) C: 5/15 (33.3%)</p> <p><u>Patients with possible/probable related AEs</u> I: 9/30 (30%) C: NA</p> <p><u>Serious adverse event</u> I: 1/30 ((3.3%) C: 0/15 (0%)</p>	<p>Definitions: -</p> <p>Remarks: The most frequent adverse event and the only experienced by more than 1 case in the IVM group was rash in 3 (10%) cases (all mild, selflimited and lasting approximately 24 h); in the control group, single events of abdominal pain, dizziness, anxiety, anguish, and hyperglycemia (all mild) were reported.</p> <p>The sponsors of the study participated in study design, but had no role in primary data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.</p> <p>Authors conclusion: In summary, our findings support the hypothesis that IVM has a concentration dependent antiviral activity against SARS-CoV-2 and provides insights into the type of evaluations to be considered in the assessment of antiviral drugs for the</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Laboratorio ELEA/Phoenix, Argentina.</p> <p><u>Conflicts of interest:</u> All other authors declare no competing interests.</p> <p>ClinicalTrials.gov: NCT04381884</p>	<p>contraceptive measures during the study period and for at least 30 days after the last study drug administration.</p> <p><u>N total at baseline:</u> N = 45 Intervention: 30 Control: 15</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 42.3 y (12.8) C: 38.1 y (11.7) P=0.29</p> <p>Sex, n/N (%) male: I: 15/30 (50%) C: 10/15 (66.7%) P=0.29</p> <p>Disease severity, mean (SD): <i>Defined by WHO-ordinal scale</i> 3: hospitalized, no oxygen therapy I: 29/30 (97%) C: 13/29 (87%) P=0.20</p> <p>4: oxygen by mask or nasal prongs I: 14/30 (47%) C: 6/15 (40%) P=0.20</p> <p>Groups comparable at baseline? Yes.</p>				<p><u>Patients with possible/probable serious adverse event</u> I: 1/30 ((3.3%) C: 0/15 (0%)</p> <p><u>Number of adverse events</u> I: N=17 C: N=5</p> <p><u>Number of AEs grade 3/4</u> I: N=3 (includes the SAE hyponatremia) and ALT and AST elevation, both in the same patient. C: N=0</p> <p><u>Virological outcomes</u> <u>Viral load</u> <i>Values under the limit of quantification of 10 copies/reaction at day 5</i> I: 6/20 (30%) C: 1/12 (8.3%)</p> <p>Subgroup analysis >160 ng/ml versus <160 ng/ml <i>Median Cmax</i> >160 ng/ml: 202 ng/ml (IQR 167 to 268) <160 ng/ml: 109 ng/ml (IQR 91 to 141) P<0.0001</p> <p><i>Proportion of subjects achieving viral load values under the limit of quantification at day 5</i> I: >160 ng/ml: 5/9 (55.6%) I: <160 ng/ml: 1/11 (9.1%) C: 1/12 (8.3%)</p>	control of COVID-19. Follow-up trials to confirm our findings and to identify the clinical utility of IVM in COVID-19 are warranted.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Viral decay rate in treated patients with IVM plasma levels</i></p> <p>>160 ng/ml: median 0.64 d⁻¹</p> <p><160 ng/ml: 0.14 d⁻¹</p> <p>C: 0.13 d⁻¹</p> <p>P=0.04</p>	
Mahmud (2021)	See evidence table of Mahmud (2021) by doxycycline.						
Shahbaznejad, 2021	<p>Type of study: RCT; double-blind</p> <p>Setting: 2 referral tertiary hospitals</p> <p>Country: Iran</p> <p>Source of funding: Not reported</p> <p>Conflicts of interest: "The authors have indicated that they have no conflicts of interest with regard to the content of this article."</p>	<p>Hospitalized COVID-19 patients, children and adult, with</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age > 5 years • weight > 15 kg • hospitalized • COVID-19 diagnosis, by any of the following: (1) positive result on COVID-19 reverse-transcription polymerase chain reaction; (2) clinical symptoms of COVID-19, with a history of contact with a patient with COVID-19; and/or (3) abnormalities on chest computed tomography (CT) compatible with COVID-19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration). <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • history of chronic liver and/or renal disease; • receipt of treatment with warfarin, an angiotensin-converting enzyme inhibitor, or a angiotensin II receptor antagonist; • acquired immunodeficiency 	<p>Ivermectin</p> <p>single oral dose (0.2 mg/kg) of ivermectin utilizing 3-mg oral tablets,*or a multiple thereof,17 on the first day of admission, at the following weight-based doses: 15 to 24 kg, 3 mg; 25 to 30 kg, 6 mg; 36 to 50 kg, 9 mg; 51 to 80 kg, 12 mg; and > 80 kg, 0.2 mg/kg</p> <p>All of the participants received appropriate antibiotics and/or supplemental oxygen as indicated.</p>	<p>Standard of care</p> <p>= supportive medical treatment for COVID-19 according to the national protocols of Iran at the time of this study (including hydroxychloroquine and/or lopinavir/ritonavir)</p> <p>All of the participants received appropriate antibiotics and/or supplemental oxygen as indicated.</p>	<p>Length of follow up: 7 days</p> <p>Loss to follow-up: I: 0/0 (0%) Reasons: - C: 4/38 (10.5%) Reasons: 'withdrawn'</p>	<p>Clinical outcomes Mortality (28-30 day) Not reported; sample size reported to be too small <i>"In the ivermectin group, a 78-year-old woman with a history of diabetes mellitus and heart failure died. She was critically ill at the time of admission and died within the first 24 hours."</i></p> <p>Duration of hospitalization Duration of hospital stay I: 7.1 (0.5) (95% CI 6.1–8.1) C: 8.4 (0.6) (95% CI 7.2–9.5), p= 0.016</p> <p>Time to symptom resolution Clinical improvement* after baseline, Duration of symptoms I: 4.2 (0.3) (95% CI 3.6–4.8) C: 5.2 (0.3) (95% CI 4.6–5.8), p= 0.023</p> <p><i>Also reported: duration of separate symptoms, such as fever, chills, cough.</i></p>	<p>Definitions: Clinical improvement: defined as resolving a patient's baseline status on persistent and continuous cough (persistent cough for > 1 hour, or ≥3 coughing episodes in 24 hours, that interferes with activities of daily living and the ability to work) and tachypnea in addition to increasing oxygen saturation to > 94%.</p> <p>Remarks:</p> <ul style="list-style-type: none"> • procedures, concealment of randomization sequence, blinding not clearly described • Results inconsistent between text and table <p>Authors conclusion: "A single dose of ivermectin was well-tolerated in symptomatic patients with COVID-19, and important clinical features of COVID-19 were improved with ivermectin use, including dyspnea, cough, and lymphopenia. Further studies with larger sample sizes, different drug dosages, dosing intervals and durations, especially in different stages of the disease, may be useful in understanding the potential clinical benefits ivermectin."</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> pregnant or breast-feeding <p><u>N total at baseline:</u> Randomized: N = 69 Intervention: 35 Control: 38 Included in analysis: I: 35 C: 34</p> <p><u>Important characteristics:</u> Age, mean \pmSD (min, max): I: 47.63 \pm22.20 (5.5, 85.0) 45.18 \pm23.11 (5.0, 86.0) Sex, n/N (%): male: I: 18 (51.4) C: 18 (52.9) Disease severity, mean (SD): <i>Need Ventilator</i> I: 2 (5.7) C: 1 (2.9), p= 1 <i>Severe COVID-19</i> I: 13 (37.1) C: 18 (52.9), p= 0.19</p> <p>Duration of symptoms before admission (days), mean \pmSD (Min, Max) I: 6.21 \pm3.60 (1, 15) C: 6.38 \pm2.86 (2, 15), p= 0.72</p> <p>Groups comparable at baseline? Yes, except for loss of appetite, insomnia, rales and arthralgia, which occurred more often in intervention group)</p>				<p><u>Respiratory support</u> Oxygen needed I: 10/35 (28.6%) C: 9/34 (26.5%) P=0.84 Invasive mechanical ventilation needed I: 2/35 C: 1/34</p> <p>Safety <u>Adverse events</u> I: 0 C: 0 "No potential adverse events, including wheezing, itching, skin rash, edema, hypotension or liver toxicity were observed in the patients of either group"</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p> <p><i>Also reported: laboratory test results at baseline and at admission day 2.</i></p>	
Okumuş, 2021	<p><u>Type of study:</u> Quasi-RCT; single-blind</p> <p><u>Setting:</u></p>	Hospitalized severely ill COVID-19 patients with pneumonia, without SNP mutation in MDR-1/ABCB1 gene and/or haplotypes and mutations of the CYP3A4 gene	Ivermectin + standard of care Ivermectin treatment in the	Standard of care hydroxychloroquine (2x400mg loading dose)	<u>Length of follow up:</u> 10 days (assessment after 5 days of treatment and 5 additional days of follow-up)	<p>Clinical outcomes <u>Mortality (28-30 day)</u> not reported <u>Mortality (average of 3 month FU)</u> I: 6/30 (20%)</p>	<p><u>Definitions:</u> * Clinical improvement: extubation in mechanically ventilated patients, respiratory rate < 26, SpO2 level in room air > 90%, PaO2 / FiO2 > 300 in patients receiving oxygen, presence of</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>May 2020 September 2020; 4 different tertiary referred Research and Education Hospital.</p> <p><u>Country:</u> Turkey</p> <p><u>Source of funding:</u> Afyonkarahisar Health Science University Scientific Research project Coordination Unit Project.</p> <p><u>Conflicts of interest:</u> "The authors declare that they have neither financial nor non-financial competing interests."</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> hospitalized pre-diagnosis of severe pneumonia (one of the following: a. Presence of tachypnea ≥ 30/min, peripheral capillary oxygen saturation (SpO₂) level < 90% in room air, Partial pressure of oxygen (PaO₂)/FiO₂ < 300 in oxygen receiving patient; b. Presence of specific radiological finding for Covid-19 in lung tomography (bilateral lobular, peripherally located, diffuse patchy ground glass opacities); c. Mechanical ventilation requirement; d. Acute organ dysfunction findings; patients with SOFA (sepsis-related organ failure assessment) score > 2) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Children < 18 years old, pregnancy, active breast feeding, concurrent autoimmune disease, chronic liver or kidney disease, immunosuppression, SNP mutation in MDR-1/ABCB1 gene and/or haplotypes and mutations of the CYP3A4 gene <p><u>N total at baseline:</u> N = 66 Intervention: 36 (30 patients without mutations included in analysis)</p>	<p>form of a solution prepared for enteral use at 200 microgr/ kg/day (9 mg between 36 and 50 kg, 12 mg between 51 and 65 kg, 15 mg between 66 and 79 kg and 200 microgram/kg in > 80 kg) for 5 days (Ivermectin 5 mg/5 ml solution was manufactured by NEUTECT[™] Pharmaceutical Company-Turkey)</p>	<p>followed by 2x200mg, po, 5 days), favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, po, total 5 days) and azithromycin (500 mg first day loading dose, followed by 250 mg/day, po, total 5 days) (HFA),</p>	<p><u>Loss to follow-up:</u> I: n/N (%) Reasons: C: n/N (%) Reasons:</p>	<p>C: 9/30 (30%) P=0.37</p> <p><u>Duration of hospitalization</u> Not reported</p> <p><u>Time to symptom resolution</u> <u>Clinical improvement*</u> Day 5 I: 14/30 (46.7%) C: 11/30 (36.7%) P=0.43 Day 10 I: 22/30 (73.3%) C: 16/30 (53.3%) P=0.10 <i>SOFA score – no data provided</i> "When the mean SOFA scores before treatment and at the end of the follow-up period were compared, a significant decrease was found in the study group (p =0.009), while an increase was found in the control group (p = 0.88). When the SOFA scores of both groups were compared at the end of the follow-up period, no significant difference was found between them (p = 0.50)."</p> <p><u>Respiratory support</u> Reported: SpO₂ values at day 5 and 10; PaO₂/FiO₂ ratios; Laboratory parameter changes</p>	<p>at least two of the 2-point reduction criteria in SOFA-score [inconsistent definition in paper for 5-day and 10-day outcome]</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Quasi-randomized controlled trial Main aim of study (<i>investigate the effectiveness of adding ivermectin to the treatment in patients with severe COVID-19 pneumonia</i>) does not fit inclusion/exclusion criteria; study focussed on individuals without mutations 16.7% of patients were excluded from the intervention group after the first dose of ivermectin, as de result of the genetic assessment became available. Short follow-up time (5 days) Inconsistency in definition of 'clinical response/improvement' at day 5 (primary outcome) and 10 after treatment (secondary outcome) Frequency of other medication (hydroxychloroquine, favipiravir, azithromycin) in standard of care not reported <p><u>Authors conclusion:</u> "According to the findings obtained, ivermectin can provide an increase in clinical recovery, improvement in prognostic laboratory parameters and a decrease in mortality rates even when used in patients with severe COVID-19. Consequently, ivermectin should be considered as an alternative drug that can be used in the treatment of COVID-19 disease or as an additional option to existing protocols."</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Control: 30 <u>Important characteristics:</u> Age, mean (SD): I: 58.17 ± 11.52 C: 66.23 ± 13.31 Sex, n/N (%) male: I: 21/30 (70) C: 19/30 (63.3) Disease severity, mean (SD): SOFA score (mean) I: 3.12 ± 1.9 C: 2.83 ± 2.1 P=0.36 Mechanic ventilation requirement, n (%) I: 1 (3.3) C: 1 (3.3) P=0.98 Groups comparable at baseline.				Safety <u>Adverse events – no data reported</u> <i>"In our study, no different side effects were observed in patients receiving ivermectin compared to patients receiving standard therapy."</i> <i>Reported: genetic examination and side effects in excluded patients with mutations (n=6) who received a single dose of ivermectin</i> Virological outcomes <u>Viral clearance – only available for sub-set, for 57.1% of intervention group and 26.7% in control group); negative RT-PCR at end of study period (10 days?)</u> I: 14/16 (87.5%) C: 3/8 (37.5%) P=0.01	
López-Medina, 2021	<u>Type of study:</u> RCT Double-blind, randomized trial <u>Setting:</u> Centro de Estudios en Infectología Pediátrica in Cali, from July 15 to December 21, 2020. <u>Country:</u> Colombia	COVID patients with mild disease (i.e., being at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or noninvasive) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> positive result from a SARS-CoV-2 reverse transcriptase–polymerase chain reaction or antigen test adult men and non–pregnant or breast-feeding women 	<u>ivermectin</u> 300 µg/kg of body weight per day of oral ivermectin in solution or the same volume of placebo for 5 days. Ivermectin was provided by Tecnoquímicas SA in bottles of 0.6% solution for oral administration. Patients were asked to take the investigational product on	<u>placebo</u> up to August 26, 2020, the placebo was a mixture of 5% dextrose in saline and 5% dextrose in distilled water, after which placebo was a solution with similar organoleptic properties to	<u>Length of follow up:</u> 21 days <u>Loss to follow-up:</u> 476 patients underwent randomization: 238 randomized to ivermectin, 238 randomized to placebo. I: 38/238 (16.0%) Reasons: Excluded from primary analysis	Clinical outcomes <u>Mortality, n (%)</u> I: 0 (0%) C: 1 (0.5%) <u>Duration of hospitalization</u> Not reported. <u>Symptom resolution</u> (defined as complete resolution of symptoms within the 21-day follow-up period; use of 8-category ordinal scale*)	<u>Definitions:</u> *8-category ordinal scale: 0 = no clinical evidence of infection; 1 = not hospitalized and no limitation of activities; 2 = not hospitalized, with limitation of activities, home oxygen requirement, or both; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, requiring nasal high-flow oxygen, noninvasive mechanical ventilation, or both; 6 = hospitalized, requiring extracorporeal membrane

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	<p><u>Source of funding:</u> -This study received an unrestricted grant from Centro de Estudios en Infectología Pediátrica (grant ScDi823). -Dr López-Medina reported receiving grants from Sanofi Pasteur, GlaxoSmithKline, and Janssen and personal fees from Sanofi Pasteur during the conduct of the study. Dr López reported receiving grants from Sanofi Pasteur, GlaxoSmithKline, and Janssen and personal fees from Sanofi Pasteur during the conduct of the study. Dr Oñate reported receiving grants from Janssen and personal fees from Merck Sharp & Dohme and Gilead outside the submitted work. Dr Torres reported receiving nonfinancial</p>	<ul style="list-style-type: none"> symptoms began within the previous 7 days mild disease <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> asymptomatic severe pneumonia received ivermectin within the previous 5 days hepatic dysfunction or liver function test results more than 1.5 times the normal level <p><u>N total at baseline:</u> N = 389 Intervention: 200 Control: 198</p> <p><u>Important characteristics:</u> Age, median (IQR), y: I: 37 y (29-47.7) C: 37 y (28.7-49.2)) Sex, n/N (%): I: 78/200 (39%) C: 89/198 (44.9%) Disease severity, n/N (%): <i>Defined by score at ordinal scale at randomization</i> 1: Not hospitalized and no limitation of activities I: 123/200 (61.5%) C: 109/198 (55.0%) 2: Not hospitalized, with limitation of activities, home oxygen requirement, or both I: 75/200 (37.5%) C: 87/198 (43.9%) 3: Hospitalized, not requiring supplemental oxygen I: 1/200 (0.5%) C: 1/198 (0.5%)</p>	<p>an empty stomach, except on the first study day, when it was administered after screening and randomization procedures took place.</p>	<p>ivermectin provided by the manufacturer.</p>	<p>due to error in labeling from September 29 to October 15, 2020 C: 40/238 (16.8%) Reasons: Error in labeling from September 29 to October 15, 2020 (including 1 who met exclusion criteria identified after randomization)</p>	<p>Time to resolution of symptoms, median, no. of days (IQR) I: 10 (9-13) C: 12 (9-13) Absolute difference (95% CI): -2 (-4 to 2); HR 1.07 (95% CI 0.87 to 1.32), p=.53 Symptoms resolved at 21 d, n/N (%) I: 164/200 (82.0%) C: 156/198 (79.0%) Absolute difference (95% CI): 3.21 (-4.58 to 11.01); OR 1.23 (95% CI 0.75 to 2.01)</p> <p><u>Need for respiratory support, n/N (%)</u> Defined as escalation of care since randomization: i.e., new-onset hospitalization in the general ward or intensive care unit or new-onset supplementary oxygen requirement for more than 24 hours. I: 4/200 (2.0%) C: 10/198 (5.0%) Absolute difference (95% CI): -3.05 (-6.67 to 0.56); OR 0.38 (95% CI 0.12 to 1.24)</p> <p>Safety <u>Adverse events</u> No. of patients with ≥1 serious adverse events I: 2/200 (1.0%) C: 2/198 (1.0%)</p>	<p>oxygenation, invasive mechanical ventilation, or both; and 7 = death.</p> <p>Time to recovery was defined as the first day during the 21 days of follow-up in which the patient reported a score of 0.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> The primary outcome was originally defined as the time from randomization until worsening by 2 points on the 8-category ordinal scale. Before the interim analysis, it became apparent that the pooled event rate of worsening by 2 points was substantially lower than the initial 18% expectation, requiring an unattainable sample size. Therefore, on August 31, 2020, the principal investigator proposed to the data and safety monitoring board to modify the primary end point to time from randomization to complete resolution of symptoms within the 21-day follow-up period. <p>Deterioration by ≥2 points in an ordinal 8-point scale was reported as a secondary outcome in the paper.</p> <ul style="list-style-type: none"> The study population was relatively young, with few comorbidities and with liver enzyme levels less than 1.5 times the normal level, so the findings may be generalizable only to such populations. <p><u>Authors conclusion:</u> Among adults with mild COVID-19, a 5-day course of ivermectin initiated in the first 7 days after evidence of infection, compared with placebo, did not</p>

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	support from Tecnoquímicas unrelated to this project during the conduct of the study.	<p>4: Hospitalized, requiring supplemental oxygen (i.e., not high-flow nasal oxygen nor mechanical ventilation) I: 1/200 (0.5%) C: 1/198 (0.5%)</p> <p>Groups comparable at baseline? Patients in both groups were balanced in demographic and disease characteristics at baseline.</p>				<p>Virological outcomes <u>Viral clearance</u> Not reported.</p> <p><u>Also available:</u> Secondary outcomes included the proportion of patients with clinical deterioration, defined as those with worsening by 2 points (from the baseline score on the 8-category ordinal scale) since randomization.</p> <p>Additional secondary outcomes were the clinical conditions as assessed by the 8-category ordinal scale on days 2, 5, 8, 11, 15, and 21; however, data for days 2 and 15 are not reported here. The proportion of patients who developed fever and the duration of fever since randomization were also reported.</p> <p>Frequency of incident cases of escalation of care, as well as the duration in both treatment groups, was reported. Evaluation of adverse events (AEs) included solicited AEs, AEs leading to treatment discontinuation, and serious AEs.</p>	significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.

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Babalola, 2021	<p><u>Type of study:</u> RCT Proof of Concept (PoC), double blind, randomized controlled trial, of a parallel group, dose-response design</p> <p><u>Setting:</u> Lagos University Teaching Hospital, between May and November 2020</p> <p><u>Country:</u> Nigeria</p> <p><u>Source of funding:</u> Not reported</p>	<p>Nigerian COVID 19 patients with RT- PCR proven SARS-CoV-2 positivity</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • COVID 19 PCR proven positive patients • either asymptomatic or had mild/moderate symptoms <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • COVID 19 negative patients • patients who had COVID pneumonia • requiring ventilator therapy • renal failure • thromboembolic complications • unconscious by reduced Glasgow Coma Scale <p><u>N total at baseline:</u> N = 62 I 6 mg: n=21 I 12 mg: n=21 Control: n=20</p> <p><u>Important characteristics:</u> Age, mean (SD): I 6mg: 48.3 y (not reported) I 12mg: 39.7 y (not reported) C: 44.1 y (14.7) Sex, n/N (%) male: I 6mg: 15/21 (71.4%) I 12 mg: 14/21 (66.7%) C: 14/20 (70%) Supplemental oxygen use, n/N (%) I 6mg: 0/21 (0%) I 12mg: 3/21 (14.3%) C: 2/20 (10%)</p> <p>Groups comparable at baseline?</p>	<p><u>Ivermectin 6mg</u> given every 84 hours) twice a week</p> <p><u>Ivermectin 12mg</u> (given every 84 hours) for 2 weeks</p>	<p><u>lopinavir / ritonavir</u> (standard of care) daily for 2 weeks plus placebo</p>	<p><u>Length of follow up:</u> Not reported.</p> <p><u>Loss to follow-up:</u> One withdrawal, reason or arm of the study not reported.</p>	<p><u>Number of Days-to-Negative (DTN) of the PCR test, mean, SD, 95% CI</u> I 6mg: 6.0 ± 2.96, 95% CI 4.61 - 7.38 I 12 mg: 4.65 ± 3.2, 95% CI 3.15- 6.15 I 6mg & 12 mg: 5.33 ± 3.12, 95% CI 4.33-6.32 C: 9.15 ± 7.42, 95% CI 5.68-12.62</p> <ul style="list-style-type: none"> • Average days-to-negative in the combined Ivermectin arms (any Ivermectin) was thus shorter by 3.83 days (95% CI 6.54 to 1.11) compared to controls P=0.0066. (Student t-test) • Mean days-to-negative for the 12mg arm was shortened by 4.5 days, and by 3.15 days for the 6mg arm compared to controls. These differences were significant. <p><u>Treatment effect by RAMOVA</u> (two-way Repeated Measures Analysis of Variance)</p> <p>There was a significant treatment (p=0.035) and time effect (p <0.0001) of Ivermectin on COVID 19 ranked scores compared to controls. The likelihood of negativity by day five was explored.</p>	<p><u>Remarks:</u> Sixty-three patients were randomised, there was one withdrawal. No baseline characteristics or results were reported of this patient.</p> <p><u>Authors conclusion:</u> In conclusion, Ivermectin exhibited a dose-dependent significant inhibitory effect on SARSCoV-2. The 12mg twice weekly regime appears to confer a superior efficacy. Ivermectin modified prognostic factors such as arterial oxygenation and platelet and hematological indices of SARS-CoV-2 infections.</p> <p>Ivermectin should be considered for use in clinical management of SARS-Cov-2.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		There was no significant difference in the distribution of the age, sex and symptoms, comorbidities, blood counts, prothrombin time, liver function and kidney function tests. There were however slight differences in the baseline Cycle threshold (Ct) values, being lower in the 6mg Ivermectin arm than the other two arms with regards to the ORF and N genes, but similar for the EN gene. The distribution of other supplemental medications taken by participants, aside from Ivermectin, was broadly similar. These included Zinc, ascorbic acid, vitamin D and Azithromycin.				The Ivermectin arm was 3.45 times more likely to go negative by or before day five, P=0.0271, 95% CI 1.12-10.63. This effect is slightly mitigated by sex (adjusted OR 3.44 P>z 0.031 CI= 1.12 -10.6) but more significantly by age (OR 2.77 P>z 0.113 CI= 0.79 to 9.8). <u>Also available:</u> Secondary outcome measures were change in clinical status, change in SPO2, change in Liver Function Tests (LFT), change in Kidney Function Tests (KFT) and change in rheological variables like platelet count and Prothrombin time.	
Chaccour, 2020	<u>Type of study:</u> RCT; pilot, double-blind, placebo-controlled <u>Setting:</u> ER of the Clínica Universidad de Navarra; July 31, 2020 - Sept 11, 2020 <u>Country:</u> Spain <u>Source of funding:</u> Funding: ISGlobal, Barcelona Institute for Global Health	<u>Outpatients attending ER with symptoms compatible with COVID-19</u> <u>Inclusion criteria:</u> • symptoms compatible with COVID-19 • 18-60y of age • Resident of Pamplona basin • ≤72 h of fever or cough • positive PCR for SARS-CoV-2 <u>Exclusion criteria:</u> • positive IgG against SARS-CoV-2 • comorbidities considered risk factors for severe disease • COVID-19 pneumonia, as diagnosed by the attending	Ivermectine (400 mcg/kg) single oral dose or placebo Protocol: The dose of ivermectin will be given using scales for tailored administration. Given that dosing is limited by the size of the tablet (3mg) the participants will receive a discrete number of tablets according to their weight band as shown in Table 1 . The individual dose will range from 400 mcg/kg to a maximum of 457 mcg/kg.	Placebo	<u>Length of follow up:</u> 28 days <u>Loss to follow-up:</u> I: 0 C: 0 <u>Missing data:</u> Carried over from last observation; seems to concern mostly symptom data; unclear which data and whether proportions were similar between groups	Clinical outcomes <u>Symptoms</u> Reported in supplement for day 1, 7, 14; described in publication: <i>“There were no major differences in the evolution of vital signs (Table S3), inflammatory markers (C reactive protein, procalcitonin, ferritin and IL-6) and rest of laboratory parameters of patients in each group (Table S4)”</i> <u>Progression to severe disease or death during the trial</u> I: 0/12	<u>Remarks:</u> • Relatively young patients (range 18-54y) • “In the analysis of the symptoms reported by patients (symptom diary), missing data was carried over from the last data available.” • More females in intervention group <u>Authors conclusion:</u> <i>“Among patients with non-severe COVID-19 and no risk factors for severe disease receiving a single 400 mcg/kg dose of ivermectin within 72 h of fever or cough onset there was no difference in the proportion of PCR positives. There was however a marked reduction of self-reported anosmia/ hyposmia, a reduction of cough and a tendency to</i>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments																																								
	and Clínica Universidad de Navarra; "JLDP reports speaker fees from Pfizer and MSD as well as research grants from Novartis, outside the scope of the submitted work. No other competing interests were disclosed"	<p>physician and identified in a chest X-ray</p> <ul style="list-style-type: none"> Known history of ivermectin allergy Hypersensitivity to any component of ivermectin Recent travel history to countries that are endemic for <i>Loa loa</i> Current use of CYP 3A4 or P-gp inhibitor drugs <p><u>N total at baseline:</u> N = 24 Intervention: 12 Control: 12</p> <p><u>Important characteristics:</u> Age, median (IQR)[range] (years) I: 26 (19-36) [18-54] C: 26 (21-44) [18-54] Sex, n/N (%) male: I: 7 (58%) C: 5 (42%) BMI, median (IQR) [range] kg/m² I: 23.5 (19.6-27.8) [18.6-29.9] C: 22.9 (21.0-24.8) [19.3-29.9]</p> <p>Also reported: Symptoms, vital signs, viral load, inflammatory markers</p> <p>Groups comparable at baseline? More females in intervention group.</p>	<table border="1"> <thead> <tr> <th>Weight in kg</th> <th>Number of 3 mg tablets</th> <th>Total dose in mg</th> <th>Dose range</th> </tr> </thead> <tbody> <tr> <td>45</td> <td>6</td> <td>18</td> <td>400</td> </tr> <tr> <td>46-52</td> <td>7</td> <td>21</td> <td>404-457</td> </tr> <tr> <td>53-60</td> <td>8</td> <td>24</td> <td>400-453</td> </tr> <tr> <td>61-67</td> <td>9</td> <td>27</td> <td>403-443</td> </tr> <tr> <td>68-75</td> <td>10</td> <td>30</td> <td>400-441</td> </tr> <tr> <td>76-82</td> <td>11</td> <td>33</td> <td>402-434</td> </tr> <tr> <td>83-90</td> <td>12</td> <td>36</td> <td>400-434</td> </tr> <tr> <td>91-97</td> <td>13</td> <td>39</td> <td>402-429</td> </tr> <tr> <td>98-100</td> <td>14</td> <td>42</td> <td>420-429</td> </tr> </tbody> </table> <p>Table 1. Discrete doses of ivermectin based on tablet size and weight</p>	Weight in kg	Number of 3 mg tablets	Total dose in mg	Dose range	45	6	18	400	46-52	7	21	404-457	53-60	8	24	400-453	61-67	9	27	403-443	68-75	10	30	400-441	76-82	11	33	402-434	83-90	12	36	400-434	91-97	13	39	402-429	98-100	14	42	420-429			<p>C: 0/12</p> <p>Safety <u>adverse events</u> Total number AE /patients I: 7/12 C: 8/12 Total patients experiencing AE I: 5/12 C: 5/12</p> <p>Viral outcomes <u>Detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swab</u> at day 7 post-treatment Gene E I: 12/12 (100%) C: 12/12 (100%) Gene N: I: 11/12 (91%) C: 12/12 (100%) RR 0.92 (95%CI 0.77 to 10.09) <u>Viral load</u></p> <p><u>Viral load (gene E)</u> day 1 I: 1.7-10⁷ (5.9-10⁶ - 3.9-10⁸) C: 2.7-10⁷ (8.3-10⁵ - 4.2-10⁸) day 4 I: 1.6-10⁵ (2820-8.8-10⁵) C: 4.9-10⁵ (1.0-10⁵ - 9.9-10⁶) day 7 I: 1018 (92-15445) C: 23550 (709-2.3-10⁵) day 14 I: 7 (0- 42) C: 30 (1- 50)</p>	lower viral loads and lower IgG titers which warrants assessment in larger trials."
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						<p>day 21 I: 1 (0- 9) C: 0 (0- 16)</p> <p><u>Viral load (gene N)</u> day 1 I: 3.7·108 (1.8·107 - 9.3·109) C: 3.3·108 (5.8·107 - 6.7·109) day 4 I: 2.7·105 (1885-1.0·106) C: 2.2·106 (73150-3.7·107) day 7 I: 2255 (938-34650) C: 36800 (4510-6.3·105) day 14 I: 86 (0- 1235) C: 75 (24- 710) day 21 I: 0 (0- 67) C: 107 (0- 183)</p> <p><i>Also reported: cycles threshold for gene E & Gene N on day 1, 4, 7, 14 and 21.</i></p> <p><u>Proportion of patients with seroconversion</u>, (negative to positive condition) at day 21 I: 12/12 C: 12/12 <u>IgG titer:</u> I: Index 4·7, IQR [3·5–8·9] C: Index 7·5, IQR [4·2–9·3]</p>	
Ahmed, 2020	<u>Type of study:</u> RCT [pilot, double-blind, placebo-controlled]	Hospitalized COVID-19 patients; disease severity unclear <u>Inclusion criteria:</u>	Ivermectine or in combination with doxycycline	Placebo	<u>Length of follow up:</u> 14 days days	Viral outcomes <u>Time for virological clearance (a negative rRT-</u>	<u>Remarks:</u> <ul style="list-style-type: none"> • No baseline data per group provided • No information about disease severity provided.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> single</p> <p><u>Country:</u> Bangladesh</p> <p><u>Source of funding:</u> "this work was supported by the Beximco Pharmaceutical Limited, Bangladesh"</p>	<ul style="list-style-type: none"> age 18-65 years admitted to hospital within the last 7 days either fever ($\geq 37.5^{\circ}\text{C}$); cough or sore throat diagnosed positive for SARS-CoV-2 by rRT-PCR <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> allergic to or had a potential drug-drug interaction for ivermectin or doxycycline chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); received ivermectin and/or doxycycline in the last 7 days; pregnant or lactating; participated in any other clinical trial within last month. <p><u>N total at baseline:</u> N = 72 Intervention-I: 23 Intervention-II: 23 Control: 23</p> <p><u>Important characteristics, total group:</u> Age, mean (SD): 42 years Sex, female (%): 54% Time ill before assessment, mean: 3.83 days</p> <p>Fever at enrolment, n/N (%): I: 1/22 (77.3%) II: 17/23 (73.9%) C: 19/23 (82.6%)</p> <p>Cough at enrolment, n/N (%): I: 18/22 (81.8%)</p>	<p><i>I: oral ivermectin alone (12 mg once daily, for 5 days)</i></p> <p><i>II: oral ivermectin alone in combination with doxycycline (12 mg ivermectin single dose and 200 mg stat doxycycline day-1 followed by 100 mg 12hrly for next 4 days)</i></p>		<p><u>Viral clearance:</u> Nasopharyngeal swabs were obtained to confirm the presence of SARS-CoV-2 using rRT-PCR on the day of enrolment, and then on day 3, 7, and 14. After day 14, patients were followed-up weekly until found test negative.</p> <p><u>Loss to follow-up:</u> I: 2/23 (8.7%) II: 1/23 (4.3%) C: 1/23 (4.3%)</p> <p><i>Reasons: due to family obligations and unwillingness to test further</i></p>	<p><u>PCR result on nasopharyngeal swab), median (CI)</u> I: 9.7 days (CI= 7.8 - 11.8) II: 11.5 days (CI= 9.8 - 13.2) C: 12.7 days (CI= 11.3 - 14.2)</p> <p><u>Day 7</u> I vs. C: HR 4.1 (CI 1.1 - 14.7) II vs. C: HR 2.7 (CI 1.2 - 6.0)</p> <p><u>Day 14</u> I vs. C: HR 2.3 (CI 0.6 - 9.0) II vs. C: HR 1.7 (CI 0.8 - 4.0)</p> <p>Clinical outcomes</p> <p><u>Remission of fever ($\geq 37.5^{\circ}\text{C}$) within 7 days.</u> I: 17/17 (100%) II: 16/17 (94.1%) C: 16/19 (84.2%)</p> <p><u>Remission of cough within 7 days.</u> I: 7/18 (61.1%) II: 7/19 (63.2%) C: 9/15 (40%)</p> <p><u>Remission of sore throat within 7 days.</u> I: 3/4 (75%) II: 1/3 (33%) C: 3/4 (75%)</p> <p><i>Note: Unclear which patients groups were used to calculate these numbers</i></p> <p><u>Failing to maintain an SpO2 >93% despite oxygenation;</u></p>	<ul style="list-style-type: none"> Patients could be hospitalized up to 7 days before enrolment in the study; it was reported that participants were "ill on average 3.83 days before assessment", but no definition of 'ill' was provided. Unclear how missing data were handled and whether analyses were performed according to intention-to-treat protocol The role of funder Beximco Pharmaceutical Limited (BPL) was not described <p><u>Authors conclusion:</u> Although the study sample was too small (n=72) to make any solid conclusions, the results provide evidence of the potential benefit of the early intervention with the drug ivermectin for the treatment of adult patients diagnosed with mild SARS-CoV-2. First, early intervention promoted faster viral clearance during disease onset which might have prevented significant immune-system involvement and speed recovery. Secondly, early intervention reduced the viral load faster, thus may help block disease transmission in the general population. A larger randomized controlled clinical trial of ivermectin treatment appears to be warranted to validate these important findings</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>II: 19/23 (82.6%) C: 15/23 (65.2%)</p> <p>Sore throat at enrolment, n/N (%) I: 4/22 (18.2%) II: 3/23 (13%) C: 4/23 (17.4%)</p> <p>Unclear whether groups were comparable at baseline: <i>"The pre-treatment characteristics (demographics, clinical history, comorbidity and laboratory values) were comparable among the three treatment groups"</i></p> <p>Note: No data per group was provided except for data extracted to this table. Cough (%) at enrolment was 65% in the control group vs. 82% in the intervention groups. It is unclear whether other baseline characteristics differed.</p>				<p><u>& Days on oxygen support:</u> <i>"None of the patient enrolled required oxygen..."</i></p> <p><u>Duration of hospitalization</u> I: 9.6 days (CI= 7.7 - 11.7) II: 10.1 days (CI 8.5 - 11.8) C: 9.7 days (CI 8.1 - 11.0)</p> <p><u>All-cause mortality.</u> Announced in methods, but not reported</p> <p>Safety</p> <p><u>Adverse events</u> <i>"None of the patient enrolled required oxygen or had serious adverse drug events recorded."</i></p> <p><u>Discontinuation of the study drug during the trial</u> Announced in methods, but not reported</p>	
13. Interferon							
13.1. Inhaled IFN-k plus TFF2 (= Interferon kappa + Trefoil factor 2)							
Fu, 2020	<p><u>Type of study:</u> open-label, randomized, clinical trial</p> <p><u>Setting:</u> Shanghai Public Health Clinical Center, between March 23 and May 23 of 2020</p> <p><u>Country:</u> China</p>	<p><u>Inclusion criteria:</u> -hospitalized patients that were positive on RT-PCR for SARS-CoV2 in throat swabs</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • 18 years of age or older; • Written consent for participation; • Male and non-pregnant females; • Peripheral capillary oxygen saturation (SpO2) was > 94% on room air at screening; 	<p><u>Aerosol inhalation treatment+standard care</u> -started from the first day of hospitalization and was administered 6 times every 24 h. -aerosolized substances were made of purified mature IFN-k and TFF2 proteins produced by the Novoprotein company. -both proteins (5 mg TFF2 plus 2 mg IFNk) were dissolved in 5 mL sterilized water, and the</p>	<p><u>Standard care</u> Symptomatic treatment with hydroxychloroquine, antibiotic agents, vasopressors, antifever medicine, vitamin C, immune enhancers, or traditional</p>	<p><u>Length of follow up:</u> all patients were followed up at the infectious disease clinic within 30 days after discharge.</p> <p><u>Loss to follow-up:</u> mentioned but all patients contributed to the outcome measure time of CT imaging improvement.</p>	<p><u>Mortality</u> I: 0/40 C: 0/40</p> <p><u>Time of viral RNA negative conversion for SARS-CoV-2</u> I: Mean, 3.80 days, 95% CI 2.07-5.53 C: 7.40 days, 95% CI 4.57 to 10.23) p = 0.031</p>	<p><u>Authors' conclusion:</u> We found that aerosol inhalation of IFN-k plus TFF2 in combination with standard care is safe and superior to standard care alone in shortening the time up to viral RNA negative conversion in all clinical samples. In addition, the patients in experimental group had a significantly shortened CT imaging improvement time than those in control group.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> -Funding was provided by the National Natural Science Foundation of China, National Major Project for Control and Prevention of Infectious Disease in China, Shanghai Science and Technology Commission, Shanghai Municipal Health Commission. - Jianqing Xu, Xiaoyan Zhang, Weihui Fu, and Songhua Yuan have applied for the patent 202010239633.3 (pending), and the patent PCT/CN2020/082195 (pending) base on these data. All authors reviewed signed the conflict of interest forms.</p>	<ul style="list-style-type: none"> Symptoms of infection include fever, cough, and myalgia, with diarrhea, with the subsequent development of dyspnea or of pneumonia. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> -physician's decision that involvement in the trial was not in the patient's best interest - presence of any condition that would not allow the protocol to be followed safely -known allergy or hypersensitivity to IFN-k and TFF2 -known severe liver disease (e.g., cirrhosis, with an alanine aminotransferase level >5 £ the upper limit of the normal range (9-50 U/L) or an aspartate aminotransferase level >5 £ the upper limit of the normal range (15-40 U/L)); breastfeeding and pregnant patients. <p><u>N total at baseline:</u> N = 80 Intervention: 40 Control: 40</p> <p><u>Important characteristics:</u> <i>Age, mean±SD</i> I: 35.3 (11.25) C: 35.2 (11.3) P=0.91</p> <p><i>Sex, N (%) male</i> I: 26 (65%) C: 25 (62.5%)</p> <p><i>Underlying diseases, N (%)</i></p>	combination aerosol was delivered to the patient for 20-30 min by a nasal mask driven by a medical compressed air atomizer (YUWELL, 403M)	Chinese medicines		<p><u>Time of CT imaging improvement (size and density reduction of lesions)</u> I: Mean 6.21 days, N = 38/40, 95% CI 5.11-7.31 C: 8.76 days, N = 34/40, 95% CI 7.57-9.96 p = 0.0021 No discomfort or complications during aerosol inhalation were reported to the nurses by any experimental patients</p> <p><u>Rates of improvement in CT imaging after continued aerosol inhalation treatment for 3 days</u> I: 7/40 (17.5%) C: 2/40 (5.3%) No statistical significance</p> <p><u>Rates of improvement in CT imaging after continued aerosol inhalation treatment for 6 days</u> I: 28/40 (70%) C: 9/40 (22.5%) P<0.0001</p> <p><u>Rates of improvement in CT imaging after continued aerosol inhalation treatment for 9 days</u> I: 34/40 (85%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Diabetes</i> I: 1 (2.5%) C: 2 (5.0%)</p> <p><i>Hypertension</i> I: 3(7.5%) C: 1(2.5%)</p> <p>Groups comparable at baseline? No significant differences were observed between the two groups at baseline.</p>				<p>C: 20/40 (50%) P<0.005</p> <p><u>Rates of improvement in CT imaging after continued aerosol inhalation treatment for 12 days</u> I: 35/40 (87.5%) C: 29/40 (72/5%) No statistical significance</p> <p><u>Adverse events</u> I: 0/40 C: 0/40</p>	
13.2. Inhaled Interferon β-1b							
Khamis, 2020	See evidence table of Khamis (2020) by favipiravir.						
13.3. Interferon α-2b							
Pandit, 2021	<p><u>Type of study:</u> RCT (phase 2, open-label)</p> <p><u>Setting:</u> 6 study centers, 08 July 2020 to 04 September 2020</p> <p><u>Country:</u> India</p> <p><u>Source of funding:</u> This trial was sponsored and funded by Cadila Healthcare Ltd., Ahmedabad, India.</p> <p>The role of the funder was not described.</p>	<p>Hospitalized patients with moderate COVID-19.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> aged >18 years RT-PCR confirmed COVID-19 with moderate symptoms pneumonia with no signs of severe disease respiratory rate 15 to 30 breaths/minute SpO2 90% to 94% for female patients of child-bearing potential, a negative pregnancy test prior to treatment C-reactive protein (CRP) <16 mg/L, IL-6 <100 pg/mL, D-dimer <2 µg/mL, interferon-γ, ferritin, tumor necrosis factor (TNF)-α, IL-1β greater than upper limit of normal (ULN) 	<p>Pegylated interferon-α2b in addition to standard of care (PEG IFN-α2b plus SOC)</p> <p>Dose: 1 µg/kg subcutaneous injection, single dose.</p>	Standard of care (SOC)	<p><u>Length of follow up:</u> 15 days (29 days for safety outcomes)</p> <p><u>Loss to follow-up:</u> I: 0/20 (0%) Reasons: n.a. C: 1/20 (5%) Reasons: withdrawal of consent (not further specified).</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> not reported</p> <p><u>Duration of hospitalization</u> not reported</p> <p><u>Symptom resolution</u> not reported</p> <p><u>Need for respiratory support</u></p> <ul style="list-style-type: none"> Duration of respiratory support <i>Supplemental oxygen</i> median (min-max) hours I: 34 (19-132) [8 patients] C: 50 (43-240) [7 patients] p>0.05 <p><i>Mechanical ventilation</i></p>	<p><u>Definitions:</u></p> <ul style="list-style-type: none"> Not applicable <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Of the 40 subjects randomized, 39 (97.50%) subjects comprised the modified intent-to-treat (mITT) and per protocol (PP) populations, respectively. 1 subject in the SOC group discontinued from the study due to withdrawal of consent. Role of pharmaceutical company was not reported. Disease severity was not reported at baseline. All subjects were hospitalized, RT-PCR tests in pharyngeal swab performed on screening, on day 7 and on day 14 and were discharged only after 2 consecutive negative RT-PCR tests and clinical cure.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> illness of any duration and radiographic infiltrates by chest x-ray or evidence of rales/crackles or other clinical symptoms on clinical examination <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >5 x ULN stage 4 severe chronic kidney disease or required dialysis pregnant or breast-feeding women severe co-morbidity comorbid condition like myocardial infarction or heart failure within 90 days of recruitment, prolonged QT interval (>450 ms) <p><u>N total at baseline:</u> N = 40 Intervention: 20 Control: 20</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 49.4 y (14.9) C: 49.1 y (12.4)</p> <p>Sex, n/N (%) male: I: 11/20 (55%) C: 19/20 (95%)</p> <p>Disease severity <i>Not reported.</i></p> <p>Groups comparable at baseline? Overall, demographic characteristics of the study</p>				<p>None of the subjects required mechanical ventilation during the study.</p> <p>Safety <u>Adverse events</u></p> <ul style="list-style-type: none"> Serious adverse events There were no deaths and serious adverse events (SAEs) reported during the study period. Number of adverse events (AEs): I: 11/20 (55%) C: 8/20 (40%) All AEs were mild in severity. <p>Virological outcomes <u>Viral clearance</u></p> <ul style="list-style-type: none"> % negative RT-PCR at day 7 and 14 Day 7: I: 16/20 (80%) C: 12/19 (63%) P>0.05 Day 14: I: 19/20 (95%) C: 13/19 (68%) P<0.05 <p>Also available: (improvement in) status on the WHO 7-point scale on day 15, serial laboratory measurements of blood levels for WBC, Hb, platelets, creatinine, glucose, total bilirubin, ALT, AST, CRP, IL-6, D-dimer,</p>	<p><u>Authors conclusion:</u> The significant improvement in clinical status on day 15 is likely due to faster viral reduction compared to SOC with the PEG IFN-α2b treated moderate COVID-19 subjects showing a difference as early as day 7 and becoming significant by day 14.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		subjects were comparable across the treatment groups. Although there were more male patients in the SOC group (95% vs. 55%).				interferon- β , ferritin, TNF- α and IL 1- β	
13.4. Interferon β-1a							
Kalil, 2021	<p><u>Type of study:</u> Double-blind, randomized, placebo-controlled trial.</p> <p><u>Setting:</u> 63 hospitals.</p> <p><u>Country:</u> Japan (one site), Mexico (two sites), Singapore (two sites), South Korea (two sites), and the USA (56 sites).</p> <p><u>Source of funding:</u> The National Institute of Allergy and Infectious Diseases (USA).</p> <p><u>Conflicts of interest:</u> The authors declare no competing interests.</p>	<p><u>Hospitalized COVID-19 patients.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients aged 18 years or older with SARS-CoV-2 infection, as confirmed by a positive RT-PCR assay result from any respiratory specimen collected less than 72 hours before randomisation, or collected 72 hours before randomisation if the patient had progressive disease consistent with ongoing SARS-CoV-2 infection; • Suggestive of lower respiratory tract infection at the time of enrolment; • The presence of radiographic infiltrates on imaging; • A peripheral oxygen saturation on room air of 94% or less; • Requiring supplemental oxygen. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients already on mechanical ventilation; • Patients with an alanine aminotransferase or an aspartate aminotransferase concentration more than five times the upper limit of normal; • Patients that had impaired renal function, as defined by an estimated glomerular filtration rate of less than 30 mL per min per 1.73 m² or the need for haemodialysis or haemofiltration; 	interferon beta-1a (up to 4 doses of 44 μ g administered subcutaneously every other day) + remdesivir (a 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily for up to 9 days)	placebo (up to 4 doses of normal saline administered subcutaneously every other day) + remdesivir (a 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily for up to 9 days)	<p><u>Length of follow-up:</u> 28 days.</p> <p><u>Loss-to-follow-up:</u> None.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality over the first 14 days, n/N (%)</u> I: 8/487 (2%) C: 11/482 (2%)</p> <p><u>Kaplan-Meier estimate of mortality</u> I: 2% (1 to 3) C: 2% (1 to 4) HR 0.73 (95% CI 0.30 to 1.83) P=0.50</p> <p><u>Mortality over entire study period, n/N (%)</u> I: 21/487 (4%) C: 16/482 (3%)</p> <p><u>Kaplan-Meier estimate of mortality</u> I: 5% (3 to 7) C: 3% (2 to 6) HR 1.33 (95% CI 0.69 to 2.55) P=0.39</p> <p><u>Duration of hospitalization</u> Not reported.</p> <p><u>Time to symptom resolution</u> <u>Number of patients who had recovered, n/N (%)</u> I: 435/487 (89%) C: 450/482 (93%)</p>	<p><u>Definitions:</u></p> <p>Ordinal scale: Patients defined by a score of: 1 were not hospitalised and had no limitations to their activities; 2 were not hospitalised but had limitations to their activities or required home oxygen supplementation, or both; 3 were hospitalised but did not require supplemental oxygen and no longer required ongoing medical care; 4 were hospitalised and did not require supplemental oxygen but did require ongoing medical care; 5 were hospitalised and required any supplemental oxygen; 6 were hospitalised and required non-invasive ventilation or use of high-flow oxygen devices; 7 were hospitalised and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 8 were those who had died.</p> <p><u>Remarks:</u> Adverse events and serious adverse events were reported for patients with an ordinal score of 4 or 5 and patients with ordinal score 6.</p> <p><u>Authors conclusion:</u> Although, we cannot conclude that imbalances between the two groups are solely the cause of the worse outcomes observed in patients with an ordinal score of 6 at baseline who received interferon beta-1a compared</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Patients who were allergic to the study product; • Pregnant patients or breast-feeding; • Patients who were anticipating discharge from the hospital or transfer to another hospital withing 72 hours of enrolment. <p><u>N total at baseline:</u> N = 969 Intervention: N = 487 Control: N = 482</p> <p><u>Important characteristics:</u> Age category, years <40 I: 65/487 (13%) C: 59/482 (12%)</p> <p>40-64 I: 236/487 (48%) C: 245/482 (51%)</p> <p>>64 I: 186/487 (38%) C: 178/482 (37%)</p> <p>Sex, n/N (%) male: I: 297/487 (61%) C: 266/482 (55%)</p> <p>Disease severity, mean (SD): <i>Defined by WHO ordinal score</i></p> <p>Score 4: I: 84/487 (17%) C: 68/482 (14%)</p> <p>Score 5: I: 368/487 (76%) C: 380/482 (79%)</p>				<p><i>Median time to recovery (95% CI)</i> I: 5 (NE to NE) days. C: 5 (NE to NE) days. RRR 0.99 (95% CI 0.87 to 1.13) P=0.88</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety (ordinal scale score 4 or 5 patients) <u>Adverse events</u> I: 172/442 (39%) C: 138/435 (32%)</p> <p><u>Serious adverse events</u> I: 65/442 (15%) C: 58/435 (13%)</p> <p>Safety (ordinal scale score 6 patients) <u>Adverse events</u> I: 24/35 (69%) C: 13/33 (39%)</p> <p><u>Serious adverse events</u> I: 21/35 (60%) C: 8/33 (24%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	with those who received placebo, we also cannot conclude that these imbalances do not play some role in explaining this difference.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Score 6: I: 35/487 (7%) C: 34/482 (7%) Groups comparable at baseline? Yes.					
Ader, 2021	See evidence table of Ader (2021) by hydroxychloroquine.						
Alavi Darazam, 2021 COVIFERON trial	<p><u>Type of study:</u> RCT; open-label</p> <p><u>Setting:</u> April 9, 2020, through April 30, 2020, at Loghman Hakim Hospital, a leading academic hospital</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> No funding or conflicts of interest (“Interestingly lack of funding and the absence of any potential conflicts of interest could be accounted as a strength for this study”)</p>	<p>Severe COVID-19 patients admitted to a medical center</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Male or non-lactating, and non-pregnant female age at least 18 years confirmed COVID-19 (positive RT-PCR) confirmed COVID-19 compatible lung involvement (positive CT Scan) peripheral capillary oxygen saturation level (SpO2) ≤ 93% on pulse oximetry OR a respiratory frequency ≥ 24/ minute while breathing ambient air at least one in every of the following: [contactless infrared forehead thermometer temperature of ≥ 37.8, muscle ache, rhinitis, headache, cough or fatigue on admission] AND [acute onset time for the symptoms (Days ≤ 14)]. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> cardiac arrhythmias (prolonged PR or QT intervals, third- or second-degree heart block) consumption of potentially interacting medications with Lopinavir/Ritonavir+HCQ, IFNβ1a, IFNβ1b, 	<p>I) IFNβ1a (Recigen) (Subcutaneous injections of 44 µg (12,000 IU) on days 1, 3, 6) + Hydroxychloroquine + Lopinavir/Ritonavir (Kaletra) [IFNβ1a group],</p> <p>II) IFNβ1b (Ziferon) (Subcutaneous injections of 0.25 mg (8,000,000 IU) on days 1, 3, 6) + Hydroxychloroquine + Lopinavir/Ritonavir (Kaletra) [IFNβ1b group], and</p>	<p>Standard care hydroxychloroquine (Single dose of 400 mg on day 1, orally, in all three arms) + Lopinavir/Ritonavir (Kaletra) (400 mg/100 mg twice a day for 10 days, orally, in all three arms)</p> <p>All three groups received standards of care consisting of the necessary oxygen support, non-invasive, or invasive mechanical ventilation.</p>	<p><u>Length of follow up:</u> 21 days</p> <p><u>Loss to follow-up:</u> No individuals lost to follow-up</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality</u> Mortality at day 21—no. (%) I: 4 (20.0%) II: 6 (30.0%) C: 9 (45.0%) Mortality in early presentation (≤ 6 days of symptom onset)—no. (%) I: 2 (16.7%) II: 3 (30.0%) C: 4 (33.3%) Mortality in late presentation (> 6 days of symptom onset)—no. (%) I: 2 (25.0%) II: 3 (30.0%) C: 5 (62.5%)</p> <p><u>Duration of hospitalization</u> Hospital stay—median no. of days; until discharge from hospital or death from any cause, whichever came first (IQR) I: 5.0 (3.0–6.0) II: 5.0 (3.2–7.7) C: 6.0 (5.0–7.0) Time from enrollment to discharge—median no. of days (IQR) I: 4.0 (3.0–5.0) II: 5.0 (2.7–6.2)</p>	<p><u>Definitions:</u> 7-step ordinal scale: (I) Not hospitalized, and has no activity limitations; (II) Not hospitalized, but has activity limitations; (III) Hospitalized, but does not need any supplemental oxygen; (IV) Hospitalized, and needs supplemental oxygen; (V) Hospitalized, and needs either High-Flow Nasal Cannula (HFNC) or non-invasive ventilation; (VI) Hospitalized, and needs invasive ventilation; and (VII) Dead</p> <p><u>Remarks:</u> -disease severity or clinical ordinal score at baseline not described</p> <p><u>Authors conclusion:</u> “In patients with laboratory-confirmed SARS-CoV-2 infection, as compared with the base therapeutic regimen, the benefit of a significant reduction in TTCI (=Time To Clinical Improvement) was observed in the IFNβ1a arm. This finding needs further confirmation in larger studies.”</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • history of alcohol use disorder, or any illicit drug dependence within the past five years, • blood AST/ALT levels \geq5x maximum limit of normal range on laboratory findings • participation refusal <p><u>N total at baseline:</u> N = 60 Intervention-I: 20 Intervention-II: 20 Control: 20</p> <p><u>Important characteristics:</u> Age, median (IQR)—year I: 71.5 (49.7–74.8) II: 65.0 (57.0–74.0) C: 76.0 (55.0–85.0) Sex, n/N (%) male: I: 11 (55.0%) II: 9 (45.0%) C: 11 (55.0%) Duration of symptoms before presentation, median (IQR)—day I: 5.5 (3.0–7.0) II: 6.0 (3.0–9.2) C: 4.0 (2.0–7.0) <i>Also described: clinical parameters (e.g. respiratory rate, temp) & laboratory performance.</i></p> <p>Groups comparable at baseline.</p>				<p>C: 5.5 (5.0–7.0) Eventuel relevant: ICU admission—no. (%) I: 16 (80.0%) II: 13 (65.0%) C: 16 (80.0%)</p> <p><u>Time to symptom resolution</u> Time To Clinical Improvement median (95% CI), defined as the time from enrollment to discharge <u>or</u> a decline of two steps on the clinical seven-step ordinal scale I: 5.0 (4.2–5.7) HR 2.36; (95% CI 1.10–5.17, P=0.031) II: 5.0 (3.6–6.4) HR 1.42, (95% CI 0.63–3.16, P=0.395) C: 7.0 (6.1–7.9)</p> <p><u>Need for respiratory support</u> Invasive mechanical ventilation—no. (%); incidence of new mechanical ventilation use from the date of randomization until day 21 I: 7 (35.0%) II: 7 (35.0%) C: 7 (35.0%)</p> <p>Safety <u>Adverse events</u> Adverse event Nausea I: 4 (20%), II: 5 (25%), C:5 (25%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Vomiting I: 1 (5%), II: 0 (0%), C: 1 (5%)</p> <p>Diarrhea I: 3 (15%), II: 4 (20%), C: 3 (15%)</p> <p>Rash I: 0 (0%), II: 0 (0%) C: 1 (5%)</p> <p>Increased ALT I: 9 (45%), II: 6 (30%), C: 8 (40%)</p> <p>Increased AST I: 12 (60%), II: 13 (65%), C: 16 (80%)</p> <p>Hyper bilirubinaemia I: 2 (10%), II: 1 (5%), C: 1 (5%)</p> <p>Increased creatinine I: 4 (20%), II: 3 (15%), C: 6 (30%)</p> <p>Prolonged QT interval I: 0 (0%), II: 0 (0%) C: 1 (5%)</p> <p>Serious adverse event ARDS I: 7 (35%), II: 8 (40%), C: 10 (50%)</p> <p>Acute kidney failure (AKI) I: 5 (25%), II: 4 (20%), C: 6 (30%)</p> <p>Shock I: 1 (5%), II: 1 (5%), C: 1 (5%)</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p> <p><i>Also reported: respiratory rate, oxygen saturation, laboratory parameters</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Pan, 2020	<p><u>Type of study:</u> RCT (open-label, non-blinded)</p> <p><u>Setting & country:</u> 405 hospitals in 30 countries; WHO Solidarity Trial</p> <p><u>Source of funding:</u> Funded by the World Health Organization; ISRCTN Registry nr, ISRCTN83971151; ClinicalTrials.gov nr, NCT04315948.)</p>	<p><u>N total at baseline:</u> N = 11,330</p> <p><i>Interferon beta-1a + Lopinavir arm</i> I: 2050 C: 2050</p> <p><u>Important characteristics:</u> <u>Age, n/N (%):</u> I: <50y: 720/2050 (35.1%) 50-69y: 934/2050 (45.6%) ≥70y: 396/2050 (19.3%) C: <50y: 697/2050 (34.0%) 50-69y: 973/2050 (47.5%) ≥70y: 380/2050 (18.5%) <u>Sex, n/N (%) male:</u> I: 1303/2050 (63.6%) C: 1278/2050 (62.3%) <u>Respiratory support</u> I: No suppl. Oxygen at entry: 482/2050 (23.5%) Suppl. Oxygen at entry 1429/2050 (69.7%) Already receiving ventilation 139/2050 (6.8%) C: No suppl. Oxygen at entry: 490/2050 (23.9%) Suppl. Oxygen at entry 1430/2050 (69.8%) Already receiving ventilation 130/2050 (6.3%) <u>Previous days in hospital</u> I: 0 days: 678/2050 (33.1%) 1 day: 681/2050 (33.2%) ≥2 days: 691/2050 (33.7%) C: 0 days: 677/2050 (33.0%)</p>	<p>Interferon beta-1a (+ Lopinavir until July 4th 2020)</p> <p>Mainly subcutaneous; 3 doses over period of 6 days (the day of randomization and days 3 and 6) of 44 µg of subcutaneous interferon beta-1a; where IV interferon was available, patients receiving high-flow oxygen, ventilation, or ECMO were instead to be given 10 µg intravenously daily for 6 days.</p> <p><i>Discontinued for futility on Oct 16, 2020 19</i></p> <p><u>Taking trial drug midway through scheduled duration*:</u> I: 94% C: 2%</p> <p><u>Use of non-study drug, n/N (%):</u> Corticosteroids I: 981 (47.9%) C: 1053 (51.4%) Convalescent plasma I: 43 (2.1%) C: 33 (1.6%) Anti-IL-6 drug I: 52 (2.5%) C: 68 (3.3%) Non-trial interferon I: 1 (0.1%) C: 26 (1.3%) Non-trial antiviral</p>	Standard of care (+ Lopinavir until July 4th 2020)	<p><u>Length of follow up:</u> 28 days, or up to discharge</p> <p><u>Loss to follow-up:</u> I: 13/2063 (0.6%) Reasons: no or unknown consent C: 14/2064 (0.7%) Reasons: no or unknown consent</p>	<p>Clinical outcomes</p> <p><u>All-cause in-hospital mortality, regardless of whether death occurred before or after day 28:</u> I: 243/2050 (11.9%) C: 216/2050 (10.5%) RR 1.13 (95% CI 0.95 to 1.34)</p> <p>HR=1.16 (0.96-1.39). Adjusted** HR=1.14 (0.96-1.35).</p> <p><u>All-cause in-hospital mortality, stratified by ventilation at randomization:</u> Ventilated: HR 1.40 (95% CI 0.93-2.11) Not ventilated: HR 1.11 (95% CI 0.90-1.36)</p> <p><u>Initiation of mechanical ventilation, in those not receiving ventilation at baseline:</u> I: 209/1911 (10.9%) C: 210/1920 (10.9%) RR 1.00 (95% CI 0.83 to 1.20)</p> <p><u>Composite death or initiation ventilation:</u> I: 344/2050 (16.8%) C: 335/2050 (16.3%) RR 1.03 (95% CI 0.90 to 1.18) Publication: RR 1.05 [0.89-1.22]</p>	<p><u>Definitions/information:</u> <u>Taking trial drug midway through scheduled duration, %</u>, calculated only among patients who died or were discharged alive, % patients who were taking the trial drug midway through its scheduled duration (or midway through the time from entry to death or discharge, if this was shorter). <u>*Adjusted model all-cause mortality:</u> some overlap between the 4 control groups; an exploratory sensitivity analysis used multivariate Cox regression to fit all 4 treatment effects simultaneously; adjusted for several prognostic factors (age, sex, diabetes, bilateral lung lesions at entry (no, yes, not imaged at entry), and respiratory support at entry (no oxygen, oxygen but no ventilation, ventilation)).</p> <p><u>Authors conclusion:</u> These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.</p>

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		1 day: 662/2050 (32.3%) ≥2 days: 711/2050 (34.7%)	I: 102 (5.0%) C: 144 (7.0%)			<u>Hospitalized, not discharged:</u> Percentage of patients (rather than number of patients) ever reported as discharged who were still in the hospital: Day 7 I: 55% C: 51% Day 14 I: 19% C: 18% Day 21 I: 8% C: 7%	
Monk, 2020	<p><u>Type of study:</u> Randomised, double-blind, placebo-controlled, phase 2 pilot trial.</p> <p><u>Setting:</u> Nine UK sites.</p> <p><u>Country:</u> United Kingdom</p> <p><u>Source of funding:</u> The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author and coauthors had full access to all the data in the study and had final</p>	<p>All eligible participants had to have a confirmed SARS-CoV-2 test result in a UK National Health Service (NHS) diagnostic, qualitative RT-PCR assay or a positive point-of-care test (FebriDx, Lumos Diagnostics, Sarasota, FL, USA) within the previous 24 h</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Positive virus test for SARS-CoV-2 using RT-PCR or positive point-of-care infection test; • Male or female >18 years old; • Admitted to hospital due to the severity of their COVID-19 disease who presented with clinical symptoms consistent with COVID-19: high temperature and/or new, continuous cough and/or loss or change to sense of smell and/or taste; • Provided informed consent; • Hospitalised female patients had to be > 1 year 	SNG001 (6 MIU interferon beta-1a) delivered via the I-neb nebulizer once daily for up to 14 days	Placebo	<p><u>Length of follow up:</u> 28 days</p> <p><u>Placebo group: 14 withdrawn</u></p> <ul style="list-style-type: none"> • 5 withdrew consent. • 2 lost to follow-up. • 2 due to investigator's decision. • 2 for other reasons. • 2 due to a fatal serious adverse reaction. • 1 due to a non-serious adverse reaction <p><u>Intervention group: 9 withdrawn</u></p> <ul style="list-style-type: none"> • 6 withdrew consent. • 2 lost to follow-up. • 1 for other reasons. 	<p>Clinical outcomes</p> <p><u>Mortality during study period (no modelling analysis was done)</u> I: 0/48 C: 3/50</p> <p>Ratio (95% CI)</p> <p><u>Severe disease or death between the first dose and day 16</u> I: 11/48 (22%) C: 6/50 (13%) OR= 0.21 (95% CI= 0.04 to 0.97) P=0.046</p> <p><u>Time to severe disease or death (OSCI >4) on day 15 or 16</u> HR= 0.50 (95% CI= 0.18 to 1.38)</p>	<p><u>Definitions:</u></p> <p><u>Remarks:</u></p> <p><u>Authors conclusion:</u> In conclusion, SNG001, a treatment already studied and shown to be well tolerated in patients with asthma and COPD, seems to also be well tolerated in patients admitted to hospital with COVID-19, with a range of clinical outcomes displaying a beneficial pattern of response to SNG001 therapy. These encouraging data provide a strong rationale for larger, international studies in the context of the ongoing clinical burden of COVID-19. In addition to a phase 3 trial of SNG001 in patients admitted to hospital with COVID-19 requiring no more than supplementary oxygen, it might be appropriate to also assess the safety and efficacy of SNG001 in ventilated, critically ill patients with COVID-19 who have evidence of active viral infection in</p>

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	responsibility for the decision to submit for publication.	<p>postmenopausal, surgically sterile, or using an acceptable method of contraception.</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Any condition constituted a risk or a contraindication for the participation of the patient into the study; • Current or previous participation in another clinical trial where the participant had received a dose of an investigational medicinal product; • Ventilation or in intensive care; • Inability to use a nebuliser with a mouthpiece; • History of hypersensitivity to natural or recombinant IFN-beta or to any of the excipients in the drug preparation; • Females who were breast-feeding, lactating, pregnant or intending to become pregnant. <p><u>N total at baseline:</u> N = 101 Intervention: 50 (48 received intervention) Control: 51 (50 received intervention)</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 57.8 y (14.6) C: 56.5 y (11.9)</p> <p>Sex, n/N (%) male: I: 27/48 (56%) C: 31/50 (62%)</p> <p>[Disease severity], mean (SD):</p>				<p><u>Odds of severe disease or death (OSCI >4) on day 15 or 16</u> OR= 0.28 (95% CI= 0.07 to 1.08) P=0.064</p> <p><u>Time to intubation or death (OSCI >5) on day 15 or 16</u> HR= 0.38 (95% CI= 0.09 to 1.65)</p> <p><u>Odds of intubation or death (OSCI >5) on day 15 or 16</u> OR= 0.42 (95% CI= 0.09 to 1.83)</p> <p><u>Time to recovery on day 15 or 16</u> HR= 2.19 (95% CI= 1.03 to 4.69)</p> <p><u>Odds of recovery on day 15 or 16</u> OR= 3.19 (95% CI= 1.24 to 8.24) P=0.017</p> <p><u>Odds of recovery on day 28</u> OR= 3.58 (95% CI= 1.41 to 9.04) P=0.007</p> <p><u>Time to hospital discharge at day 15 or 16</u> HR= 1.37 (95% CI= 0.85 to 2.20)</p> <p><u>Time to hospital discharge at 28 days</u></p>	the lungs. In view of the broad antiviral effects of interferon-β, the results of this pilot trial suggest that the efficacy of SNG001 should also be assessed in the hospital setting against other seasonal respiratory viruses, which cause considerable morbidity and mortality every year, including cases of SARS-CoV-2 coinfection, which could overwhelm health-care systems during the coming months in the northern hemisphere.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Defined by Limitation of activities; hospitalised (no oxygen); oxygen by mask or nasal prongs; non-invasive ventilation or high-flow oxygen; duration of symptoms</i></p> <p><u>No limitation of activities, n/N (%)</u> I: 0/48 (0%) C: 1/50 (2%)</p> <p><u>Limitation of activities, n/N (%)</u> I: 0/48 (0%) C: 1/50 (2%)</p> <p><u>Hospitalised (no oxygen therapy), n/N (%)</u> I: 11/48 (23%) C: 19/50 (38%)</p> <p><u>Non-invasive ventilation or high-flow oxygen, n/N (%)</u> I: 1/48 (2%) C: 1/50 (2%)</p> <p><u>Duration of symptoms (days), median (IQR)</u> I: 10.0 (8.0 to 11.0) C: 9.5 (7.0 to 12.0)</p> <p>Groups comparable at baseline?</p> <p>Yes apart from a few characteristics → In general, patients in the treatment groups were well matched by baseline characteristics, apart from disease severity measured with the OSCI and the frequencies of specific comorbidities. Patients in the SNG001 group had more severe</p>				<p>OR= 1.84 (95% CI= 0.64 to 5.29)</p> <p><u>Odds of hospital discharge on day 15 or 16</u> OR= 1.63 (95% CI= 0.61 to 4.35) P=0.33</p> <p><u>Odds of improvement on the OSCI at day 15 or 16</u> OR= 2.32 (95% CI= 1.07 to 5.04) P=0.033</p> <p><u>Odds of improvement on the OSCI at day 28</u> OR= 3.15 (95% CI= 1.39 to 7.14) P=0.006</p> <p><i>*OSCI = WHO Ordinal Scale for Clinical Improvement</i></p> <p>Treatment-emergent adverse events, n/N (%)</p> <p><u>Any treatment-emergent adverse event</u> I: 26/48 (54%) C: 30/50 (60%)</p> <p><u>Any treatment-emergent adverse event during treatment period</u> I: 23/48 (48%) C: 25/50 (50%)</p> <p><u>Any serious treatment-emergent adverse event</u> I: 7/48 (15%) C: 14/50 (28%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		disease as judged by 37 (77%) patients receiving oxygen therapy (OSCI ≥ 4) compared with 29 (58%) in the placebo group (table 2). More patients in the placebo group than those in the SNG001 group had diabetes (nine [33%] vs three [12%]) or cardiovascular disease (eight [30%] vs five [19%]), and fewer had hypertension (11 [41%] vs 18 [69%]).				<p><u>Any treatment-related treatment-emergent adverse event</u> I: 7/48 (15%) C: 2/50 (4%)</p> <p><u>Any fatal treatment-emergent adverse event</u> I: 0/48 (0%) C: 3/50 (6%)</p> <p><u>Any treatment-emergent adverse event that led to study withdrawal</u> I: 0/48 (0%) C: 3/50 (6%)</p>	
Davoudi-Monfared, 2020	<p><u>Type of study:</u> RCT, open-label randomized clinical trial</p> <p><u>Setting:</u> Imam Khomeini Hospital Complex, between February 29, and April 3, 2020</p> <p><u>Country:</u> Teheran, Iran</p> <p><u>Source of funding:</u> -The authors did not receive any fund for this work. ReciGen was a generous gift from CinnaGen Co. -The authors have declared that no competing interest exists.</p>	<p>Patients with severe COVID-19* admitted to the hospital.</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> patients diagnosed with COVID-19 (according to either a positive real-time PCR (RT-PCR) of the deep nasopharyngeal secretions or clinical signs/symptoms plus imaging findings highly suspicious for COVID-19 aged ≥ 18 years severe disease* <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Allergy to IFNs receiving IFNs for any other reason severe depression previous suicide attempts alanine amino transferase (ALT) >5 x the upper limit of the normal range pregnant women 	<p><u>IFN β-1a group</u> Patients in the IFN group received IFN β-1a in addition to the national protocol medications.</p> <p>Each 44-g/ml (12 million IU/ml) dose of interferon -1a (ReciGen, CinnaGen Co., Iran) was subcutaneously injected three times weekly for two consecutive weeks.</p>	<p><u>Control group</u> The control group received only the standard of care. The standard of care (the hospital protocol) consisted of hydroxychloroquine (400 mg twice a day [BID] on the first day and then 200 mg BD) plus lopinavir-ritonavir (400 and 100 mg, respectively, BD) or atazanavir-ritonavir (300</p>	<p><u>Length of follow up:</u> Patients were monitored for 4 weeks.</p> <p><u>Loss to follow-up:</u> I: 4/46 (8.7%) Reasons: 4 patients were dropped out (2 patients died before the second dose of FN, 2 patients died before the third dose of IFN)</p> <p>C: 7/46 (15.2%) Reasons: 7 patients were dropped out (they entered other trial)</p>	<p><u>Time to reach clinical response (day), mean (SD)</u> Defined as the number of days required to at least two scores of improvement on the scale or patient's discharge, whichever occurred sooner I: 9.74 (5.8) C: 8.39 (4.9) P=0.95</p> <p><u>Required invasive mechanical ventilation, n (%)</u> I: 15 (35.71%) C: 17 (43.58%) P=0.30</p> <p><u>Duration of mechanical ventilation, (days), mean (SD)</u> I: 10.86 (5.38) C: 7.82 (7.84)</p>	<p><u>Definitions</u> Clinical response was defined according to the six-category ordinal scale (47). This scale classifies patients into six categories according to the severity of the viral pneumonia: (1) discharge; (2) hospital admission, not requiring oxygen; (3) hospital admission, requiring oxygen; (4) hospital admission, requiring noninvasive positive pressure ventilation; (5) hospital admission, requiring invasive mechanical ventilation; (6) death.</p> <p><u>Remarks</u> -The control group received multiple treatments. -An allocation ratio of 1:1 was accounted between IFN and the control group in randomization, but the patients had to receive at least four injections of IFN to be included in the final analysis.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>N total at baseline:</u> N = 81 Intervention: 42 Control: 39</p> <p><u>Important characteristics:</u> Age, (median with IQR): I: 56.50 y (47.25–67.25) C: 61.00 y (50.00–70.00) Sex, n/N (%) male: I: 22/42 (52.38 %) C: 22/39 (56.4 %)</p> <p>Groups comparable at baseline? There was no significant difference in terms of demographic data and baseline diseases between the groups.</p> <p>*These patients had at least one of the following conditions: (i) hypoxemia (need for noninvasive or invasive respiratory support to provide capillary oxygen saturation above 90%), (ii) hypotension (systolic blood pressure less than 90 mm Hg or vasopressor requirement), (iii) renal failure secondary to COVID-19 (according to KDIGO definition) (46), (iv) neurologic disorder secondary to COVID-19 (decrease of 2 or more scores on the Glasgow Coma Scale), (v) thrombocytopenia secondary to COVID-19 (platelet count less than 150,000/mm³), and (vi) severe gastrointestinal symptoms secondary to COVID-19 (vomiting/diarrhea that caused at least mild dehydration).</p>		and 100 mg, respectively, daily) for 7–10 days.		<p>P=0.47</p> <p><u>Duration of ICU stay (days), mean (SD)</u> I: 7.71 (8.75) C: 8.52 (7.48) P=0.42</p> <p><u>Duration of hospital stay (days), mean (SD)</u> I: 14.80 (8.45) C: 12.25 (7.48) P=0.69</p> <p><u>Discharge on day 14, n (%)</u> I: 28 (66.66%) C: 17 (43.58%) OR 2.5 (95% CI 1.05–6.37)</p> <p><u>28-day mortality, n (%)</u> I: 8 (19%) C: 17 (43.6%) P=0.015</p> <p><u>Also available:</u> Effect of early or late (before or after 10 days of the onset of symptoms) administration of IFN on mortality, adverse effects, and complications during the hospitalization.</p>	<p><u>Authors conclusion:</u> Although IFN did not change the time to reach a clinical response, added to the national protocol, it significantly increased the discharge rate on day 14 and decreased 28-day mortality. Improved survival rate was significant when patients received IFN -1a in the early phase of the disease. Adverse effects of IFN -1a were injection-related, neuropsychiatric problems, and hypersensitivity reactions that all were tolerable and resolved during the follow-up period.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Huang, 2020	See evidence table of Huang (2020) by lopinavir and ritonavir.						
13.5. Interferon β-1b							
Alavi Darazam, 2021	See evidence table of Alavi-Darazam (2021) by interferon β -1a.						
COVIFERON trial							
Rahmani, 2020	<p><u>Type of study:</u> Open-label randomized clinical trial</p> <p><u>Setting:</u> One of the largest referral hospitals</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> No funding</p>	<p><u>Inclusion criteria:</u> Adult patients (≥ 18 years old) with positive PCR and clinical symptoms/signs of pneumonia (including dyspnea, cough and fever), peripheral oxygen saturation (SPO₂) $\leq 93\%$ in ambient air or arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂) < 300 or SPO₂/FiO₂ < 315 and lung involvement in chest imaging were included. These criteria indicated severe form of the disease.</p> <p><u>Exclusion criteria:</u> Patients with serious allergic reactions to IFN, history of suicide thoughts and attempts, alanine amino transferase (ALT) $> 5\times$ the upper limit of the normal range, uncontrolled underlying diseases such as neuropsychiatric disorders, thyroid disorders, cardiovascular diseases and pregnant and lactating women were excluded.</p> <p><u>N total at baseline:</u> N = 73 Intervention: 37* Control: 36*</p>	<p>Interferon β-1b (250 mcg subcutaneously every other day for two consecutive weeks)</p> <p>Patients also received national protocol medications (see control)</p>	<p>National protocol medications and other supportive care</p> <p>National protocol medications: lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days.</p> <p>Supportive care: e.g. fluid therapy, stress ulcer prophylaxis, deep vein thrombosis, treatment of electrolyte disorders and antibiotic</p>	<p>4 weeks (study duration was 2 weeks)</p>	<p><u>Time to clinical improvement (days, median (IQR))*</u> I: 9(6–10) C: 11(9–15) HR (95%CI): 2.30 (1.33 to 3.96) HRadj (95%CI): 3.41 (1.33–8.72) P=0.001</p> <p><u>ICU admission (n/N, %)</u> I: 14(42.4) C: 22(66.7) P=0.04</p> <p><u>Intubation (n/N, %)</u> I: 2/33 (6.1) C: 6/33 (18.2) P=0.12</p> <p><u>Length of hospital stay (days, median (IQR))</u> I: 11(9–13) C: 13(10–17) P=0.05</p> <p><u>Length of ICU stay (days, median (IQR))</u> I: 9(6–13) C: 8 (4–12) P=0.55</p> <p><u>28-day all-cause mortality (n/N, %)</u> I: 2(6.1)</p>	<p><u>Remarks:</u> - The 6-category ordinal scale contains the subsequent categories: (1) death (2) hospital admission requiring invasive mechanical ventilation (3) hospital admission, requiring non-invasive positive pressure ventilation (4) hospital admission, requiring oxygen (5) hospital admission, not requiring oxygen (6) discharge - Use of medications other than interferon was different between the groups, with higher use of AB, corticosteroids, vasopressors and diphenhydramine in the control group. More patients in the intervention group received vitamin C.</p> <p><u>Authors conclusion:</u> IFN β-1b was effective in shortening the time to clinical improvement without serious adverse events in patients with severe COVID-19. Furthermore, ICU admission rate and need for invasive mechanical ventilation significantly reduced by administration of IFN β-1b. Although compared with the control group, IFN β-1b reduced duration of hospitalization, length of ICU stay, intubation rate and 28-day mortality were not statistically different between the groups. Further randomized clinical trials with enough sample size are</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>* of which respectively 33 patients in each group completed the study.</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 60(47–73) C: 61(50–71) P=not reported Sex, n/N (%): male: I: 20/33(61) C: 19/33(58) P=not reported</p> <p>Groups comparable at baseline? Groups differs (not significantly) with regard to comorbid conditions and symptoms at admission.</p>		therapy, according to the hospital protocol.		C: 6(18.2) P= 0.12 <u>Common adverse events (n)**</u> I: 47 C: 62 P=not reported <u>Serious adverse events (n/N, %)**</u> I: 9 C: 24 P=not reported *Defined as improvement of at least 2 points from the baseline status on the 6-category ordinal scale. **Including e.g. flu like symptoms, injection site reaction, abdominal pain (...). ***Including ARDS, nosocomial infection, septic shock, AKI and AHL.	needed to accurately estimate survival benefit of IFN β-1b.
Hung (2020)	See evidence table of Hung (2020) by ribavirin.						
13.6. Peginterferon Lambda							
Feld, 2021	<p><u>Type of study:</u> Randomised, double-blind, placebo-controlled trial.</p> <p><u>Setting:</u> Outpatient testing centers at six institutions.</p> <p><u>Country:</u></p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Individuals with SARS-CoV-2 infection confirmed by nasopharyngeal swab. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Pregnancy; Pre-existing immunosuppressive or other medical conditions that could be worsened by peginterferon lambda. 	A single subcutaneous injection of 180 µg of peginterferon lambda	Saline placebo	<p><u>Length of follow up:</u> 14 days</p> <p><u>Loss to follow-up:</u> I: 1/30 (3.3%) Reasons: not reported. C: 0/30 (0%) Reasons:-</p>	<p>Clinical outcomes</p> <p><u>Viral outcomes</u> <i>Proportion of individuals with a negative mid-turbinate swab for SARS-CoV-2 at day 7, n/N (%)</i> I: 24/30 (80%) C: 19/30 (63%) Unadj. OR= 2.32 (95% CI= 0.74 to 0.81);P=0.15</p>	<p><u>Definitions: /</u></p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> Before receiving the study medication, participants were taught proper self-collection technique for midturbinate nasal swabs followed by witnessed collection of the initial swab. Following the administration of the study medication, participants were observed for 30–60 min.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Toronto, Canada</p> <p><u>Source of funding:</u> The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.</p>	<p><u>N total at baseline:</u> N = 60 Intervention: 30 Control: 30</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 48y (30-53) C: 39y (33-55) Sex, n/N (%) male: I: 12/30/ (40%) C: 13/30 (43%)</p> <p>Disease severity, mean (SD): <i>Not described</i></p> <p>Groups comparable at baseline? Yes, apart from the median baseline SARS-CoV-2 RNA concentration.</p>				<p>Adj. viral load OR= 4.12 (95% CI= 1.15 to 16.73);P=0.029</p> <p><i>Association between symptoms and a viral load of 10⁶ copies per mL or higher, OR (95% CI)</i> <i>Overall</i> OR= 5.88 (95% CI= 1.37 to 25.00); P=0.017</p> <p><i>Fever or systemic</i> OR= 6.06 (95% CI= 1.48 to 25.00); P=0.012</p> <p><i>Respiratory</i> OR= 4.93 (95% CI= 0.94 to 25.64); P=0.060</p> <p><i>Gastrointestinal</i> OR= 11.9 (95% CI= 2.24 to 62.50); P=0.038</p> <p><i>Musculoskeletal</i> OR= 5.81 (95% CI= 1.31 to 25.64); P=0.020</p> <p><i>Skin</i> OR= 0.37 (95% CI= 0.05 to 2.99); P=0.36</p> <p><i>Mood</i> OR= 8.00 (95% CI= 0.98 to 66.67); P=0.052</p> <p><i>Neurological and vascular</i> OR= 52.63 (95% CI= 1.93 to infinity); P=0.019</p> <p><u>Safety (severe symptoms), n/N</u> <i>Adverse events</i></p>	<p>Participants were given written instructions and access to a video showing proper self-collection technique, and self-collection was observed by the study staff during remote follow-up visits using videoconferencing software whenever possible.</p> <p><u>Authors conclusion:</u> In conclusion, peginterferon lambda is among the first antiviral therapies to show benefit among outpatients with COVID-19. Peginterferon lambda accelerated viral clearance, particularly in those with high baseline viral load. This treatment might have potential to avert clinical deterioration, shorten the duration of infectiousness, and reduce isolation time, with substantial public health and societal effects.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I: 2/30 (6.6%) C: 1/30 (3.3%) <i>Serious adverse events</i> I: 1/30 (3.3%) C: 1/30 (3.3%) <i>Treatment-related adverse events</i> I: 0/30 (0%) C: 0/30 (0%) <i>Treatment related serious adverse events</i> I: 0/30 (0%) C: 0/30 (0%) <i>Emergency room visits</i> I: 1/30 (3.3%) C: 4/30 (13.3%) <i>Hospital admissions</i> I: 1/30 (3.3%) C: 1.30 (3.3%)	
13.7. Peginterferon Lambda-1a							
Jagannathan, 2021	<p><u>Type of study:</u> RCT; single-blind, placebo-controlled</p> <p><u>Setting:</u> Stanford Health Care System; enrolment: April 25 and July 17</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> "The study was funded by anonymous donors"</p>	<p>Outpatients with mild to moderate COVID-19; symptomatic and asymptomatic</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age 18–65 years • RT-PCR positive for SARS-CoV-2 • within 72 h from swab to the time of enrollment <p><i>Symptomatic individuals</i></p> <ul style="list-style-type: none"> • presence of mild to moderate symptoms without signs of respiratory distress <p><i>Asymptomatic individuals</i></p> <ul style="list-style-type: none"> • infection was initial diagnosis of SARS-CoV-2 infection 	<p>Peginterferon Lambda-1a</p> <p>single dose of Peginterferon Lambda-1a: 180 mcg subcutaneous injection of 0.45 ml volume</p>	<p>Placebo</p> <p>single dose of subcutaneous injection of saline of 0.45 ml</p>	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: n/N (%) Reasons: C: n/N (%) Reasons:</p> <p>The proportion of missing follow-up visits was 44/960 (4.6%). Only 16/960 visits were missed among patients not hospitalized or</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> not reported</p> <p><u>Duration of hospitalization</u> n.a.; not hospitalized</p> <p>Other: <u>Hospitalizations by Day 28</u>, n (%) I: 2 (3.3%) C: 2 (3.3%) <u>Emergency Department visits by Day 28</u>, n participants (%) I: 5 (8.3%) C: 3 (5%)</p>	<p><u>Definitions:</u> * resolution of symptoms, defined as the first day when no symptoms were reported ** disease progression, defined as hospitalization, presentation to the emergency department, or worsening cough or shortness of breath defined as an increase in severity of two points or more on a five-point scale.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In this work, we show that a single subcutaneous injection of Lambda in</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	to Stanford University, and Lambda provided by Eiger BioPharmaceuticals. Additional support was provided from NIH/NIAID (U01 AI150741-01S1 to P.J. and T.W.). The funders had no role in data collection and analysis or the decision to publish.”	<p>Exclusion criteria:</p> <ul style="list-style-type: none"> • current or imminent hospitalization, • respiratory rate >20 / min • room air O2 saturation <94%, • pregnancy or breastfeeding, • history of decompensated liver disease, • recent use of interferons, antibiotics, anticoagulants or other investigational and/or immunomodulatory agents for treatment of COVID-19 • prespecified lab abnormalities. <p>N total at baseline: N = 120 Intervention: 60 Control: 60</p> <p>Important characteristics: Age, median (range): I: 37 (18–66) C: 34 (20–71) Sex, n/N (%) male: I: 36 (60%) C: 34 (56.7%) Duration of symptoms in days prior to randomization, median (IQR) I: 4 (3–6) C: 5 (3–5)</p> <p>Groups comparable at baseline.</p>			prematurely withdrawn.	<p>Time to symptom resolution <u>Duration until resolution of symptoms* in days</u>, median (95% CI) I: 8 (6–11) C: 9 (5–11) aHR 0.94 (95% CI 0.64, 1.39)</p> <p><u>Duration until sustained symptom resolution in days</u>, median (95% CI) I: 20 (16–27) C: 20 (17–24) aHR 0.92 (0.60, 1.41), p=0.70</p> <p><u>Duration until respiratory symptom resolution in days</u>, median (95% CI) I: 6 (4–7) C: 4 (2–7) aHR 0.99 (0.64, 1.53), p=0.95</p> <p><u>Duration until systemic and respiratory symptom resolution in days</u>, median (95% CI) I: 8 (6–11) C: 5.5 (5–10) aHR 0.93 (0.63, 1.38), p=0.73</p> <p><u>Time to disease progression in days</u>, median among those who progress** (IQR) I: 5 (1) C: 2 (1) aHR 1.38 (0.52, 3.63), p=0.52</p> <p><u>Need for respiratory support</u></p>	outpatients with uncomplicated SARS-CoV-2 infection did not significantly reduce time to viral clearance or resolution of symptoms compared with placebo. Lambda was well-tolerated, with few adverse effects, though asymptomatic liver transaminase elevations occurred more frequently in participants randomized to Lambda compared with placebo.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>not reported</p> <p>Safety</p> <p><u>Adverse events</u> Serious adverse events, n (%) I: 2 (3.3%) C: 2 (3.3%), p=1</p> <p>Number of adverse events, n I: 36 C: 30</p> <p>Participants with adverse events, n (%) I: 25 (41.7%) C: 21 (35.0%), p=0.57</p> <p>LFT-related adverse events, n I: 16 C: 5</p> <p>Participants with LFT-related adverse events, n (%) I: 15 (25.0%) C: 5 (8.3%), p=0.027</p> <p>Virological outcomes</p> <p><u>Time to cessation of oropharyngeal viral shedding</u>, median (95% CI) I: 7 (5–13 days) C: 7 (5–10 days) aHR 0.81, 95% CI 0.56–1.19; p = 0.29</p> <p><i>as treated population:</i> aHR 0.83, 95% CI 0.56–1.21; p = 0.33</p> <p><i>symptomatic patients only:</i> aHR 0.77, 95% CI 0.52–1.15, p = 0.21</p> <p><u>Log Oropharyngeal viral load over time</u>, mean</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						change at day 14 (SD); I: -4.3 (4.3) C: -4.9 (4.7) Δ Log change -0.06 (95% CI -1.23, 1.11), p=0.91 <u>Log10 viral load area under the curve through day 14</u> , median (IQR); I: 28.5 (20.1) C: 29.6 (19.0) Δ AUC 1.01 (95% CI 0.85, 1.16), p=0.95	
13.8. Pegylated Interferon-2b							
Bhushan, 2021	<p><u>Type of study:</u> RCT, open-label</p> <p><u>Setting:</u> 20 centres, enrolment between 16/12/2020 and 25/03/21</p> <p><u>Country:</u> India</p> <p><u>Source of funding:</u> Cadila Healthcare Ltd., Ahmedabad, India.</p> <p><u>Conflicts of interest:</u> Some authors are speaker and/or take part in advisory boards at pharmaceutical companies. Some</p>	<p>Hospitalized moderate COVID-19 adults</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ≥ 18 years • RT-PCR confirmed COVID-19 • Pneumonia (no signs of severe disease) • Respiratory rate ≥ 24/min • SpO2 90-94% • Negative pregnancy test <p><u>Exclusion criteria:</u> NR</p> <p><u>N total at baseline:</u> N = 250 Intervention: 120 Control: 130</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 49.6 y (15.0) C: 50.1 y (15.6)</p> <p>Sex, n/N (%) male:</p>	<p>Pegylated Interferon-2b (PEG IFN-α2b) on top of standard of care</p> <p>PEG IFN-α2b: 1 µg/kg, subcutaneous injection (SC), single dose. Each vial of PEG IFN-α2b was reconstituted with 0.7 ml of water for injection for administration of up to 0.5 ml of solution. Each 0.5 ml of solution for SC injection delivers 100 µg of PEG IFN-α2b.</p>	<p>Standard of care</p> <p>Standard of care treatments (i.e., antipyretics, cough suppressants, antibiotics, steroids, vitamins, anticoagulants, hydroxychloroquine and antivirals e.g. remdesivir) were administered as per the COVID-19 clinical management guidelines of the ministry of</p>	<p><u>Length of follow-up:</u> 15-29 days</p> <p><u>Loss-to-follow-up:</u> Intervention: N=7 Control: N=7</p> <p>Reasons*: serious adverse events (n=2), lost to follow-up (n=6) and consent withdrawn (n=6) <i>*Not stratified by treatment group</i></p> <p><u>Incomplete outcome data:</u> Intervention: NR Reasons: NR Control: NR</p>	<p>Clinical outcomes <u>Mortality (28-30 day)</u> I: 2/120* C: 0/130 Effect (95%CI): NR P=NR <i>*not related to the study drug</i></p> <p><u>Duration of hospitalization</u> I: 9 C: 9 Effect (95%CI): NR P>0.05</p> <p><u>Clinical improvement from day 0 to day 11*, n/N (%)</u> I: 109/119 (91.6) C: 112 /123(92.6) Effect (95%CI): -0.97 (-8.38 to 6.42) P= 0.7818 <i>*day 8 and 15 are also reported</i></p>	<p><u>Definitions:</u> <i>Treatment emergent adverse event</i> Number of subjects with at least one treatment emergent adverse event. <i>Clinical improvement</i> Measured using the WHO 7-point ordinal scale</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> • Some important baseline characteristics are not reported (e.g. disease severity) • It is an open-label study. • Some of the authors are employees of Cadila Healthcare. All authors were involved in conceptualization of the study, data interpretation, manuscript writing and review. • Standard of care was not uniform for all centres. • Subjects were on multiple treatments, but details are not reported. <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	of the authors are employees of Cadila Healthcare.	<p>I: 87/120 (72.5%) C: 90/130 (69.2%)</p> <p>Disease severity, mean (SD): NR</p> <p>Groups comparable at baseline? Unclear, since some important characteristics were not reported (e.g. disease severity)</p>		health, Government of India and the individual institutional practice.	Reasons: NR	<p><u>Time to symptom resolution in days, median</u> I: 5 C: 6 Effect (95%CI): NR P<0.05</p> <p><u>Respiratory support</u> <i>Oxygen support, n (%)</i> I: 64 (61.5) C: 67 (59.3) Effect (95%CI): NR P= NR</p> <p><i>Duration of oxygen support in hours, median</i> I: 56 C: 84 Effect (95%CI): P<0.05</p> <p><i>Mechanical ventilation, n (%)</i> I: 2 (1.7) C:1 (0.8) Effect (95%CI): NR P= NR</p> <p>Safety <u>Adverse events</u> <i>Treatment emergent adverse event, n/N (%)</i> I: 8/120 (6.7) C: 13/130 (10.0) Effect (95%BI): NR P= NR</p> <p>Virological outcomes <u>Viral clearance, n/N (%)</u> <i>Negative PCR at day 7*</i> I: 103/119 (91.2) C: 86/123 (78.9) Effect (95%CI): NR P=0.0103</p>	Early treatment with PEG IFN-α2b induced early viral clearance and improved the clinical status of patients with moderate COVID-19 disease. It also decreased the duration of supplemental oxygen. Treatment with PEG IFN-α2b provides a viable treatment option during the current pandemic situation. It can also limit the spread of virus in the community.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>*day 11 and 15 are also reported</i></p> <p>Other reported outcome measures: duration of supplemental oxygen, Per protocol analyses are also available in supplementary materials. Serial laboratory measurements of blood levels for CRP, IL-6, D-dimer and ferritin were also conducted (not reported, but P>0.05). For the outcome measure clinical improvement, a post hoc analysis was performed for the subgroup 'with and without Remdesivir' and 'with and without steroids'.</p>	
14. JAK-inhibitors							
14.1. Baricitinib (selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)							
Ely, 2022	<p><u>Type of study:</u> multicentre, randomised, double-blind, placebo-controlled, parallel-group trial</p> <p><u>Setting:</u> hospital-based, between December 23, 2020 and April 10, 2021</p> <p><u>Country:</u> 18 centres in four countries (Argentina, Brazil, Mexico, USA).</p>	<p><u>Critically ill hospitalized COVID-19 patients on invasive mechanical ventilation or extracorporeal membrane oxygenation (NIAID-OS 7)</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Hospitalized COVID-19 patients with use of IMVO or ECMO • ≤18 years • Indicators of progression risk with at least one elevated inflammatory maker >upper limit of normal range (CRP, D-dimer, lactate dehydrogenase, or ferritin) <p><u>Exclusion criteria:</u></p>	<p>Baricitinib</p> <p>4 milligrams (mg) of baricitinib once daily for up to 14 days or until discharge from hospital, whichever occurred first</p> <p>+</p> <p>Standard treatment</p>	<p>Matched placebo + standard treatment</p> <p>Standard treatment: All participants received standard of care in keeping with local clinical practice for COVID-19 management, which could include concomitant</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> I: 24/51 (47%)</p> <p><u>Reasons</u></p> <ul style="list-style-type: none"> • <i>Randomized but not dosed (n=1)</i> • <i>Deceased(n=18)</i> • <i>Other (n=4)</i> <p>C: 31/50 (62%)</p> <p><u>Reasons</u></p> <ul style="list-style-type: none"> • <i>Randomized but not dosed (n=1)</i> • <i>Deceased (n=28)</i> 	<p><u>Clinical outcomes</u></p> <p><u>All-cause mortality at day 28</u> I: 20/51 (39%) C: 29/50 (58%) HR 0.54 (0.31 to 0.96), p=0.030</p> <p><u>All-cause mortality at day 60</u> I: 23/51 (45%) C: 31/50 (62%) HR 0.56 (0.33 to 0.97), p=0.027</p> <p><u>Duration of hospitalization</u> Days, mean (SD) I: 23.7 (7.1) C: 26.1 (3.9)</p>	<p><u>Outcome:</u></p> <ul style="list-style-type: none"> • All-cause mortality at day 28, 60 • Number of ventilator-free days • Overall improvement at days 4, 7, 10, 14, 28 • Proportion of participants with at least 1-point improvement on the NIAID-OS or live discharge from hospital at days 4, 7, 10, 15 and 28 • Duration of hospitalization • Time to recovery through day 28 <p><u>Definitions:</u></p> <p>-</p> <p><u>Remarks:</u> As the cohort reported here was an addition to the parent trial study design, all endpoints</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> Eli Lilly and Company. The funder of the study had a role in study design, data analysis, data interpretation, and writing of the report, but had no role in data collection.</p> <p><u>Conflicts of interest:</u> Transparently reported.</p>	<ul style="list-style-type: none"> Receiving high-dose corticosteroids, immunosuppressants, biologics, T-Cell or B-cell targeted therapies, IFN, or Jak inhibitors Received convalescent plasma or IV immunoglobulin for COVID-19 Suspected serious bacterial, fungal, or other infection, or untreated TB infection <p><u>N total at baseline:</u> N = 101 Intervention: 51 Control: 50</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 58.4 y (12.4) C: 58.8 y (15.2)</p> <p>Sex, n/N (%) male: I: 25/51 (49%) C: 30/50 (60%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline.</p>		<p>medications such as corticosteroids, antivirals, and other treatments, including vasopressors.</p>	<ul style="list-style-type: none"> <i>Lost to follow-up (n=1)</i> <i>Withdrawal by participant (n=1)</i> 	<p>Least square mean difference: -2.30 (-4.59 to 0.00) p=0.050</p> <p><u>Time to symptom resolution</u> not reported</p> <p><u>Invasive respiratory support</u> not reported</p> <p><u>Non-invasive respiratory support</u> not reported</p> <p><u>Ventilator-free days</u> Days, mean (SD) I: 8.1 (10.2) C: 5.5 (8.4) Least square mean difference: 2.36 (-1.38 to 6.09) p=21</p> <p>Safety <u>Serious adverse events</u> C: 25/50 (50%) I: 35/49 (71%)</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p>	<p>are considered exploratory.</p> <p><u>Authors conclusion:</u> In conclusion, treatment with baricitinib plus standard of care (including use of corticosteroids) in critically ill patients with COVID-19 who were receiving IMV or ECMO at enrolment resulted in reduction in all-cause mortality at 28 days and 60 days compared with placebo plus standard of care in this exploratory trial</p>
Marconi, 2021	<p><u>Type of study:</u> randomized, double-blind, placebo-controlled, multicentre phase 3 trial</p> <p><u>Setting:</u></p>	<p>hospitalised adults with COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age ≥ 18 y laboratory confirmed SARS-CoV-2 infection 	<p>baricitinib 4 mg/day (oral) for up to 14 days or until hospital discharge; 2 mg/day if eGFR at baseline was 30-60 mL/min per 1.73 m²</p>	<p>placebo</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention: N = 120 (15.7%) <i>Reasons</i></p>	<p>Prespecified subgroup analyses for the primary and selected key secondary endpoints evaluated treatment effect across the following subgroups: baseline severity, baseline systemic corticosteroid use,</p>	<p><u>Definitions:</u> * Population 1 includes all randomised participants. Population 2 includes participants who, at baseline, required O₂ supplementation and were not receiving dexamethasone or other systemic corticosteroids for the primary study condition.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>hospital-based, between June 11 2020 and January 15 2021</p> <p><u>Country:</u> 101 centres from 12 countries in Asia, Europe, North America and South America</p> <p><u>Source of funding:</u> Eli Lilly and Company. The trial was designed jointly by consultant experts and representatives of the sponsor. Data were collected by investigators and analysed by the sponsor. All authors participated in the interpretation of the data analysis, draft, and final manuscript review, and provided critical comment, including the decision to submit the manuscript for publication with medical writing support provided by the sponsor. The authors had full access to the data and authors</p>	<ul style="list-style-type: none"> evidence of pneumonia or active and symptomatic COVID-19 ≥ 1 inflammatory marker <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> invasive mechanical ventilation required receiving immunosuppressants received convalescent plasma or intravenous immunoglobulin for COVID-19 in past neutropenia lymphopenia ALT or AST > 5 ULN eGFR < 30 mL/min per 1.73 m² <p><u>N total at baseline:</u> Randomized: N = 1525 Intervention: N = 764 Control: N = 761</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 57.8 y (14.3) C: 57.5 y (13.8)</p> <p>Sex, n/N (%) male: I: 490/764 (64%) C: 473/761 (62%)</p> <p>Disease severity, mean (SD): <u>Defined by NIAID-OS score</u> I: score 4: 89/762 (12%) score 5: 490/762 (64%) score 6: 183/762 (24%) C: score 4: 97/756 (13%) score 5: 472/756 (62%) score 6: 187/756 (25%)</p>			<ul style="list-style-type: none"> no doses received or lost to follow-up before first post-baseline visit (n = 14) died (n = 61) lost to follow-up (n = 20) withdrawal by participant (n = 12) adverse events (n = 3) physician's decision (n = 1) other (n = 9) <p>Control: N = 157 (20.6%) <u>Reasons</u></p> <ul style="list-style-type: none"> no doses received or lost to follow-up before first post-baseline visit (n = 9) died (n = 98) lost to follow-up (n = 22) withdrawal by participant (n = 7) adverse events (n = 5) physician's decision (n = 1) other (n = 15) 	<p>baseline remdesivir use, geographical region, sex, disease duration at baseline, and age at baseline.</p> <p>Clinical outcomes <u>Mortality</u> <u>All-cause mortality at day 28</u> I: 62/764 (8%) C: 100/761 (13%) HR: 0.57 (0.41-0.78)</p> <p><u>Duration of hospitalisation in days</u> LSM (SE) I: 12.9 (0.40) C: 13.7 (0.40) LSMD: -0.76 (-1.6-0.0)</p> <p><u>Time to symptom resolution</u> <u>Time to recovery in days</u> Median (95% CI) I: 10.0 (9.0-11.0) C: 11.0 (10.0-12.0) RR: 1.11 (0.99-1.24)</p> <p><u>Likelihood of overall improvement on the NIAID-OS score</u> Day 4: OR: 1.21 (1.00-1.47) Day 7: OR: 1.25 (1.04-1.49) Day 10: OR: 1.17 (0.97-1.41) Day 14: OR: 1.28 (1.05-1.56)</p> <p>≥ 1-point improvement on the NIAID-OS score or live discharge from hospital Day 4: OR: 1.26 (0.98-1.61)</p>	<p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Although there was no significant reduction in the frequency of disease progression overall, treatment with baricitinib in addition to standard of care (including dexamethasone) had a similar safety profile to that of standard of care alone, and was associated with reduced mortality in hospitalised adults with COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>from the sponsor verified the veracity, accuracy, and completeness of the data and analyses as well as the fidelity of this report to the protocol.</p> <p><u>Conflicts of interest:</u> Several authors received research grants, honoraria or research support from the sponsor. Several authors are employees and shareholders of the sponsor. Several authors served as an advisory board member, speaker or consultant, or scientific advisor of the sponsor.</p>	Groups were comparable at baseline.				<p>Day 7: OR: 1.18 (0.95-1.46) Day 10: OR: 1.07 (0.86-1.34) Day 14: OR: 1.21 (0.95-1.55)</p> <p><u>Change from baseline in O₂ saturation from < 94% to ≥ 94%</u> Day 4: OR: 1.20 (0.86-1.69) Day 7: OR: 0.97.18 (0.95-1.46) Day 10: OR: 1.07 (0.86-1.34) Day 14: OR: 1.21 (0.95-1.55)</p> <p><u>Respiratory support</u> <u>Number of ventilator-free days</u> LSM (SE) I: 24.5 (0.39) C: 23.7 (0.39) LSMD: 0.75 (-0.0-1.5)</p> <p><u>Progression to high-flow O₂, non-invasive ventilation, invasive mechanical ventilation, or death at day 28 – primary outcome</u> <i>Population 1*</i> I: 27.8% C: 30.5% OR: 0.85 (95% CI: 0.67-1.08)</p> <p><i>Population 2*</i> I: 28.9% C: 27.1% OR: 1.12 (95% CI: 0.58-2.16)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Safety <u>Serious adverse events</u> I: 110/750 (15%) C: 135/752 (18%) Virological outcomes Not reported	
Kalil, 2020	<p><u>Type of study:</u> Double-blind, placebo-controlled RCT</p> <p><u>Setting:</u> 67 trials sites in 8 countries</p> <p><u>Country:</u> USA (55 sites), Singapore (4 sites), South Korea (2 sites), Mexico (2 sites), Japan (1 site), Spain (1 site), UK (1 site) and Denmark (1 site).</p> <p><u>Source of funding:</u> The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council.</p>	<p>Hospitalized adults with COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age >18 years; • Hospitalized with symptoms of COVID-19; • Suggestive of lower respiratory tract infection at time of enrolment; • Radiographic infiltrates by imaging study; • Peripheral oxygen saturation <95% on room air; • Requiring supplemental oxygen; • Mechanical ventilation; • Extracorporeal membrane oxygenation. • Agreeing not to participate in another COVID-19 treatment clinical trial through day 29; • Practicing heterosexual abstinence or using study-specific contraception through day 29 for woman of childbearing potential. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Having either an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 x upper limit of normal range; • Need for hemodialysis or hemofiltration; 	<p><u>Remdesivir + Baricitinib</u></p> <p><u>Remdesivir:</u> intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death <u>Baricitinib:</u> 4-mg daily dose (either orally) or through a nasogastric tube) for 14 days or until hospital discharge or death.</p>	<p><u>Remdesivir + placebo</u></p> <p><u>Remdesivir:</u> intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death <u>Placebo:</u> matching oral placebo, administered according to same schedule as active drug.</p>	<p><u>Length of follow up:</u> 29 days</p> <p><u>Loss to follow-up:</u> I: 40/515 (7.8%) Reasons: not reported C: 41/518 (7.9%) Reasons: not reported</p>	<p>Clinical outcomes</p> <p><u>(Overall) Mortality over first 14 days</u> HR= 0.54 (0.23 to 1.28) I: N = 8/515 (7.0%) C: N = 15/518 (2.9%)</p> <p><u>Subgroups - Mortality over first 14 days</u></p> <p><u>baseline ordinal score of 4</u> HR= Not estimable I: N = 0/70 (0%) C: N = 0/72 (0%)</p> <p><u>baseline ordinal score of 5</u> HR= 0.73 (95% CI= 0.16 to 3.26) I: N = 3/288 (1.0%) C: N = 4/276 (1.4%)</p> <p><u>baseline ordinal score of 6</u> HR= 0.21 (95% CI= 0.02 to 1.80) I: N = 1 /103 (1.0%) C: N = 5/113 (4.4%)</p> <p><u>baseline ordinal score of 7</u> HR= 0.69 (95% CI= 0.19 to 2.44) I: N = 4/54 (7.4%) C: N = 6/57 (10.5%)</p>	<p><u>Definitions:</u> Baseline score on ordinal scale 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care 5 = Hospitalized, requiring supplemental oxygen 6 = Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices 7 = Hospitalized, receiving invasive mechanical ventilation or EMCO</p> <p><u>Remarks:</u> A total of 498 patients in the intervention group and 495 in the control group completed the trial through day 29, recovered or died.</p> <p><u>Authors conclusion:</u> Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status, notably among patients receiving high-flow oxygen or non-invasive mechanical ventilation. The combination was associated with fewer serious adverse events.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> Allergy to study product; Pregnancy or breast-feeding; Anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrolment. <p><u>N total at baseline:</u> N = 1033 Intervention: N = 515 Control: N = 518</p> <p><u>N intension-to-treat population</u> 706 patients with moderate disease (ordinal scale 4 or 5) and 327 patients with severe disease (ordinal scale 6 or 7).</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 55 y (15.4) C: 55.8 y (16.0)</p> <p>Sex, n/N (%) male: I: 319/515 (61.9%) C: 333/518 (64.3%)</p> <p>Disease severity, N (%): <i>Classified as moderate or severe</i> Moderate I: 358/515 (69.5%) C: 348/518 (67.2%) Severe I: 157/515 (30.5%) C: 170/518 (32.8%)</p> <p>Baseline score on ordinal scale 4 = Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care I: 70/515 (13.6%) C: 72/518 (13.9%)</p>				<p><u>(Overall) mortality over entire trial period (28 days)</u> HR= 0.65 (95% CI= 0.39 to 1.09) I: N = 24/515 (4.7%) C: N = 37/518 (7.1%)</p> <p><u>Subgroups - Mortality over entire trial period (28 days)</u> <u>baseline ordinal score 4</u> HR= Not estimable I: N = 0/70 0(%) C: N = 0/72 (0%) <u>baseline ordinal score 5</u> HR= 0.40 (95% CI= 0.14 to 1.14) I: N = 5/288 (1.7%) C: N = 12/276 (4.3%) <u>baseline ordinal score 6</u> HR= 0.55 (95% CI= 0.22 to 1.38) I: N = 7/103 (6.8%) C: N = 13/113 (11.5%) <u>baseline ordinal score 7</u> HR= 1.00 (95% CI= 0.45 to 2.22) I: N = 12/54 (22.2%) C: N = 12/57 (21.1%)</p> <p><u>(Overall) Median time to recovery, in days; (rate ratio for recovery [95% CI]</u> I: 7 days C: 8 days Rate ratio for recovery= 1.16 (95% CI= 1.01 to 1.32) p=0.03</p> <p><u>Median time to recovery (baseline ordinal score of</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>5 = Hospitalized, requiring supplemental oxygen I: 288/515 (55.9%) C: 276/518 (53.5%)</p> <p>6 = Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices I: 103/515 (20.0%) C: 113/518 (21.8%)</p> <p>7 = Hospitalized, receiving invasive mechanical ventilation or EMCO I: 54/515 (10.5%) C: 57/518 (11.0%)</p> <p>Groups comparable at baseline? Yes</p>				<p><u>4) in days; (rate ratio for recovery [95% CI]</u> I: 5 (4 to 6) days C: 4 (4 to 6) days Rate ratio for recovery= 0.88 (95% CI= 0.63 to 1.23)</p> <p><u>Median time to recovery (baseline ordinal score of 5) in days; (rate ratio for recovery [95% CI]</u> I: 5 (5 to 6) days C: 6 (5 to 6) days Rate ratio for recovery= 1.17 (95% CI= 0.98 to 1.39)</p> <p><u>Median time to recovery (baseline ordinal score of 6) in days; (rate ratio for recovery [95% CI]</u> I: 10 (9 to 13) days C: 18 (13 to 21)days Rate ratio for recovery= 1.51 (95% CI= 1.10 to 2.08)</p> <p><u>Median time to recovery (baseline ordinal score of 7) in days; (rate ratio for recovery [95% CI]</u> I: Not estimable (25 to NE) C: Not estimable (26 to NE) Rate ratio for recovery= 1.08 (95% CI= 0.59 to 1.97)</p> <p><u>(Overall) Improvement in clinical status at day 15</u> OR= 1.3 (95% CI= 1.0 to 1.6)</p> <p><u>Subgroups - Improvement in clinical status at day 15 baseline score of 4</u> OR= 0.6 (95% CI= 0.3 to 1.1)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>baseline score of 5</u> OR= 1.2 (95% CI= 0.9 to 1.6)</p> <p><u>baseline score of 6</u> OR= 2.2 (95% CI= 1.4 to 3.6)</p> <p><u>baseline score of 7</u> OR= 1.7 (95% CI= 0.8 to 3.4)</p> <p><u>Median duration of initial hospitalization IQR) in days (with imputation of data for those who died)</u> I: 8 (5 to 15) days C: 8 (5 to 20) days Rate ratio= 0.0 (95% CI= -1.1 to 1.1)</p> <p><u>Median duration of initial hospitalization IQR) in days (among those who did not die)</u> I: 8 (5 to 13) days C: 8 (5 to 15) days Rate ratio= 0.0 (-1.0 to 1.0)</p> <p><u>% patients re-hospitalized (95% CI)</u> I: 3% (2 to 5) C: 2% (1 to 4) Rate ratio= 1.0 (95% CI= -1.1 to 3.1)</p> <p><u>Median days receiving oxygen if receiving oxygen at baseline (IQR) (with imputation of data for those who died)</u> I: 10 (4 to 27) days C: 12 (4 to 28) days Rate ratio= -2.0 (95% CI= -5.2 to 1.2)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>Median days receiving oxygen if receiving oxygen at baseline (IQR) (among those who did not die)</u> I: 9 (4 to 23) days C: 10 (4 to 28) days Rate ratio= -1.0 (95% CI= -3.5 to 1.5)</p> <p><u>Median days of mechanical ventilation or ECMO during trial if receiving these interventions at baseline (IQR) (with imputation of data for those who died)</u> I: 20 (9 to 28) days C: 24 (19 to 28) days Rate ratio= -4.0 (95% CI= -10.1 to 2.1)</p> <p><u>Median days of mechanical ventilation or ECMO during trial if receiving these interventions at baseline (IQR) (among those who did not die)</u> I: 13 (7 to 24) days C: 16 (6 to 28) days Rate ratio= -2.0 (95% CI= -11.4 to 7.4)</p> <p><u>Adverse events (grade 3 or 4)</u> I: N = 207 (40.7%) C: N = 238 (46.8%)</p>	
14.2. Fedratinib							
NA	NA	NA	NA	NA	NA	NA	NA
14.3. Filgotinib							
NA	NA	NA	NA	NA	NA	NA	NA
14.4. Nezulcitinib							

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
NA	NA	NA	NA	NA	NA	NA	NA
14.5. Oclacitinib							
NA	NA	NA	NA	NA	NA	NA	NA
14.6. Peficitinib							
NA	NA	NA	NA	NA	NA	NA	NA
14.7. Ruxolitinib (Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)							
Han, 2022	<p><u>Type of study:</u> Double-blind, multi center, placebo-controlled, phase 3 randomized clinical trial</p> <p><u>Setting:</u> Hospitalized, between May 4 and September 2020</p> <p><u>Country:</u> 61 center across 12 countries (Russia, USA, Brazil, Spain, Argentina, Peru, Turkey, Mexico, UK, Colombia, France, and Germany)</p> <p><u>Source of funding:</u> Novartis and Incyte</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported</p>	<p>Hospitalized COVID-19 patients</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • ≥12 years • Confirmed COVID-19 by PCR or another rapid test • At least one of the following criteria: <ul style="list-style-type: none"> - respiratory frequency of at least 30 breaths per min - requiring supplementary oxygen - oxygen saturation of 94% or less on room air - or arterial oxygen partial pressure (PaO₂)/fraction of inspired oxygen (FiO₂) of less than 300 mm Hg (40 kPa). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Uncontrolled infection besides COVID-19 • Currently intubated or intubated between screening and randomisation • In ICU at time of randomisation • On antirejection, immunosuppressant, or immunomodulatory drugs • Unable to ingest tablets at randomisation • Pregnant or nursing. 	<p>Ruxolitinib 5 mg twice per day, for 14 days.</p> <p>An additional 14 days of study drug was allowed if, in the opinion of the investigator, the patient's clinical signs and symptoms were not improving or worsened, and the potential benefit outweighed the risk.</p> <p>+ Standard of care</p>	<p>Oral matching-image placebo for 14 days</p> <p>+ standard of care.</p> <p>Study treatment was given in combination with standard-of-care therapy according to the investigator's clinical judgment, with appropriate monitoring of potential drug-drug interactions.</p> <p>Permitted concomitant therapies included antivirals (including remdesivir), corticosteroids (including dexamethasone), heparin,</p>	<p>Length of follow-up: 29 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: 18/287 (6.3%) discontinued study</p> <p>36/287 (12.6%) permanently discontinued study treatment</p> <p>Reasons: adverse events (n=14), patient decision (n=10), physician decision (n=6), progressive disease (n=3), death (n=2), protocol deviation (n=1)</p> <p>-----</p> <p>Control: 6/145 (4.1%) discontinued study</p> <p>11/145 (7.6%) permanently discontinued study treatment</p> <p>Reasons: adverse events (n=5), patient</p>	<p>Clinical outcomes</p> <p><u>Mortality rate by day 29, n/N (%):</u> I: 9/286 (3%) C: 3/145 (2%) OR 1.21 (0.35-5.11)</p> <p><u>Duration of hospitalization</u> Median (95% CI) I: 9 (8-10) C: 9 (8-12) HR: 1.04 (0.84-1.28)</p> <p><u>Time to symptom resolution</u> Defined as time to recovery in days (no longer infected, or ambulatory with no or minimal limitations), median (95% CI) I: 8 (8-9) C: 9 (7-11) HR: 1.10 (0.89-1.36)</p> <p><u>Invasive respiratory support</u> Not reported, is embedded in the composite endpoint</p> <p><u>Non-invasive respiratory support</u> Not reported</p> <p>Safety <u>Serious adverse events</u> Grade 3 or more</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Composite of death, respiratory failure (requiring invasive mechanical ventilation), or ICU care, by day 29 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Mortality rate by day 29 • Duration of hospitalization • Changes in clinical status • changes in the NEWS2 <p><u>Definitions:</u> -</p> <p><u>Remarks:</u> The overall therapeutic landscape and standard of care changed substantially during the study, and this change might have impacted the proportion of patients meeting the primary endpoint in the control group. Remdesivir became the standard of care in the USA, but not in all countries where our study took place. More recent studies, like ACTT-2, demonstrated the benefit of combination therapy in this setting.</p> <p><u>Authors conclusion:</u> Ruxolitinib 5 mg twice per day showed no benefit in the overall study population. A larger sample is required to determine the clinical importance of trends for increased efficacy in patient subgroups.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>N total at baseline:</u> N = 432 Intervention: N=287 Control: N=145</p> <p><u>Important characteristics:</u> Age, median (SD): I: 56.4 y (13.7) C: 56.9 y (12.5)</p> <p>Sex, n/N (%) male: I: 162/287 (56%) C: 73/145 (50%)</p> <p>Disease severity Based on WHO (0-8) clinical status, n/N (%)</p> <p>3, hospitalised with mild disease (no oxygen therapy [defined as SpO2 ≥94% on room air]) I: 94/287 (33%) C: 47/145 (32%)</p> <p>4, hospitalised with mild disease (oxygen by mask or nasal prongs) I: 175/287 (61%) C: 93/145 (64%)</p> <p>5, hospitalised with severe disease (non-invasive ventilation or high-flow oxygen) I: 17/287 (6%) C: 5/145 (3%)</p> <p>Groups comparable at baseline? Yes</p>		<p>anticoagulants, antiemetics, calcineurin inhibitors, azole fungal prophylaxis, broad-spectrum antibiotics, narcotics, and sedatives.</p> <p>Prohibited medications were other JAK inhibitors, aspirin (>150 mg/day), and fluconazole (>200 mg/day).</p>	<p>decision (n=2), physician decision (n=2), progressive disease (n=1), death (n=1)</p>	<p>I: 31/281 (11%) C: 14/143 (10%)</p> <p>All adverse events are specified in the original publication.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	
Cao, 2020b Preprint, definitive	<u>Type of study:</u> Multicenter, single-blind RCT	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> Met the diagnostic criteria for COVID-19 Between 18 and 75 years of age 	Oral intake of ruxolitinib 5mg twice a day plus standard-of-care (SoC)	Placebo (100mg vitamin C) twice a day with SoC	<u>Length of follow-up:</u> 28 days <u>Loss-to-follow-up:</u>	<u>Time to clinical improvement</u> Patients treated with ruxolitinib had a	<u>General remarks:</u> <ul style="list-style-type: none"> Small sample size Few endpoints reach statistical significance

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
version not published yet	<p><u>Setting:</u> 42 patients were randomly assigned to treatment with either ruxolitinib or placebo, in the Tongji 139 hospital, No.1 hospital and the Third Xiangya hospital in China.</p> <p><u>Country:</u> Wuhan, China</p> <p><u>Source of funding:</u> Principal investigators who has no role in the study</p>	<ul style="list-style-type: none"> Severe cases, as defined according to the Chinese management guideline for COVID-19 (version 5.0) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients with concomitant malignant tumours Patients with severe cardiovascular and metabolic disease that is not medically controlled Patients with a mental or severe psychiatric disorder Patients in need of invasive mechanic ventilation at recruitment Patients who could not guarantee to complete all the scheduled treatment plans and follow-ups Women of child-bearing age with positive pregnancy tests or those in the lactating period Patients whose condition was further complicated with other active infections. <p><u>N total at baseline:</u> N = 42</p> <p><u>Important characteristics:</u> Mean age: 63 years (58-68 year) Male gender: 58,5%</p>	SoC: antiviral therapy, supplemental oxygen, non-invasive and invasive ventilation, corticosteroid, antibiotic agents, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation (ECMO).		N/a	<p>numerically shorter median time to clinical improvement (12 days vs 15 days, P=0.147)</p> <p><u>Clinical improvement rate</u> No statistical differences were detected between groups</p> <p><u>Time from randomization to lymphocyte recovery and to invasive mechanical ventilation</u> Lymphocyte recovery: Ruxolitinib: 5 days Control group: 8 days (P=0,033)</p> <p>Invasive mechanical ventilation: Time to invasive mechanical ventilation is not reported, however the incidence is reported: Ruxolitinib: 0 patients Control group: 3 patients</p> <p><u>Duration of hospitalization in survivors</u> No significant difference in days from randomization to discharge between two treatment groups (P=0,941)</p> <p><u>Time from treatment initiation to death and virus clearance time</u> 28-day overall mortality: Ruxolitinib: 0% Control group: 14,3%</p>	<p><u>Author conclusion:</u> Ruxolitinib added to SoC treatment does not lead to significantly accelerated clinical improvement in severe patients with COVID-19.</p> <p>As at Chest CT at D14 a significant faster improvement is reported in Ruxolitinib (90%) versus control group (61,9%), (P=0,0495), and no deaths occurred in the Ruxolitinib group, authors suggest further investigation in the effect of Ruxolitinib treatment on deterioration and death of COVID-19 patients</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Median time from randomization to death in control group: 15 days</p> <p>Virus clearance time: Ruxolitinib: 13 days Control group: 12 days (P=0.6549)</p> <p><u>Incidence of serious adverse events occurring up to 28 days</u> Adverse events from randomization to D28: Ruxolitinib: 16 patients (80%), Control group: 15 patients (71,4%), differences were not statistically significant.</p> <p><u>Adverse events and serious adverse events that occurred during treatment</u> Ruxolitinib group: 1 patients with Grade 3 lymphocytopenia, 1 patient with Grade 3 hypertension Control group: serious adverse events, as secondary infection, sepsis, shock, acute heart failure.</p>	
14.8. Tofacitinib							
Murugesan, 2021	<p><u>Type of study:</u> open-label RCT (pilot)</p> <p><u>Setting:</u></p>	<p>hospitalized patients with COVID-19 pneumonia</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age: 18-65 y 	<p>Tofacitinib was administered in a dose of 10 mg PO BID for 14 days</p> <p>+</p>	<p>Standard of care included: Ceftriaxone, Enoxaparin, Heparin, Remdesivir,</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Not reported</p>	<p>Clinical outcomes</p> <p>Mortality</p> <p>There was no mortality in both groups.</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u></p> <p><u>Authors conclusion:</u> Administering Tofacitinib</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>hospital-based, between October, 2020 and December 2020</p> <p><u>Country:</u> 1 hospital, Chennai, India</p> <p><u>Source of funding:</u> This trial was supported by Pfizer.</p> <p><u>Conflicts of interest:</u> Not reported.</p>	<ul style="list-style-type: none"> • SARS-CoV-2 infection confirmed by RT-PCR and radiological imaging • presence of bilateral pneumonia with or without ground glass opacity • not requiring intubation at enrolment • arterial oxygen saturation (SpO2) > 94% (mild) or 90-93% (moderate) at room-air • respiratory rate of 16-30/min <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • patients on mechanical ventilation at time of admission • known allergies to tofacitinib • concurrent immunosuppression with biological agents • receiving any corticosteroid treatment • history of major cardiovascular events and/or recent revascularization • history of deep venous thrombosis or pulmonary embolism, • pre-existent neurodegenerative disease • severe hepatic or renal impairment • severe anemia (Hb <8) • history of any malignancy or lymphoproliferative disorders that requires active treatment <p><u>N total at baseline:</u> Randomized: N = 100</p> <p>Intervention : N = 50 Control: N = 50</p>	standard of care	Dexamethasone , Methylprednisolone at the recommended dosing and supplementary oxygen wherever required		<p><u>Duration of hospitalisation</u> Not reported</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> <u>FiO2 N(%)</u> I: 14 (28)% C: 13 (26%) P=0.822</p> <p><u>Safety</u> <u>Adverse events</u> No adverse events were reported.</p> <p><u>Virological outcomes</u> Not reported</p> <p><i>Also available: CRP levels, ferritin levels, D-Dimer levels, CBC, RFT, LFT and electrolytes levels of the participants</i></p>	at a 10 mg dose for a period of 14 days along with the standard of care treatment seems to have an added benefit of an anti-inflammatory response in patients with mild-to-moderate COVID-19 infections.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>Important characteristics:</u></p> <p>Age, median (IQR): I: 47.0 (39.0-54.0) C: 46.0 (37.0-57.0)</p> <p>Sex, n/N (%) male: I: 38/50 (76%) C: 36/50 (72%)</p> <p>SpO2 at baseline, median (IQR): I: 96 (94-97) C: 97 (95-98)</p> <p>CT-score at baseline, n(%) Grade 1 I: 15 (30%) C: 23 (46%)</p> <p>Grade 2 I: 27 (54%) C: 22 (44%)</p> <p>Grade 3 I: 8 (16%) C: 5 (10%)</p> <p>Groups comparable at baseline? Most of the patients in the control group had a lower CT score of grade-1, whereas most of the patients in the treatment group had higher CT-score of grade-2 and 3.</p>					
Guimarães, 2021	<u>Type of study:</u> Randomized, placebo-controlled, blinded parallel-group clinical trial	<p><u>Hospitalized COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Male or female participants older than 18 years; • Laboratory-confirmed novel coronavirus (SARS-CoV-2) 	Tofacitinib Oral tofacitinib at a dose of 10 mg twice daily for up to 14 days or until hospital discharge, whichever was earlier.	Placebo Oral placebo at a dose of 10 mg twice daily for up to 14 days or until hospital	<u>Length of follow-up:</u> 28 days. <u>Loss-to-follow-up:</u> All the patients in both groups completed the 28-day	Clinical outcomes <u>Mortality or respiratory failure through day 28</u> I: 26/144 (18.1%) C: 42/145 (29.0%) HR 0.63 (95% CI 0.41 to 0.97)	<u>Definitions:</u> ECMO = extracorporeal membrane oxygenation <u>Remarks:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> Academic Research Organization of the Hospital Israelita Albert Einstein in São Paulo</p> <p><u>Country:</u> Brazil</p> <p><u>Source of funding:</u> The trial was sponsored by Pfizer and was designed and led by a steering committee that included academic investigators and representatives from Pfizer.</p> <p><u>Conflicts of interest:</u> Not reported.</p> <p>ClinicalTrials.gov NCT04469114</p>	<p>infection as determined by polymerase chain reaction (PCR) or other commercially available or public health assay prior to Day 1;</p> <ul style="list-style-type: none"> Evidence of COVID-19 pneumonia assessed by radiographic imaging (chest x-ray or chest CT scan); Hospitalized and receiving standard care for COVID-19. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Require non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) on Day 1; History of or known current thrombosis. If current thrombosis is suspected by the investigator, imaging testing is recommended to exclude thrombosis; Personal or first-degree family history of blood clotting disorders; Participants who are immunocompromised, with known immunodeficiencies, or taking potent immunosuppressive agents (e.g., azathioprine, cyclosporine); Any current malignancy or lymphoproliferative disorders that requires active treatment; Severe hepatic impairment, defined as Child-Pugh class C. • Severe anemia (hemoglobin 20 		discharge, whichever was earlier.	follow-up or died. No patient was lost to follow-up or withdrew consent.	<p>P=0.04</p> <p><u>Mortality through day 28</u> I: 4/144 (2.8%) C: 8/145 (5.5%) HR 0.49 (95% CI 0.15 to 1.63)</p> <p><u>Duration of hospitalization</u> <i>Median length of initial hospitalization (IQR) in days</i> I: 5.5 (3.0 to 8.25) C: 6.0 (3.0 to 11.0) HR 1.18 (95% CI 0.94 to 1.48)</p> <p><i>Median length of initial hospitalization at the ICU (IQR) in days</i> I: 5.0 (3.0 to 11.0) C: 5.0 (2.0 to 11.5) HR 1.11 (95% CI 0.72 to 1.70)</p> <p><i>Median duration of mechanical ventilation (IQR) in days</i> I: 12.5 (9.25 to 17.0) C: 12.0 (6.0 to 21.0) Difference in median: 1.00 (-7.0 to 7.0)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> <i>Respiratory failure (1,2 or 3 on the 8-point NIAID ordinal scale of disease severity at day 28</i></p>	<p>- Cure refers to resolution of fever, cough, and need for ventilatory or oxygen support</p> <p><u>Authors conclusion:</u> In this trial, among hospitalized adult patients with Covid-19 pneumonia, tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>mg/day for equal or more than 14 consecutive days prior to screening</p> <p><u>N total at baseline:</u> N = 289 Intervention: 144 Control: 145</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 55 y (14) C: 57 y (14)</p> <p>Sex, n/N (%) female: I: 50/144 (34.7%) C: 51/145 (35.2%)</p> <p>Disease severity, mean (SD): <i>Defined by NIAID ordinal scale</i></p> <p>4: hospitalized, not receiving supplemental oxygen but receiving ongoing medical care, Covid-19 related or otherwise I: 34/144 (23.6%) C: 37/145 (25.5%)</p> <p>5: hospitalized, receiving supplemental oxygen through low-flow devices I: 91/144 (63.2%) C: 90/145 (62.1%)</p> <p>6: hospitalized, receiving supplemental oxygen through high-flow devices I: 19/144 (13.2%) C: 18/145 (12.4%)</p> <p>Groups comparable at baseline? Yes.</p>				<p>1: not hospitalized, with no limitations on activities; I: 129/144 (89.6%) C: 119/145 (82.1%)</p> <p>2: was not hospitalized but had limitation on activities or was receiving supplemental oxygen at home; I: 5/144 (3.5%) C: 10/145 (6.9%)</p> <p>3: was hospitalized, without use of supplemental oxygen and no longer required ongoing medical care; I: 0/144 (0%) C: 1/145 (0.7%)</p> <p>4: hospitalized, not receiving supplemental oxygen but receiving ongoing medical care, Covid-19 related or otherwise I: 0/144 (0%) C: 2/145 (1.4%)</p> <p>5: hospitalized, receiving supplemental oxygen through low-flow devices I: 4/144 (2.8%) C: 1/145 (0.7%)</p> <p>6: hospitalized, receiving supplemental oxygen through high-flow devices I: 1/144 (0.7%) C: 0/145 (0%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>7: hospitalized and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (EMMO) I: 1/144 (0.7%) C: 4/145 (2.8%)</p> <p>8: died I: 4/144 (2.8%) C: 8/145 (5.5%)</p> <p><u>Respiratory support</u> <i>Respiratory failure (1,2 or 3 on the 8-point NIAID ordinal scale of disease severity at day 14</i></p> <p>1: not hospitalized, with no limitations on activities; I: 110/144 (76.4%) C: 96/145 (66.2%)</p> <p>2: was not hospitalized but had limitation on activities or was receiving supplemental oxygen at home; I: 11/144 (7.6%) C: 15/145 (10.3%)</p> <p>3: was hospitalized, without use of supplemental oxygen and no longer required ongoing medical care; I: 1/144 (0.7%) C: 2/145 (1.4%)</p> <p>4: hospitalized, not receiving supplemental oxygen but receiving ongoing medical care,</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>Covid-19 related or otherwise I: 5/144 (3.5%) C: 6/145 (4.1%)</p> <p>5: hospitalized, receiving supplemental oxygen through low-flow devices I: 7/144 (4.9%) C: 6/145 (4.1%)</p> <p>6: hospitalized, receiving supplemental oxygen through high-flow devices I: 1/144 (0.7%) C: 6/145 (4.1%)</p> <p>7: hospitalized and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (EMMO) I: 7/144 (4.9%) C: 9/145 (6.2%)</p> <p>8: died I: 2/144 (1.4%) C: 5/145 (3.4%)</p> <p><u>Status at day 14:</u> <i>Alive and not using mechanical ventilation or ECMO</i> I: 135/144 (93.8%) C: 131/145 (90.3%) RR 1.04 (95% CI 0.97 to 1.12)</p> <p><i>Alive and not hospitalized</i> I: 121/144 (84.0%) C: 111/145 (76.6%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						RR 1.11 (95% CI 0.99 to 1.24) <u>Status at day 28</u> <i>Alive and not using mechanical ventilation or ECMO</i> I: 139/144(96.5%) C: 133/145 (91.7%) 1.06 (95% CI 1.00 to 1.12) <i>Alive and not hospitalized</i> I: 134/144 (93.1%) C: 129/145 (89.0%) RR 1.05 (95% CI 0.97 to 1.13) <i>Cured</i> I: 134/144 (93.1%) C: 132/145 (91.0%) RR 1.03 (95% CI 0.95 to 1.10) Safety <u>Adverse events</u> <i>Any event</i> I: 37/142 (26.1%) C: 32/142 (22.5%) <i>Acute respiratory failure</i> I: 8/142 (5.6%) C: 5/142 (3.5%) *All adverse events are specified in the original publication. Virological outcomes <u>Viral clearance</u> Not reported.	
14.9. Upadacitinib							
NA	NA	NA	NA	NA	NA	NA	NA

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
15. IL1-remmers							
15.1. Anakinra (humane interleukine-1-receptorantagonist)							
Declercq, 2021	<p><u>Type of study:</u> Multicentre, open-label, 2x2 factorial, randomised, controlled phase 3 trial</p> <p><u>Setting:</u> Hospital-based, between April 4 and December 6, 2020</p> <p><u>Country:</u> 16 hospitals in Belgium</p> <p><u>Source of funding:</u> Belgian Health Care Knowledge Centre and VIB Grand Challenges program. The funder of the study (Belgian Health Care Knowledge Centre) was involved in purchasing study medication and study design, but was not involved in data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit. The funder (VIB Grand Challenges) was involved in</p>	<p>Hospitalised patients with COVID-19, hypoxia, and signs of a cytokine release syndrome</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age > 18 y • laboratory proven diagnosis of COVID-19 with symptoms between 6 and 16 days • P_aO₂/F_iO₂ < 350 mmHg on room temperature or < 280 mmHg on supplemental oxygen and bilateral pulmonary infiltrates • COVID-19-associated cytokine release* • use of one of the following: <ul style="list-style-type: none"> ○ invasive mechanical ventilation, OR ○ non-invasive ventilation or continuous use of CPAP for hypoxia, OR ○ oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • mechanical ventilation for more than 24 h at randomization • a clinical frailty score greater than 3 before SARS-CoV-2 infection • unlikelihood to survive beyond 48 h based on clinical assessment • an active co-infection defined on clinical grounds (positive blood or sputum cultures) 	<p>Intervention 1: anakinra 100 mg 1 dd s.c. for 28 days or until hospital discharge + standard care</p> <p>Intervention 2: siltuximab 11 mg/kg i.v. (single injection) (= intervention 2a)</p> <p>OR</p> <p>tocilizumab 8 mg/kg i.v. (not exceeding 800 mg; single injection) (= intervention 2b)</p>	<p>Control 1: standard care</p> <p>Control 2: standard care</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up:</u> I1: 0/112 (0%) <i>Reasons:</i> -</p> <p>C1: 6/230 (3%) <i>Reasons:</i></p> <ul style="list-style-type: none"> • withdrew consent (n = 4) • transfer to other hospital (n = 2) <p>I2a: 2/113 (2%) <i>Reasons:</i></p> <ul style="list-style-type: none"> • withdrew consent (n = 2) <p>I2b: 2/114 (2%) <i>Reasons:</i></p> <ul style="list-style-type: none"> • transfer to other hospital (n = 2) <p>C2: 2/115 (2%) <i>Reasons:</i></p> <ul style="list-style-type: none"> withdrew consent (n = 2) 	<p>Clinical outcomes</p> <p>Mortality</p> <p><u>Number of deaths</u></p> <p>I1: 10/44 (23%) I1+I2a: 5/32 (16%) I1+I2b: 6/36 (17%) I2a: 10/81 (12%) I2b: 15/75 (20%) C: 9/74 (12%)</p> <p><u>Estimated mortality at day 28</u></p> <p>I1: 16% (95%CI: 8-31) I1+I2a: 13% (95%CI: 5-30) I1+I2b: 17% (95%CI: 8-33) I2a: 11% (95%CI: 6-20) I2b: 13% (95%CI: 7-23) C: 10% (95%CI: 5-20)</p> <p><u>Estimated mortality at day 90</u></p> <p>I1: 23% (95%CI: 13-38) I1+I2a: 16% (95%CI: 7-34) I1+I2b: 17% (95%CI: 8-33) I2a: 12% (95%CI: 7-22) I2b: 19% (95%CI: 12-30) C: 13% (95%CI: 7-23)</p> <p>Duration of hospitalization</p> <p><u>Time until discharge</u></p> <p>Days, median I1: 14 (95%CI: 11-19) C1: 12 (95%CI: 11-18) HR 0.90 (95%CI: 0.70-1.16)</p> <p>I2: 12 (95%-CI: 11-18) C2: 13 (95%-CI: 11-19) HR 1.02 (95%CI: 0.80-1.31)</p> <p><u>Number of days in hospital</u></p>	<p><u>Definitions:</u></p> <p>* Patients needed to have either a single ferritin concentration measurement of more than 2000 µg/L at inclusion when they immediately required high flow oxygen or mechanical ventilation, or a ferritin concentration of more than 1000 µg/L, which had been increasing over the previous 24 h, or lymphopenia below 800/mL with two of the following criteria: an increasing ferritin concentration of more than 700 µg/L; an increasing lactate dehydrogenase concentration of more than 300 international units (IU)/L; an increasing CRP concentration of more than 70 mg/L; or an increasing D-dimers concentration of more than 1000 ng/mL. If the patient had three of the previous criteria at hospital admission with lymphopenia of less than 800/µL, there was no need to document an increase over 24 h.</p> <p>† Defined as the time in days from randomisation until either an increase of at least two points on a 6-category ordinal scale (compared with the worst status at day of randomisation) or to discharge from the hospital alive, whichever occurred first. The 6-category ordinal scale was defined as 1=death; 2=hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 3=hospitalised, on non-invasive ventilation or high-flow oxygen devices; 4=hospitalised, requiring supplemental oxygen; 5=hospitalised, not requiring</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>purchasing reagents for measuring biomarkers.</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported.</p>	<ul style="list-style-type: none"> thrombocytopenia of less than 50 000/μL or neutropenia of less than 1500/μL history of bowel perforation or diverticulitis high dose systemic steroid or immunosuppressive drug use for a COVID-19-unrelated disorder <p><u>N total at baseline:</u> Randomized: N = 342 ITT population: N = 342</p> <p>Intervention 1:: N = 112 Control 1: N = 230 Intervention 2a: N = 113 Intervention 2b: N = 114 Control 2: N = 115</p> <p><u>Important characteristics:</u> Age, median (IQR): I1: 67 y (56-74) C1: 64 y (54-72)</p> <p>I2: 59 y (52-74) C2: 62 y (55-71)</p> <p>Sex, n/N (%) male: I1: 87/112 (78%) C1: 178/230 (77%)</p> <p>I2: 175/227 (77%) C2: 90/115 (78%)</p> <p>Mechanical ventilation at day of randomisation <i>Invasive</i> I1: 17/112 (15%) C1: 22/230 (10%)</p> <p>I2: 22/227 (10%) C2: 17/115 (15%)</p>				<p>Mean I1: 19 (95%CI: 17-22) C1: 19 (95%CI: 17-21) expected count ratio 1.01 (95%CI: 0.85-1.21)</p> <p>I2: 20 (95%-CI: 18-22) C2: 19 (95%-CI: 16-22) expected count ratio 1.03 (95%CI: 0.86-1.22)</p> <p><u>Number of days in ICU</u> Mean I1: 11 (95%CI: 8-15) C1: 10 (95%CI: 8-13) expected count ratio 1.05 (95%CI: 0.69-1.59)</p> <p>I2: 11 (95%-CI: 8-14) C2: 10 (95%-CI: 7-15) expected count ratio 1.03 (95%CI: 0.68-1.56)</p> <p><u>Number of days in ICU in patients ventilated at day of randomisation</u> Mean I1: 20 (95%CI: 15-27) C1: 22 (95%CI: 17-29) expected count ratio 0.89 (95%CI: 0.60-1.32)</p> <p>I2: 20 (95%-CI: 16-27) C2: 22 (95%-CI: 16-29) expected count ratio 0.94 (95%CI: 0.64-1.40)</p> <p><u>Number of days in ICU relative to the number of days alive the first 28 days after randomisation</u> Mean I1: 42% (95%CI: 31-56)</p>	<p>supplemental oxygen; 6=not hospitalised.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Drugs targeting IL-1 or IL-6 did not shorten the time to clinical improvement in this sample of patients with COVID-19, hypoxic respiratory failure, low SOFA score, and low baseline mortality risk.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><i>Non-invasive or high flow oxygen device</i></p> <p>I1: 44/112 (39%) C1: 84/230 (37%)</p> <p>I2: 89/227 (39%) C2: 39/115 (34%)</p> <p>Groups were comparable at baseline.</p>				<p>C1: 36% (95%CI: 29-46) expected count ratio 1.14 (95%CI: 0.79-1.66)</p> <p>I2: 38% (95%-CI: 30-48) C2: 40% (95%-CI: 29-54) expected count ratio 0.96 (95%CI: 0.66-1.39)</p> <p><u>Time to symptom resolution</u> <u>Time to clinical improvement (primary outcome)†</u> Days, median I1: 12 (95%CI: 10-16) C1: 12 (95%CI: 10-15) HR 0.94 (95%CI: 0.73-1.21)</p> <p>I2: 11 (95%-CI: 10-16) C2: 12 (95%-CI: 11-16) HR 1.00 (95%CI: 0.78-1.29)</p> <p><u>Estimated probability of having experienced clinical improvement at day 28</u> I1: 75% (95%CI: 67-83) C1: 73% (95%CI: 67-79)</p> <p>I2: 74% (95%-CI: 68-79) C2: 74% (95%-CI: 66-82)</p> <p><u>Respiratory support</u> <u>Median time until independence from supplemental O₂ or discharge</u> Days, median I1: 12 (95%CI: 10-20) C1: 12 (95%CI: 10-15) HR 0.91 (95%CI: 0.71-1.17)</p> <p>I2: 11 (95%-CI: 10-15)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C2: 12 (95%-CI: 10-15) HR 1.00 (95%CI: 0.78-1.28)</p> <p><u>Median time until independence from invasive ventilation</u> Days, median I1: 21 (95%CI: 8-not estimable) C1: 27 (95%CI: 9-not estimable) HR 1.21 (95%CI: 0.54-2.71)</p> <p>I2: 23 (95%-CI: 8-not estimable) C2: 54 (95%-CI: 9-not estimable) HR 1.45 (95%CI: 0.63-3.33)</p> <p><u>Median time until first use of high-flow oxygen device, ventilation, or death</u> Days, median I1: < 50% reached event C1: < 50% reached event HR 0.97 (95%CI: 0.52-1.82)</p> <p>I2: < 50% reached event C2: < 50% reached event HR 0.85 (95%CI: 0.47-1.55)</p> <p><u>Number of days without supplemental O2 use up to 28 days after randomisation</u> Mean I1: 9 (95%CI: 7-12) C1: 9 (95%CI: 7-12) expected count ratio 0.97 (95%CI: 0.68-1.38)</p> <p>I2: 10 (95%-CI: 8-12)</p>	

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						<p>C2: 8 (95%-CI: 6-11) expected count ratio 1.17 (95%CI: 0.82-1.68)</p> <p><u>Number of invasive ventilator days</u> Mean I1: 5 (95%CI: 3-9) C1: 5 (95%CI: 3-7) expected count ratio 1.05 (95%CI: 0.54-2.03)</p> <p>I2: 5 (95%-CI: 3-7) C2: 5 (95%-CI: 3-9) expected count ratio 0.89 (95%CI: 0.46-1.72)</p> <p><u>Number of invasive ventilator days in patients ventilated at day of randomisation</u> Mean I1: 15 (95%CI: 11-20) C1: 16 (95%CI: 13-21) expected count ratio 0.93 (95%CI: 0.63-1.37)</p> <p>I2: 15 (95%-CI: 12-20) C2: 16 (95%-CI: 12-22) expected count ratio 0.96 (95%CI: 0.65-1.42)</p> <p><u>Number of invasive ventilator days relative to the number of days alive the first 28 days after randomisation</u> Mean I1: 23% (95%CI: 14-38) C1: 21% (95%CI: 14-31) expected count ratio 1.08 (95%CI: 0.57-2.05)</p>	

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						<p>I2: 21% (95%-CI: 14-30) C2: 23% (95%-CI: 14-38) expected count ratio 0.89 (95%CI: 0.47-1.70)</p> <p><u>Number of invasive ventilator-free days up to 28 days after randomisation</u> Mean I1: 18 (95%CI: 15-21) C1: 18 (95%CI: 16-20) expected count ratio 1.00 (95%CI: 0.84-1.19)</p> <p>I2: 18 (95%-CI: 17-20) C2: 17 (95%-CI: 15-20) expected count ratio 1.07 (95%CI: 0.90-1.27)</p> <p><u>Number of invasive ventilator-free days up to 28 days after randomisation in patients ventilated at day of randomisation</u> Mean I1: 6 (95%CI: 3-14) C1: 6 (95%CI: 3-13) expected count ratio 1.01 (95%CI: 0.33-3.07)</p> <p>I2: 7 (95%-CI: 4-15) C2: 5 (95%-CI: 2-12) expected count ratio 1.39 (95%CI: 0.46-4.20)</p> <p>Safety <u>Serious infections</u> <i>Sepsis</i> I1: 5/44 (11%) I1+I2a: 2/32 (6%) I1+I2b: 3/36 (8%)</p>	

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						<p>I2a: 4/81 (5%) I2b: 11/75 (15%) C: 6/74 (8%)</p> <p><i>Septic shock</i> I1: 5/44 (11%) I1+I2a: 1/32 (3%) I1+I2b: 3/36 (8%) I2a: 3/81 (4%) I2b: 6/75 (8%) C: 3/74 (4%)</p> <p><u>Serious adverse events not leading to mortality</u> <i>Infectious disorder (not COVID-19)</i> I1: 1/44 (2%) I1+I2a: 2/32 (6%) I1+I2b: 1/36 (3%) I2a: - I2b: 4/75 (5%) C: 1/74 (1%)</p> <p><i>Bleeding</i> I1: 2/44 (5%) I1+I2a: 1/32 (3%) I1+I2b: - I2a: 1/81 (1%) I2b: - C: 1/74 (1%)</p> <p><i>Thrombosis</i> I1: 1/44 (2%) I1+I2a: - I1+I2b: 1/36 (3%) I2a: - I2b: 1/75 (1%) C: 1/74 (1%)</p> <p><i>Acute kidney injury</i> I1: 1/44 (2%) I1+I2a: - I1+I2b: -</p>	

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						<p>I2a: - I2b: 1/75 (1%) C: 1/74 (1%)</p> <p><i>Cardiac disorder</i> I1: - I1+I2a: - I1+I2b: - I2a: 1/81 (1%) I2b: 1/75 (1%) C: 1/74 (1%)</p> <p><i>Other</i> I1: - I1+I2a: 2/32 (6%) I1+I2b: 2/36 (6%) I2a: 3/81 (4%) I2b: 1/75 (1%) C: 1/74 (1%)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p> <p>Several subgroups were prespecified on the basis of allocated treatment for the other randomisation, invasive ventilation and serum concentrations of CRP, IL-1β, and IL-6 on the day of randomisation. Post-hoc subgroup analyses included serum concentrations of IL-1RA, admission status to ICU or concomitant glucocorticoid use at randomisation.</p>	
Kharazmi, 2021	<u>Type of study:</u> Open-label, randomized controlled trial.	<u>Patients with severe COVID-19</u> <u>Inclusion criteria:</u>	Anakinra group Patients in the intervention group	Control group In the control group, patients	<u>Length of follow-up:</u> 14 days. <u>Loss-to-follow-up:</u>	Clinical outcomes <u>Mortality (28-30 day)</u> Not reported.	<u>Definitions:</u> - <u>Remarks:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting:</u> Imam Hossein Medical Centre affiliated with Shahid Beheshti University of Medical Sciences</p> <p><u>Country:</u> Iran</p> <p><u>Source of funding:</u> No information.</p> <p><u>Conflicts of interest:</u> The authors declare that there are no conflict of interests.</p>	<ul style="list-style-type: none"> • Patients who had an age of 18 years or older; • Elevated C-reactive protein levels; • Oxygen saturation less than or equal to 93% measured using a peripheral capillary pulse oximeter; • Fever (core temperature of 37.8 or more); • Cough or shortness of breath; • PaO₂/FiO₂ less than 300. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients who had positive results for tuberculosis; • Viral hepatitis B or C; • Hemoglobin less than 7,5 g/dl; • Platelet count of fewer than 100.000 cells/uL; • Serum glutamic-oxaloacetic transaminase; • Serum glutamic-pyruvic transaminase more than five upper limits of normal; • Untreated active infection, and previous administration of canakinumab or anakinra. <p><u>N total at baseline:</u> N = 30 Intervention: N= 15 Control: N = 15</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 49.25 y (19.12) C: 59.00 y (1.79) P=0.424</p> <p>Sex, n/N (%) male: I: 8/15 (53.3%) C: 11/15 (73.3%)</p>	received 100 mg anakinra as an intravenous (IV) infusion once daily in addition to the standard protocol for COVID-19 based on the sixth and seventh national COVID-19 committee guideline, until discharge or a maximum of 14 days.	received medication based on the sixth and seventh national protocol released on April 29, 2020 and June 27, 2020, respectively.	None. <u>Incomplete outcome data:</u> None.	<p><u>Length of hospital stay, mean (SD)</u> I: 9.50 (4.45) C: 19.00 (12.04)</p> <p><u>ICU length of stay, mean (SD)</u> I: 5.43 (1.72) C: 16.60 (9.04)</p> <p><u>Disease severity day 7, n/N (%)</u> <i>1. death</i> : 4/15 (26.7%) C: 5/15 (33.3%)</p> <p><i>2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation.</i> I: 1/15 (6.7%) C: 5/15 (33.3%)</p> <p><i>3. Hospitalized, on noninvasive ventilation or high flow oxygen</i> I: 1/15 (6.7%) C: 0/15 (0%)</p> <p><i>4. Hospitalized, requiring low flow supplemental oxygen</i> I: 4/15 (26.7%) C: 4/15 (26.7%)</p> <p><i>5. Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise).</i> I: 1/15 (6.7%) C: 0/15 (0%)</p>	<p>There are some limitations to our study. First, this is a pilot study with a small sample size. Second, we did not control the trial with a placebo.</p> <p><u>Authors conclusion:</u> According to the study results, in general, anakinra is effective in improving the respiratory condition and significantly reduces the need for invasive mechanical ventilation in patients with severe COVID-19. And also, the reduction was observed in hospitalization duration, which makes the medication an effective immunomodulatory agent to combat cytokine storm. As an important consideration, the reliable safety of anakinra in patients with critical conditions is one of this medication's most important properties</p>

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		<p><u>Disease severity ordinal scale, n/N (%)</u></p> <p>1. <i>death</i> I: 0/0 (0%) C: 0/0 (0%)</p> <p>2. <i>Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation.</i> I: 2/15 (13.3%) C: 3/15 (20.0%)</p> <p>3. <i>Hospitalized, on noninvasive ventilation or high flow oxygen</i> I: 10/15 (66.7%) C: 6/15 (40%)</p> <p>4. <i>Hospitalized, requiring low flow supplemental oxygen</i> I: 3/15 (20%) C: 6/15 (40%)</p> <p>5. <i>Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise).</i> I: 0/15 (0%) C: 0/15 (0%)</p> <p>6. <i>Hospitalized, not requiring supplemental oxygen—no longer required ongoing medical care.</i> I: 0/15 (0%) C: 0/15 (0%)</p> <p>7. <i>Not hospitalized</i> I: 0/15 (0%) C: 0/15 (0%)</p> <p>Groups comparable at baseline? Yes.</p>				<p>6. <i>Hospitalized, not requiring supplemental oxygen—no longer required ongoing medical care.</i> I: 0/15 (0%) C: 0/15 (0%)</p> <p>7. <i>Not hospitalized</i> I: 4/15 (26.7%) C: 1/15 (6.7%)</p> <p><u>Disease severity day 14, n/N (%)</u></p> <p>1. <i>death</i> : 5/15 (33.3%) C: 7/15 (46.7%)</p> <p>2. <i>Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation.</i> I: 0/15 (0%) C: 2/15 (13.3%)</p> <p>3. <i>Hospitalized, on noninvasive ventilation or high flow oxygen</i> I: 0/15 (0%) C: 2/15 (13.3%)</p> <p>4. <i>Hospitalized, requiring low flow supplemental oxygen</i> I: 0/15 (0%) C: 4/15 (26.7%)</p> <p>5. <i>Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise).</i> I: 0/15 (0%)</p>	

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						<p>C: 0/15 (0%)</p> <p>6. Hospitalized, not requiring supplemental oxygen—no longer required ongoing medical care.</p> <p>I: 0/15 (0%) C: 0/15 (0%)</p> <p>7. Not hospitalized</p> <p>I: 10/15 (66.7%) C: 5/15 (33.3%)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Adverse events</u> I: 1/15 (6.7%) (sputum culture) C: 3/15 (20%) (positive microbiologic culture: one blood culture, two sputum cultures)</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
Kyriazopoulou, 2021	<p><u>Type of study:</u> Prospective, double-blind randomized controlled trial.</p> <p><u>Setting:</u> 37 study sites</p>	<p><u>Patients with COVID-19 at risk of progressing to respiratory failure</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Adult patients of either sex; • For women, unwillingness of remain pregnant during the study period; 	<p>Anakinra</p> <p>Patients allocated to the active drug were daily injected with 100mg of anakinra at a final volume of 0.67ml.</p>	<p>Placebo</p> <p>Patients allocated to placebo treatment were daily injected with 0.67ml of</p>	<p><u>Length of follow-up:</u> Until day 28.</p> <p><u>Loss-to-follow-up:</u> Intervention: N = 1 Reasons: not reported.</p>	<p>Clinical outcomes <u>Mortality day 28</u> I: 13/405 (3.2%) C: 13/189 (6.9%)</p> <p><u>Duration of hospitalization</u> <i>Median (IQR) time to hospital discharge in days</i> I: 11 (7.8)</p>	<p><u>Definitions:</u> WHO-CPS: World Health Organisation Clinical Progression Scale SOFA: Sequential Organ Failure Assessment Score suPAR: “denotes the presence of danger associated molecular patterns (DAMPs), namely calprotectin (S100A8/A9) and IL-1α3, 4, both of</p>

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	<p><u>Country:</u> 29 sites in Greece and eight in Italy.</p> <p><u>Source of funding:</u> Not reported.</p> <p><u>Conflicts of interest:</u> G.P. has received independent educational grants from Pfizer, MSD, Angelini and Bio-Rad. H.M. reports receiving honoraria, consulting fees and non-financial support from healthcare companies, including Amgen, Angelini, Bayer, Mylan, MSD, Pfizer and Servier. L.D. received consultation honoraria from Sobi. M.B. has received funds for research grants and/or advisor/consultant and/or speaker/chairman from Angelini, Astellas, Bayer, bioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, Roche, Shionogi</p>	<ul style="list-style-type: none"> Confirmed infection by SARS-CoV-2 by molecular test; Findings in chest X-ray or chest computed tomography compatible with lower respiratory tract infection; Need for hospitalization; Plasma suPAR ≥ 6 ng ml⁻¹. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Any stage IV malignancy; Any do-not-resuscitate order; Ratio or partial oxygen pressure to fraction of inspired oxygen less than 150 mmHg; Need for NIV (CPAP or BPAP) or mechanical ventilation; Any primary immunodeficiency; Fewer than 1500 neutrophils per mm³; Oral or intravenous intake of corticosteroids at a daily dose greater than or equal to 0.4 mg/kg⁻¹ or prednisone for a period longer than the last 15 days; Any anti-cytokine biological treatment including JAK inhibitors, during the last 1 month; Severe hepatic failure; End-stage renal failure necessitating hemofiltration or peritoneal hemodialysis; Pregnancy of lactation. <p><u>N total at baseline:</u> N = 594 Intervention: N = 405 Control: N = 189</p> <p><u>Important characteristics:</u></p>		0.9% sodium chloride.	Control: N = 0 Reasons: not reported.	<p>C: 12 (8.5) OR 1.22 (95% CI 1.02 to 1.47) P=0.033</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Median (IQR) time of ICU stay in days</u> I: 10 (21) C: 14 (22) OR 2.33 (95% CI 1.11 to 4.92) P=0.026</p> <p><u>Respiratory support WHO-CPS by day 28</u></p> <p><u>Fully recovered PCR, n/N (%)</u> I: 204/405 (50.4%) C: 50/189 (26.5%)</p> <p><u>Asymptomatic PCR*, n/N (%)</u> I: 40/405 (9.9%) C: 6/189 (3.2%)</p> <p><u>Symptomatic independent, n/N (%)</u> I: 93/405 (23.0%) C: 74/189 (39.2%)</p> <p><u>Symptomatic assistance needed, n/N (%)</u> I: 25/405 (6.2%) C: 21/189 (11.1%)</p> <p><u>Hospitalized with no need for oxygen, n/N (%)</u> I: 9/405 (2.2%)</p>	<p>which contribute to pathogenic inflammation in COVID-19." Serious adverse events: infections and infestations, ventilator-associated pneumonia, septic shock and multiple organ dysfunction, bloodstream infection, probable hospital-acquired infection, hospital-acquired pneumonia, acute pyelonephritis and pulmonary embolism.</p> <p>Adverse events: anemia, neutropenia, thrombocytopenia, rash at the infection site, constipation, diarrhea, increase of liver function tests, bradycardia, headache, anxiety, creatinine increase, hyperglycemia, hyponatremia, hypernatremia, hypokalemia, hyperkalemia and hypocalcemia.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, the SAVE-MORE trial showed that early start of treatment with anakinra guided by suPAR levels in patients hospitalized with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcome at day 28.</p>

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	<p>and Nabriva. M.G.N. is supported by an ERC Advanced Grant (no. 833247) and a Spinoza grant of the Netherlands Organization for Scientific Research. He has also received independent educational grants from TTxD, GSK and ViiV Healthcare. J.E.-O. is a co-founder, shareholder and CSO of ViroGates, Denmark, and is a named inventor on patents on suPAR owned by Copenhagen University Hospital Hvidovre, Denmark. P.P. has received honoraria from Gilead, Janssen and MSD. G.N.D. is an advisor or lecturer for Ipsen, Pfizer, Genkyotex, Novartis and Sobi, has received research grants from Abbvie and Gilead and has served as principal investigator in studies for Abbvie,</p>	<p>Age, mean (SD): I: 62.0 y (11.4) C: 61.5 y (11.3)</p> <p>Sex, n/N (%) male: I: 236/405 (58.3%) C: 108/189 (57.1%)</p> <p>Disease severity, mean (SD): <i>Defined by WHO classification for COVID-19 at the time of screening (%)</i> <u>Moderate pneumonia</u> I: 39/405 (9.6%) C: 11/189 (5.8%)</p> <p><u>Severe pneumonia</u> I: 366/405 (90.4%) C: 178/189 (94.2%)</p> <p>) Groups comparable at baseline? Yes.</p>				<p>C: 3/189 (1.6%)</p> <p><u>Hospitalized with nasal/mask oxygen, n/N (%)</u> I: 8/405 (2.0%) C: 10/189 (5.3%)</p> <p><u>Need for HFO or NIV, n/N (%)</u> I: 1/405 (0.2%) C: 1/189 (0.5%)</p> <p><u>Mechanical ventilation with P/F >150 mmHg, n/N (%)</u> I: 1/405 (0.2%) C: 1/189 (0.5%)</p> <p><u>MV with P/F <150 mmHg or vasopressors, n/N (%)</u> I: 5/405 (1.2%) C: 4/189 (2.1%)</p> <p><u>MV with P/F <150 mmHg and vasopressors or hemodialysis or ECMO, n/N (%)</u> I: 6/405 (1.5%) C: 6/189 (3.2%)</p> <p><u>Absolute decrease of WHO-CPS at day 28 from baseline day 1, median (IQR)</u> I: 4 (2.0) C: 3 (2.5) OR 0.40 (95% CI 0.29 to 0.55) P<0.0001</p> <p><u>Absolute decrease of WHO-CPS at day 14 from</u></p>	

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	Novartis, Gilead, Novo Nordisk, Genkyotex, Regulus Therapeutics, Tiziana Life Sciences, Bayer, Astellas, Pfizer, Amyndas Pharmaceuticals, CymaBay Therapeutics, Sobi and Intercept Pharmaceuticals. E.J.G.-B. has received honoraria from Abbott, bioMérieux, Brahm, GSK, InflaRx, Sobi and XBiotech; independent educational grants from Abbott, AxisShield, bioMérieux, InflaRx, Johnson & Johnson, MSD, Sobi and XBiotech; and funding from the Horizon 2020 Marie-Curie Project European Sepsis Academy (granted to the National and Kapodistrian University of Athens) and the Horizon 2020 European Grants ImmunoSep and RISKinCOVID					<p><u>baseline day 1, median (IQR)</u> I: 3 (2.0) C: 2 (3.0) OR 0.63 (95% CI 0.46 to 0.86) P=0.003</p> <p><u>Absolute decrease of SOFA score at day 7 from baseline day 1, median (IQR)</u> I: 1 (2) C: 0 (1) OR 0.64 (0.47 to 0.88) P=0.007</p> <p>Safety <u>Adverse events</u> <i>At least one serious adverse event, n/N (%)</i> I: 65/405 (16.0%) C: 41/189 (21.7%) P=0.107</p> <p><i>At least one non-serious adverse event, n/N (%)</i> I: 335/405 (82.7%) C: 156/189 (82.5%) P=1.00</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	

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	(granted to the Hellenic Institute for the Study of Sepsis). The other authors do not have any competing interests to declare.						
Mariette, 2021 CORIMUNO-ANA-1 trial	<p>Type of study: RCT; open-label</p> <p>Setting: 16 University hospitals; sub-study of CORIMUNO-trial</p> <p>Country: France</p> <p>Source of funding: The Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research, and AP-HP Foundation; The funders of the study had no role in the study design,</p>	<p>Patients with mild-to-moderate, RT-PCR confirmed, COVID-19 pneumonia</p> <p>Inclusion criteria: CORIMUNO-trial overall:</p> <ul style="list-style-type: none"> confirmed SARS-CoV-2 infection (RT-PCR and/or chest CT) mild-to-moderate, severe, or critical pneumonia (ie, receiving oxygen at a flow of >3 L/min via mask or nasal cannula and a score of ≥5 points on the WHO Clinical Progression Scale [WHO-CPS] 10-point ordinal scale, which is described in the appendix 2 [pp 12–13]). <p>CORIMUNO-ANA-1 trial:</p> <ul style="list-style-type: none"> C-reactive protein serum concentration > 25 mg/L not requiring admission to hospital ICU at time of admission mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving at least 3 L/min of oxygen but 	<p>Anakinra + usual care</p> <p>Anakinra (Sobi, Puteaux, France); intravenously; Day 1-3 after randomization: 200 mg twice a day (total 400 mg) Day 4: 100 mg twice a day (total 200 mg) Day 5: 100 mg once</p> <p>If no improvement was seen on the morning of day 4 (improvement was determined as a reduction in requirement of oxygen of more than 50%, but the decision was left to the treating physician), 3 supplementary days of treatment at 400 mg per day</p>	<p>Usual care</p> <p>Usual care (antibiotic drugs, antiviral drugs, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the site clinicians.</p>	<p>Length of follow up: 90 days</p> <p>Loss to follow-up: I: 4/59 (6.8%) Reasons: lost contact C: 2/57 (3.5%) Reasons: withdrew consent</p>	<p><i>Also reported: composite score for non-invasive ventilation, high-flow oxygen, mechanical ventilation, or death; mechanical ventilation of death at day 14;</i></p> <p>Clinical outcomes Mortality <i>Survival with no need for mechanical or non-invasive ventilation</i> median posterior HR 0.97 (90% CrI 0.62 to 1.52)</p> <p>Mortality, incidence, day 90 I: 16/59 patients C: 15/55 patients died</p> <p>Overall survival; adjusted HR (95% CI) Day 14 0.56 (0.23–1.39)</p>	<p>Definitions: WHO-CPS score <i>Uninfected</i></p> <ul style="list-style-type: none"> 0, Uninfected; <p><i>Ambulatory: Mild disease</i></p> <ul style="list-style-type: none"> 1, Asymptomatic; viral RNA detected; 2, Symptomatic; independent; 3, Symptomatic; assistance needed; <p><i>Hospitalised: moderate disease</i></p> <ul style="list-style-type: none"> 4, hospitalized, not requiring oxygen; 5, hospitalized, requiring oxygen by mask or nasal prongs; <p><i>Hospitalised: severe disease</i></p> <ul style="list-style-type: none"> 6, hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 7, hospitalized, requiring intubation and mechanical ventilation, pO₂/FIO₂ ≥150 or SpO₂/FIO₂ ≥ 200; 8, hospitalized, requiring mechanical ventilation, (pO₂/FIO₂ <150 OR SpO₂/FIO₂ < 200) OR vasopressors (norepinephrine < 0.3 microg/kg/min);

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	data collection, data analysis, data interpretation, or writing of the report.	<p>without ventilation assistance (eg, high-flow oxygen, non-invasive ventilation, or mechanical ventilation).</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • known hypersensitivity to anakinra or any of its excipients • pregnancy • current documented bacterial infection • absolute neutrophil count of 1.0×10^9 per L or less • platelet concentration <50 G/L • serum aspartate aminotransferase or serum alanine aminotransferase > 5x upper limit of normal • severe renal insufficiency defined by an estimated glomerular filtration rate of < 30 mL/min. <p><i>See full list of criteria in appendix 2</i></p> <p><u>N total at baseline:</u> N = 116 Intervention: 59 Control: 57 (55 included in baseline characteristics and analysis)</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 67.0 (55.5–74.3) C: 64.9 (59.5–78.3) Sex, n/N (%) male: I: 43/59 (73%) C: 37/55 (67%) Time from symptoms onset to randomisation, median (IQR) days I: 10.0 (8.0–13.0; n=59)</p>	<p>were done on days 4–6, followed by a decrease to 200 mg per day on day 7 and 100 mg per day on day 8, and no treatment thereafter.</p> <p>Actual treatment:</p> <ul style="list-style-type: none"> • All received 2–15 injections of anakinra (median 11 [IQR 9–15]). • Median dose of anakinra by • Perfusion: 180 mg (IQR 167–186) • 55 (93%) patients • received seven perfusions or more. • Median cumulative dose of anakinra was 1900 mg (1500–2700). 			<p><i>Day 28</i> 0.77 (0.33–1.77) <i>Day 90</i> overall survival 72% (95% CI 61 to 85) overall survival 72%, (95% CI 62 to 85) adjusted HR 0.97 (95% CI 0.46 to 2.04)</p> <p><u>Duration of hospitalization</u> Discharge from hospital, day 28 I: 34/59; 58% (95% CI 44–69) C: 34/55; 62% (47–73) Adjusted HR 0.91 (95% CI 0.56 to 1.48)</p> <p><u>Symptom resolution</u> WHO-CPS score ≥ 5, day 4 I: 21/59 (36%) C: 21/55 (38%) Absolute risk diff –2.5% (90% CrI –17.1 to 12.0)</p> <p><u>WHO-CPS score (10-point scale); median (IQR) and median posterior odds ratio adjusted for age and centre.</u> <i>Day 4</i> I: 5 (5 to 6) C: 5 (5 to 6) OR 0.80 (95% CrI 0.38 to 1.68) <i>Day 7</i> I: 5 (5 to 7) C: 5 (5 to 7) OR 0.69 (95% CrI 0.33 to 1.43) <i>Day 14</i> I: 5 (2 to 8)</p>	<ul style="list-style-type: none"> • 9, Mechanical ventilation, pO₂/FIO₂ < 150 AND vasopressors (norepinephrine > 0.3 • microg/kg/min), OR dialysis OR ECMO <p><i>Dead</i></p> <ul style="list-style-type: none"> • 10, Dead. <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In summary, this randomised clinical trial suggests that anakinra was not effective in reducing the need for non-invasive or mechanical ventilation or death in patients with COVID-19 and mild-to-moderate pneumonia. These results are relevant for this patient population at the dose we used and cannot be extended to other populations with other doses. Further studies are needed to assess the efficacy of anakinra in other selected groups of patients with more severe COVID-19 and at other doses.</p>

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		<p>C: 10·0 (7·0–13·0; n=54)</p> <p>Groups comparable at baseline.</p>				<p>C: 5 (3 to 8) OR 0·70 (95% CrI 0·35 to 1·38) <i>Day 2 to 14 (longitudinal analysis)</i> OR 0·92 (95% CrI 0·32 to 2·65)</p> <p><u>Need for respiratory support</u> Oxygen independence, day 28 I: 63% (95% CI 49–74) C: 69% (55–80) adjusted HR 1·01 (95% CI 0·64 to 1·61)</p> <p>Safety <u>Adverse events</u> (I: n=59; C: n=55) <i>Patients with at least one AE</i> I: 29 (49%) C: 23 (42%) <i>Patients with multiple AEs</i> I: 19 (32%) C: 14 (25%) <i>Total number of adverse events</i> I: 113 C: 60 <u>Serious adverse events</u> <i>Patients with at least one SAE</i> I: 27 (46%) C: 21 (38%) <i>Patients with multiple SAEs</i> I: 8 (14%) C: 5 (9%) <i>Total number of SAEs</i> I: 42 C: 28</p>	

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						Virological outcomes <u>Viral clearance</u> not reported <i>Also reported: C-reactive protein, neutrophil count, lymphocyte count, lymphocyte to neutrophil ratio</i>	
15.2. Canakinumab							
Caricchio, 2021	<u>Type of study:</u> RCT (double blind) <u>Setting:</u> 39 hospitals in Europe and the United States <u>Country:</u> Europe and the United States <u>Source of funding:</u> Novartis Pharma AG, Basel, Switzerland. <u>Conflicts of interest:</u> All authors received funding from Novartis during the conduct of the study. Dr Caricchio reported receiving grants from Janssen and personal fees from Janssen, GlaxoSmithKline, Bristol Myers Squibb, Eli Lilly, and	Hospitalized patients with severe COVID-19. <u>Inclusion criteria:</u> <ul style="list-style-type: none"> at least 12 years old (United States) or 18 years old (Europe); Had hypoxemia but did not require IMV; diagnosis of infection with SARSCoV-2 within 7 days prior to randomization; diagnosis of pneumonia with pulmonary infiltrates on chest x-ray or computed tomographic scan within 5 days prior to randomization; peripheral capillary oxygen saturation of 93% or less on room air or arterial oxygen partial pressure/fraction of inspired oxygen less than 300mmHg; blood levels of CRP of 20mg/L or greater or ferritin of 600 µg/L or greater <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Had been treated with therapies targeting IL-1 or IL-6 	Canakinumab single dose of canakinumab (450mg for body weight of 40-<60 kg, 600mg for 60-80 kg, and 750 mg for >80 kg) in 250 mL of 5% dextrose infused intravenously over 2 hours	Placebo placebo in 250 mL of 5% dextrose infused intravenously over 2 hours	<u>Length of follow-up:</u> 127 days; Interim analysis reported for 29 days follow up <u>Loss-to-follow-up:</u> Intervention: 1 Control: 1 (2%) <u>Incomplete outcome data:</u> Intervention: 13 Discontinued the study (12 Died; 1 Participant decision (hospitalized)) Control: 16 Discontinued the study (died)	Clinical outcomes <u>Mortality (28-30 day)</u> Day 29: No. (%) I: 12 (5.3) C: 16 (7.1) OR :0.67 (95% CI, 0.30-1.50). <u>Survived without requiring IMV (3-29 day)</u> I:198/223 (88.8%) C: 191/223 (85.7%) OR: 1.39 (95% CI, 0.76-2.54; P =.29). <u>Duration of hospitalization</u> Discharged at day 29 I: 199/211 C: 187/206 <u>Time to symptom resolution</u> Not reported <u>Respiratory support</u> Intubation and mechanical ventilation I: 5 (2.2) C: 2 (0.9) Ventilation plus additional organ support (pressors, KRT, ECMO): I: 2 (0.9)	<u>Definitions:</u> World Health Organization's 9-point ordinal scale: 0 No clinical or virological evidence of infection 1 No limitation of activities 2 Limitation of activities 3 Hospitalized, no oxygen therapy 4 Oxygen by mask or nasal prongs 5 Noninvasive ventilation or high-flow oxygen 6 Intubation and mechanical ventilation 7 Ventilation plus additional organ support (pressors, KRT, ECMO) 8 Death. <u>Primary end point:</u> the proportion of patients who survived without ever requiring IMV from day 3 to day 29 (inclusive). <u>The key secondary outcome:</u> the proportion of patients who died of COVID-19 (causality assessed by investigators) between days 1 and 29. <u>Remarks:</u> The sponsor, in consultation with investigators, designed and conducted the study. Collection of data and management of trial sites were conducted by the

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Siemens outside the submitted work. Dr Abbate reported receiving grants from Kiniksa, Janssen, Olatec, and Serpin Pharma; personal fees from Janssen, Kiniksa, Cromos, Olatec, Serpin Pharma, Eli Lilly, and Merck; and nonfinancial support from Swedish Orphan Biovitrum outside the submitted work. Dr Hsue reported receiving honoraria from Gilead and Merck outside the submitted work. Dr Neogi reported receiving personal fees from Novartis outside the submitted work. Drs Chen, Li, Whelan, and Noviello reported being employees of Novartis. Dr Whelan reported having a patent pending through Novartis. Dr Noviello reported being a former/employee/	<ul style="list-style-type: none"> had a suspected or known untreated active infection due to another pathogen or if progression to death was imminent within 24 hours according to the investigator. <p><u>N total at baseline:</u> N = 454 Intervention:227 Control: 227</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 59 (49-69) C: 57 (50-68)</p> <p>Sex, n/N (%) male: I:135/227 (59%) C:132/227 (58%)</p> <p>Disease severity, mean (SD): <i>Defined by WHO ordinal scale</i> I: 0: 0 1:0 2:0 3: 3: 14 (6.2) 4: 161 (70.9) 5: 52 (22.9) 6: 0 7: 0 8: 0 C: 0: 0 1:0 2:0 3: 12 (5.4) 4: 160 (71.4) 5: 52 (23.2) 6: 0</p>				<p>C: 8 (3.6)</p> <p>Safety <u>Adverse events</u> Any AE: No. (%) I: 122 (54.2) C: 120 (53.8)</p> <p>SAEs: No. (%) I: 36 (16.0) C: 46 (20.6)</p> <p>Virological outcomes <u>Viral load > day 22:</u> <u>≥ 500</u> I: 1/15 (6.7) C: 5/17 (29.4) <u><500</u> I: 14/ 15 (93.3) C: 12/ 17 (70.6)</p>	<p>sponsor. An independent data monitoring committee reviewed trial safety data weekly. All authors contributed to the interpretation of the data, including sponsor co-authors. A preliminary draft of the manuscript was prepared by a writer contracted by Novartis.</p> <p><u>Authors conclusion:</u> Among patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV at day 29.</p>

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	<p>stockholder of Bristol Myers Squibb and stockholder of Johnson & Johnson; in addition, Dr Noviello reported having a patent pending through Novartis.</p> <p>ClinicalTrials.gov: NCT04362813</p>	<p>7: 0 8: 0</p> <p>Groups comparable at baseline? Yes</p>					
16. IL6-remmers							
16.1. Clazakisumab							
NA	NA	NA	NA	NA	NA	NA	NA
16.2. Levilimab (Monoclonal antibody- IL-6 inhibitor-BCD-089; IIsira)							
Lomakin, 2021	<p><u>Type of study:</u> multicenter double-blind, placebo-controlled phase III trial</p> <p><u>Setting:</u> hospital-based, between April 2020 and August 2020</p> <p><u>Country:</u> 12 investigational sites in the Russian Federation</p> <p><u>Source of funding:</u> This study was funded by JSC BIOCAD grant no. BCD-089-4/CORONA.</p>	<p>hospitalized patients with severe COVID-19 not requiring mechanical ventilation</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • positive for SARS-CoV-2 RNA • hospitalized with radiologically confirmed pneumonia with at least 1 criteria of disease severity: <ul style="list-style-type: none"> • respiratory rate > 30/min • SpO₂ ≤ 93 • PaO₂/FiO₂ < 300 mmHg • increase of the lung involvement > 50% after 24-48 h • decreased consciousness level • agitation • unstable hemodynamics • arterial blood lactate > 2 mmol/L 	levilimab 324 mg s.c.	placebo	<p><u>Length of follow-up:</u> 60 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention: N = 1 (1.0%) <i>Reason</i> • <i>early withdrawal (n = 1)</i></p> <p>Control: N = 4 (3.9%) <i>Reason</i> • <i>withdrawal before study medication was administered (n = 2)</i> • <i>early withdrawal (n = 1)</i> <i>lost to follow-up (n = 1)</i></p>	<p>Clinical outcomes</p> <p>Mortality Not reported; initial primary endpoint was overall mortality, but because the mortality was significantly lower than assumed, the study did not have enough power to detect a meaningful difference</p> <p>Duration of hospitalisation <u>Duration of hospital stay</u> Days, median (IQR) I: 11 (8-16) C: 11 (7-18) p = 0.4852</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support</p>	<p><u>Definitions:</u></p> <ul style="list-style-type: none"> - qSOFA = quick sequential organ failure assessment score - SBP = systolic blood pressure - GCS = Glasgow Coma Scale - ESR = erythrocyte sedimentation rate <p>* The 7-category ordinal scale includes the following categories: 1 not hospitalized/discharged; 2 hospitalized, not requiring O₂ therapy or other medical care; 3 hospitalized, not requiring O₂ therapy, requiring other medical care; 4 hospitalized, requiring O₂ therapy; 5 hospitalized, requiring high-flow O₂ therapy or non-invasive ventilation; 6 hospitalized, requiring mechanical ventilation or ECMO; 7 death.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> Several authors are JSC BIOCAD employees. The sponsor designed the trial, was responsible for the monitoring, collected the data, and performed the data analysis. Sponsor's representatives were not IDMC members, had no access to the blinded data, and did not participate in voting.</p>	<ul style="list-style-type: none"> • qSOFA > 2, defined by the presence of any 2 symptoms (SBP ≤ 100 mmHg, respiratory rate ≥ 22/min, GCS ≤ 14) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • critical form of COVID-19, defined by the presence of respiratory failure and need of the invasive mechanical ventilation, septic shock or multiple organ failure • suspected active bacterial, fungal, viral, or other infection (besides COVID-19) • confirmed active tuberculosis • life expectancy < 24 h, in the opinion of the investigator or who were unlikely to remain at the investigational site beyond 48 h • treated with other monoclonal antibodies, immunosuppressive agents or participating in a clinical trials of other drug • history of allergic reaction to monoclonal antibodies • any illness or laboratory findings that, in the opinion of the study investigator, might pose an additional risk to the patient by their participation in the study • pregnant or breastfeeding • ALT and/or AST levels > 10 x ULN • platelet count < 50 x 10⁹/L • absolute neutrophil count < 1.0 x 10⁹/L <p><u>N total at baseline:</u> Randomized: N = 206</p>				<p>Not reported</p> <p>Other <u>Sustained clinical improvement on 7-category ordinal scale on day 14 (primary outcome)*</u></p> <p><i>Day 7</i> I: 6/103 (5.8%) C: 6/103 (5.8%) p = 1.0000</p> <p><i>Day 14</i> I: 65/103 (63.1%) C: 44/103 (42.7%) p = 0.0017</p> <p><i>Day 21</i> I: 79/103 (76.7%) C: 49/103 (47.6%) p < 0.0001</p> <p><i>Day 28</i> I: 87/103 (84.5%) C: 57/103 (55.3%) p < 0.0001</p> <p><i>Day 30</i> I: 87/103 (84.5%) C: 57/103 (55.3%) p < 0.0001</p> <p><u>Transfer to ICU</u> I: 3/103 (2.9%) C: 10/103 (9.7%) p = 0.0449</p> <p><u>Duration of fever</u> Days, median (IQR) I: 1 (1-3) C: 2 (1-3) p = 0.1065</p>	<p>In patients with radiologically confirmed SARS-CoV-2 pneumonia, requiring or not oxygen therapy (but not ventilation) with no signs of other active infection administration of LVL + SOC results in an increase of sustained clinical improvement rate.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>ITT population: N = 206</p> <p>Intervention: N = 103 Control: N = 103</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 58.5 y (12.9) C: 58.2 y (10.8)</p> <p>Sex, n/N (%) male: I: 58/103 (56.3%) C: 51/103 (49.5%)</p> <p>The proportion of patients aged \geq 75 y was higher in the intervention group than in the control group (11.7 vs. 3.9%). Patients in the intervention group more often had cardiac disorders (19.4 vs. 11.7%). More patients in the control group received corticosteroids (4.9 vs. 8.7%)</p>				<p><u>Change in ESR from baseline</u> mm/h, median (IQR)</p> <p><i>Day 3</i> I: 30 (18-44.5) C: 38 (23-56) $p = 0.0035$</p> <p><i>Day 5</i> I: 25 (15-41) C: 40 (24-55) $p = 0.0002$</p> <p><i>Day 7</i> I: 23 (15-36) C: 31 (21-45) $p = 0.0009$</p> <p><u>Change in CRP from baseline</u> mg/L, median (IQR)</p> <p><i>Day 3</i> I: 14.6 (5.1-29.8) C: 31.7 (12-62.6) $p < 0.0001$</p> <p><i>Day 5</i> I: 5.3 (1.5-15) C: 17.7 (6.9-44) $p < 0.0001$</p> <p><i>Day 7</i> I: 3.9 (1.3-8.4) C: 9.2 (4.1-19) $p < 0.0001$</p> <p><u>Change in IL-6 from baseline</u> pg/mL, median (IQR)</p> <p><i>Day 3</i> I: 65.9 (16.5-20.1) C: 16.4 (3.9-80.4)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>$p = 0.0017$</p> <p><i>Day 4</i> I: 64.2 (18.3-247.1) C: 20.1 (1.5-119.1) $p = 0.0121$</p> <p><i>Day 14</i> I: 25.4 (12.6-77.8) C: 108.7 (22.1-10.5) $p = 0.1000$</p> <p>Safety <u>Adverse drug reactions</u> I: 28/103 (27.2%) C: 24/101 (9.3%) $p = 0.5750$</p> <p><u>Grade ≥ 3 adverse drug reactions</u> I: 10/103 (9.7%) C: 7/101 (6.9%) $p = 0.4279$</p> <p><u>Serious adverse events</u> I: N = 1 C: N = 2</p> <p><u>Grade 4 neutropenia</u> I: N = 0 C: N = 0</p> <p><u>Hypersensitivity</u> I: N = 0 C: N = 0</p> <p><u>Injection site reactions</u> I: N = 0 C: N = 0</p> <p>Virological outcomes Not reported</p>	
16.3. Olokizumab							

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
NA	NA	NA	NA	NA	NA	NA	NA
16.4. Sarilumab (human monoclonal antibody; against the interleukin-6 receptor; sold under the brand name Kevzara)							
García-Vicuña, 2022	<p><u>Type of study:</u> A randomized, single center, open label study</p> <p><u>Setting:</u> Hospitalized patients, between April 13, 2020 and December 04, 2020 (SARCOVID study)</p> <p><u>Country:</u> Spain</p> <p><u>Source of funding:</u> This work was supported by a grant (IIS SGZ-2020-13059) to RG-V from Sanofi Spain, which also provided experimental medication (sarilumab, Kevzara®).</p> <p><u>Conflicts of interest:</u> Yes, transparently reported</p>	<p>Hospitalized patients with moderate-to-severe COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Hospitalized and confirmed COVID-19 on chest imaging and a documented diagnosis of COVID-19 by RT-PCR or a positive IgM/IgA serologic ELISA test • At least 2 of the following additional criteria: <ul style="list-style-type: none"> - Fever $\geq 37.8^{\circ}\text{C}$; - IL-6 in serum ≥ 25 pg/mL or PCR > 5 ng / dL; - Lymphocytes $< 600/\text{mm}^3$; ferritin > 300 $\mu\text{g} / \text{L}$ doubling in 24 h; - ferritin > 600 $\mu\text{g} / \text{L}$ in the first determination; - LDH > 250 or D-dimer > 1mg / L. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • IMV at inclusion • AST/ALT values more than 5-folds the upper normal limit • Absolute neutrophil count $< 500/\text{mm}^3$ • absolute platelet count $< 50,000 / \text{mm}^3$ • superimposed infection by pathogens other than COVID-19 • complicated diverticulitis or intestinal perforation • immunosuppressive antirejection therapy • Pregnant or breastfeeding • Previous treatment with TCZ or SAR 	<p>400mg single dose in 2 subcutaneous injections 200mg each in pre-filled syringe</p> <p>+</p> <p>Standard care</p>	<p>Standard of care.; including corticosteroids, or full supportive care according to the best SC updated in the local protocol for COVID-19. Patients in the SC were given the option to receive intravenous TCZ after randomization if they worsened at the investigator's discretion, as this agent had become the SC in our center when the protocol was designed</p> <p>Other immunomodulators or investigational drugs in trials were prohibited.</p>	<p><u>Length of follow-up:</u> 30days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: No lost to follow-up</p> <p>Control: N=1 (10%) Reason: discharged alive at day 13 and no later contact (n=1)</p>	<p>Clinical outcomes</p> <p><u>Mortality (28 day):</u> Mortality, n/N (%): I: 2/20 (10%) C: 0/10 (0%) P=0.54</p> <p><u>Duration of hospitalization</u> Median (IQR), days I: 7 (6-11) C: 6 (4-12) HR=0.65 P=0.27</p> <p><u>Time to symptom resolution</u> Defined as time to become afebrile for a minimum of 48, days I: 3 (3-6) C: 4 (4-8) Eleven patients in the SAR+SC arm and 5 in the SC arm were febrile at randomization</p> <p><u>Invasive respiratory support</u> Progression to IMV, n/N (%) I: 3/20 (15%) C: 0/10 (0%)</p> <p><u>Non-invasive respiratory support</u> Progression to NIMV, n/N (%) I: 4/20 (20%) C: 0/10 (0%)</p> <p>Safety</p> <p><u>Serious adverse events</u></p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Mortality by 30 days • Mean change in functional status at day 7 on the WHO scale <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Time to become afebrile during 48 h without antipyretic • Mean change in 7-category ordinal scale at day 14 • Time to NIMV and IMV • Time to oxygen supply independence • Progression to NIMV and IMV • Adverse events <p><u>Definitions:</u> Functional status was assessed using a 7-category ordinal scale: 1. death; 2. hospitalized, requiring ECMO, IMV, or both; 3. hospitalized, requiring high-flow oxygen therapy, NIMV, or both; 4. hospitalized, requiring supplementary oxygen; 5. hospitalized, not requiring supplementary oxygen but in need of ongoing medical care; 6. hospitalized, not requiring ongoing medical care; and 7. not hospitalized</p> <p><u>Remarks:</u> Standard of care was not described</p> <p>Assigned treatment groups were not well-balanced with several data that point to higher baseline severity in SAR arm patients.</p> <p><u>Authors conclusion:</u> This pragmatic open pilot RCT in hospitalized patients with</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Contraindication to SAR or excipients • Comorbidities that can likely lead to unfavourable results <p><u>N total at baseline:</u> N = 30 Intervention: N=20 Control: N=10</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 61.5 y (50.5-72) C: 62 y (58-71)</p> <p>Sex, n/N (%) male: I: 15/20 (75%) C: 5/10 (50%)</p> <p>Disease severity: Defined as receiving high-flow supplemental oxygen therapy or NIV, n/N (%) I: 4/20 (20%) C: 0/10 (0%)</p> <p>Groups are not comparable at baseline Patients on SAR were randomized earlier after disease onset compared to SC participants, suggesting a more advanced or poor prognostic disease leading to meeting the inclusion criteria in a shorter time. A higher proportion was male, had a fever, needed high-flow oxygen requirements including NIMV, or presented larger radiological lung involvement compared to SC patients.</p>				<p>Number of events I: 5 (within 4 patients, 20%) C: 0</p> <p>The full list of adverse events can be consulted in the original publication of the study.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<p>moderate-to-severe COVID-19 has failed to demonstrate the benefit of adding subcutaneous SAR to the SC for preventing high oxygen requirements, invasive ventilation, or death. Additionally, serious adverse events also occurred in the intervention arm, although no definite relationship with SAR could be demonstrated.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Sivapalasingam, 2022	<p>Type of study: An adaptive, phase 2/3, randomized, double-blind, placebo-controlled trial</p> <p>Setting: 65 sites, between March 18, 2020 and July 2, 2020</p> <p>Country: United States</p> <p>Source of funding: Funded by Merck Sharp and Dohme</p> <p>Conflicts of interest: This work was supported by Regeneron Pharmaceuticals, Inc., Sanofi, and the Biomedical Advanced Research and Development Authority. Certain aspects of this project were funded in whole or in part with federal funds from the Department of Health and Human Services, Office of the Assistant</p>	<p>Critical hospitalized patients with COVID-19 receiving mechanical ventilation</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> >18 years of age Hospitalized with laboratory-confirmed SARS-CoV-2 infection Requiring supplemental oxygen and/or assisted ventilation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Not expected to survive for more than 48 h from screening Abnormal laboratory values Treatment with anti-interleukin (IL)-6, anti IL6R antagonist or Janus kinase inhibitors Current treatment with simultaneous combination of leflunomide and methotrexate Tuberculosis Known active systemic bacterial or fungal infections Participating in any other clinical trial Known hypersensitivity to treatment <p>N total at baseline: N = 1365 Intervention I (200 mg IV): N=489 Intervention II (400 mg IV): N=582 Control: N=294</p> <p>Important characteristics: Age, median (IQR): I (200 mg): 59 y (50-69) I (400 mg): 63 y (52-72) C: 60.5 y (51-70)</p>	<p>Intervention I (200 mg) Sarilumab 200 mg, was administered IV over 1 h</p> <p>Intervention II (400 mg) Sarilumab 400 mg, was administered IV over 1 h</p> <p>+</p> <p>Standard care</p>	<p>normal saline was administered IV over 1 h</p> <p>+</p> <p>Standard care: All patients received local standard of care (SOC), including corticosteroids and open-label use of putative treatments for COVID-19</p>	<p>Length of follow-up: 60 days</p> <p>Incomplete outcome data & loss-to-follow-up: Intervention I: N=160 (32.7%) Reasons: Investigator/sponsor decision (n=1), withdrawal of consent (n=3), lost to follow-up (n=30), death (n=126)</p> <p>329/489 (67.3%) completed the study</p> <p>Intervention II: N=212 (36.4%) Reasons: withdrawal of consent (n=3), lost to follow-up (n=28), death (n=181)</p> <p>370/582 (63.6%) completed the study</p> <p>Control: N=107 (36.4%) Reasons: withdrawal of consent (n=3), lost to follow-up (n=17), death (n=87)</p> <p>187/294 (63.6%) completed the study</p>	<p>Clinical outcomes Mortality (day 29): Mortality, n/N (%): I (200 mg): 60/242 (24.8%) I (400 mg): 103/338 (30.5%) C: 43/170 (25.3%)</p> <p>Mortality (day 60) Mortality, n/N (%): I (200 mg): 70/242 (28.9%) I (400 mg): 114/338 (33.7%) C: 59/170 (34.7%)</p> <p>Duration of hospitalization Not reported</p> <p>Time to symptom resolution Reported as primary endpoint in the phase 2 study</p> <p>Invasive respiratory support Not reported</p> <p>Safety Serious adverse events, n/N (%) Patients with any SAE I (200 mg): 119/242 (49.2%) I (400 mg): 183/338 (54.1%) C: 89/170 (52.4%)</p> <p>A detailed list of SAE is provided in the article.</p> <p>Virological outcomes Viral clearance</p>	<p>Primary outcome: • proportion of patients with ≥ 1-point improvement in clinical status from baseline to day 22</p> <p>Secondary outcome(s): • proportion who died (day 29, day 60) • proportion who recovered (day 22)</p> <p>Definitions: Critical" COVID-19 was defined as requiring supplemental oxygen by nonbreather mask or high-flow nasal device, non-invasive ventilation, invasive mechanical ventilation, or management in an intensive care unit</p> <p>Remarks: Unclear which patients were included in the ITT analysis</p> <p>Data is extracted from phase 3, cohort I (all critical patients)</p> <p>The phase 3 sample size estimation based on the phase 2 interim data may have led to an underpowered study, which was further impacted by the 2:1 randomization ratio, leading to a small placebo treatment group</p> <p>Important information of the clinical trial can be found in the supplementary files, but is missing in the article itself</p> <p>Due to the novel nature of COVID-19, efficacy endpoints at the time of study design were not well established.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under OT number: HHSO1002017000 20C</p> <p><u>Conflicts of interest:</u> Yes, transparently reported</p>	<p>Sex, n/N (%) male: I (200 mg): 175/242 (72.3%) I (400 mg): 227/338 (67.2%) C: 111/170 (65.3%)</p> <p>Disease severity: All patients were classified as "critical" COVID-19</p> <p>Groups are comparable at baseline</p>				Not reported	<p><u>Authors conclusion:</u> This study did not establish the efficacy of sarilumab in hospitalized patients with severe/critical COVID-19. Post-hoc analyses were consistent with other studies that found a benefit of sarilumab in patients receiving corticosteroids</p>
Merchante, 2021	<p><u>Type of study:</u> Phase II, open-label, multicentre randomized clinical trial</p> <p><u>Setting:</u> hospital-based, between 13 July 2020 and 5 March 2021</p> <p><u>Country:</u> 10 clinical sites in Andalusia, Spain</p> <p><u>Source of funding:</u> This study was funded by the COVID-19 Research Program of the Regional</p>	<p>hospitalized patients</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • confirmed SARS-CoV-2 infection (positive on RT-PCR) no later than 4 days prior inclusion • interstitial pneumonia confirmed by the presence of infiltrates on chest radiograph or a computer tomograph • IL-6 levels ≥ 40 pg/mL and/or D-dimer > 1500 ng/mL or ≥ 1000 if progressive increments were documented in at least two determination after admission <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • ARDS requiring HFNO • Mechanical ventilation <p><u>N total at baseline:</u> Randomized: N = 115</p>	<p><u>Intervention I</u> single subcutaneous dose of 200 mg sarilumab (Sarilumab-200) + Usual care</p> <p><u>Intervention II</u> single subcutaneous dose of 400 mg sarilumab (Sarilumab-400) + Usual care</p>	<p>Usual care up to 14 days according to local practice as listed in the protocol of the Spanish Ministry of Health and the Spanish Agency of Medicines and Medical products.</p> <p>Dexamethasone was the preferred therapy.</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> One patient withdrew informed consent (intervention I group) and there was a protocol violation (n=1)</p> <p>One patient withdrew informed consent (intervention II group) and one patient did not receive the allocated intervention.</p>	<p>Clinical outcomes Progression to HFNO, NIMV, IMV (event within 28 days)</p> <p>Events, n (%) I (I): 10/37 (27%) I (II): 10/39 (26%) C: 5/39 (13%)</p> <p>I (I) compared to C HR 0.87 (95%CI: 0.37-2.06), p=0.76</p> <p>I (II) compared to C HR 0.41 (95%CI: 0.14-1.18), p=0.09</p> <p>Need for mechanical ventilation</p> <p>Events, n (%) I (I): 6/37 (16%) I (II): 3/39 (8%) C: 4/39 (10%)</p>	<p><u>Definitions:</u> The primary outcome variable was the development of ARDS requiring HFNO, NIMV or IMV during the first 28 days after randomization.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In patients recently hospitalised with COVID-19 pneumonia and features of systemic inflammation, early IL-6 blockade with a single dose of sarilumab 400 mg was safe and associated with a trend for better outcomes.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Government of Andalusia.</p> <p><u>Conflicts of interest:</u> The authors declare no competing interest.</p>	<p>Intervention I (200 mg Sarilumab): N = 37 Intervention II (400 mg Sarilumab): N = 39</p> <p>Control: N = 39</p> <p><u>Important characteristics:</u> Age, median (IQR): I(I) (200 mg): 65 y (53-72) I (II) (400 mg): 57 y (49-67) C: 57 y (51-71)</p> <p>Sex, n/N (%) male: I (I) (200 mg): 23/37 (65%) I (II) (400 mg): 29/39 (74%) C: 26/39 (66%)</p> <p>Diabetes mellitus I (I) (200 mg): 9/37 (24%) I (II) (400 mg): 2/39 (5%) C: 6/39 (15%)</p> <p>Groups were comparable at baseline. Slightly more patients with DM in de Sarilumab 200 mg group (p=0.06)</p>				<p>I(I) compared to C HR 1.68 (95%CI: 0.47-5.98), p=0.41</p> <p>I(II) compared to C HR 0.78 (95%CI: 0.17-3.48), p=0.74</p> <p>Death Events, n (%) I(I): 4/37 (8%) I (II): 0/39 (0%) C: 3/39 (8%)</p> <p>I(I) compared to C HR 1.41 (95%CI: 0.31-6.31), p=0.64</p> <p>I(II) compared to C HR 0.01 (95%CI: 0.00-160.68), p=0.07</p> <p>Also clinical improvement on an ordinal scale, discontinuation of supplemental oxygen in patients receiving it at baseline and discharge alive from hospital were reported as well as a detailed overview of the occurred adverse events.</p>	
CORIMUNO-19 Collaborative Group, 2021 (CORIMUNO-SARI-1 trial)	<p><u>Type of study:</u> multicentre, open-label, randomized controlled phase 2/3 clinical trial, nested within the CORIMUNO-19 cohort</p> <p><u>Setting:</u></p>	<p>hospitalized patients with moderate-to-severe COVID-19 pneumonia</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age ≥ 18 y confirmed SARS-CoV-2 infection (positive on RT-PCR or typical chest CT scan) 	sarilumab (fixed dose of 400 mg i.v. on day; additional fixed dose of 400 mg i.v. on day 3 was recommended if O ₂ requirement had not decreased by more than 50%, but the decision was left to the treating physician) + usual care	usual care alone(antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants)	<p><u>Length of follow-up:</u> 90 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> none</p>	<p>A subgroup analysis according to antiviral drug use at baseline was prespecified in the protocol. Analyses according to the use of corticosteroids and particularly dexamethasone were</p>	<p><u>Definitions:</u> † Moderate or greater benefit was defined as an ARD <-5.5% for the day 4 outcome and a HR <0.85 for the day 14 outcome.</p> <p><u>Remarks:</u> * Four patients in the control group withdrew consent after randomization,</p>

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	<p>hospital-based, between March 27 and April 6, 2020</p> <p><u>Country:</u> 6 centres in France</p> <p><u>Source of funding:</u> This trial was publicly funded by the Ministry of Health, Programme Hospitalier de Recherche Clinique, and Assistance Publique – Hôpitaux de Paris Foundation and Foundation for Medical Research. Sanofi donated sarilumab as an unrestricted grant and had no role in the study design, no role in the collection, analysis, or interpretation of the data, and no role in the writing of the report.</p> <p><u>Conflicts of interest:</u> None to declare.</p>	<ul style="list-style-type: none"> • moderate-to-severe pneumonia not requiring ICU at admission with WHO CPS score of 5 • receiving $\geq 3\text{L}/\text{min}$ of O_2 without ventilation assistance that included high-flow O_2, non-invasive ventilation, or mechanical ventilation <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • known hypersensitivity to sarilumab or any of its excipients • pregnancy • current documented bacterial infection • any of following laboratory results out of the ranges detailed below at screening: <ul style="list-style-type: none"> • absolute neutrophil count $\leq 1.0 \times 10^9/\text{L}$ • platelets $< 50 \text{ G/L}$ • serum glutamicoxaloacetic transaminase or serum glutamic-pyruvic transaminase $> 5\text{N}$. <p><u>N total at baseline:</u> Randomized: N = 148 ITT population: N = 144*</p> <p>Intervention: N = 68 Control: N = 76</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 61.7 y (53.0-71.1) C: 62.8 y (26.0-71.7)</p> <p>Sex, n/N (%) male: I: 49/68 (72%) C: 59/76 (78%)</p>	(antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants)			<p>added post-hoc considering recent publications.</p> <p>Clinical outcomes</p> <p><u>Mortality</u></p> <p><u>Mortality at day 14</u> I: 6/68 (9%) C: 8/76 (11%) Adjusted HR 0.68 (95%CI: 0.23-2.03)</p> <p><u>Mortality at day 28</u> I: 8/68 (12%) C: 14/76 (18%) aHR 0.65 (95%CI: 0.27-1.59)</p> <p><u>Mortality at day 90</u> I: 10/68 (15%) C: 16/76 (21%) aHR 0.70 (95%CI: 0.31-1.58)</p> <p><u>Duration of hospitalisation</u></p> <p><u>Discharged at day 28</u> I: 51/68 (75%) C: 53/76 (70%) aHR 1.19 (95%CI: 0.81-1.75)</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support independent from O_2 at day 28</u> I: 50/68 (74%) C: 54/76 (71%) aHR 1.06 (95%CI: 0.72-1.57)</p>	<p>and asked their personal data to be erased.</p> <p><u>Authors conclusion:</u> Sarilumab treatment did not improve early outcomes in patients with moderate-to-severe COVID-19 pneumonia. Further studies are warranted to evaluate the effect of sarilumab on long-term survival.</p>

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		<p>Coexisting conditions</p> <p><i>Chronic cardiac disease</i> I: 17/67 (25%) C: 19/76 (25%)</p> <p><i>Diabetes</i> I: 22/68 (32%) C: 22/76 (29%)</p> <p><i>Chronic kidney disease (stage 1-3) or dialysis</i> I: 10/67 (15%) C: 7/76 (9%)</p> <p><i>Asthma</i> I: 3/67 (4%) C: 8/76 (11%)</p> <p><i>Chronic pulmonary disease (not asthma)</i> I: 6/67 (9%) C: 3/76 (4%)</p> <p><i>Active malignant neoplasm</i> I: 3/67 (4%) C: 1/76 (1%)</p> <p>Groups were comparable at baseline.</p>				<p>Other</p> <p><u>Dead or needing non-invasive ventilation or mechanical ventilation on day 4 (i.e. WHO-CPS score > 5; coprimary outcome)</u> I: 18/68 (26%) C: 20/76 (26%)</p> <p>Median posterior ARD 0.2% (90%CrI: -11.7-12.2) Median posterior aOR 1.02 (90%CrI: 0.54-1.94) Posterior probability of any benefit 48.9% Posterior probability of moderate or greater benefit than usual care† 21.6%</p> <p><u>Survival with no need for non-invasive ventilation (including high-flow O₂) or mechanical ventilation at day 14 (coprimary outcome)</u> I: 25/68 (37%) C: 26/76 (34%) Median posterior aOR 1.10 (90%CrI: 0.69-1.74) Posterior probability of any benefit 37.4% Posterior probability of moderate or greater benefit than usual care† 18.6%</p> <p>Safety</p> <p><u>Adverse events</u> <u>Patients with at least one adverse event</u> I: 37/68 (54%) C: 33/76 (43%)</p>	

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						<p>p = 0.24</p> <p><u>Patients with multiple adverse events</u> I: 17/68 (25%) C: 11/76 (14%)</p> <p><u>Number of adverse events</u> I: 77 C: 58</p> <p>Incidence rate per 1000 patient-day I: 14.6 (95%CI: 11.7-18.2) C: 10.3 (95%CI: 8.0-13.4)</p> <p>IRR 1.41 (95%CI: 1.00-1.98); control group is reference group p = 0.048</p> <p><u>Serious adverse events</u> <u>Patients with at least one serious adverse event</u> I: 27/68 (40%) C: 28/76 (37%) p = 0.73</p> <p><u>Patients with multiple serious adverse events</u> I: 10/68 (15%) C: 9/76 (12%)</p> <p><u>Number of serious adverse events</u> I: 44 C: 40</p> <p>Incidence rate per 1000 patient-day I: 8.3 (95%CI: 6.2-11.2) C: 7.1 (95%CI: 5.2-9.7)</p>	

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						IRR 1.16 (95%CI: 0.76-1.79); control group is reference group p = 0.47 <u>Deaths</u> I: 10/68 (15%) C: 16/76 (21%) Virological outcomes Not reported	
Sancho-López, 2021 [SARTRE-trial]	Type of study: RCT, open-label Setting: Eight tertiary hospitals Country: Spain Source of funding: Biomedical Research Foundation of the Puerta de Hierro Majadahonda University Hospital and Sanofi (provided sarilumab free of charge). None of the funders had any role in the study's design, collection, management, analysis and interpretation of data, writing of the report and the decision to submit	Hospitalized patients with COVID-19, requiring supplemental oxygen by mask or nasal prongs Inclusion criteria: • ≥ 18 years; • Hospitalized, due to COVID-19 confirmed by RT-PCR or antigen test; • Pneumonia (radiographic evidence of pulmonary infiltrates or rales/crackles); • Standard oxygen supplementation due to SpO2 ≤94%; • ≥7 days between time from symptom onset and inclusion; • IL-6>40 pg/mL or d-dimer>1.0mcg/ml or ≥ two of the following inflammatory parameters elevated (CRP, LDH, serum ferritin or lymphopenia). Exclusion criteria: • High oxygen requirements; • Previous treatment with corticosteroids (CS) > 1 day; • Admission to the ICU; • Pregnant or lactating; • Allergy or hypersensitivity to sarilumab or CS;	Sarilumab + usual care Sarilumab (IV) at a single dose of 200 mg for patients <75 kg body weight, or 400 mg for patients weighing > 75 kg.	Usual care CS were given to all patients at a 1 mg/kg/day of methylprednisolone for at least 3 days (background medication). Standard of care also included antibiotic agents, antiviral agents, steroid boluses, vasopressor support, and anticoagulants that were provided at the discretion of the investigators.	Length of follow-up: 28 days Loss-to-follow-up: Intervention: 5 (5.1%) Reasons: loss of FU after discharge (n=4) or after admission at ICU in another hospital (n=1) Another patient did not receive the allocated intervention, due to withdrawing consent to participate. Control: 5 (4.9%) Reasons: loss of FU after discharge (n=4) or after admission at ICU in another hospital (n=1) Another patient did not receive the allocated intervention, due to withdrawing consent to participate. Incomplete outcome data:	Clinical outcomes Mortality (28 day) I: 2/99 (2.02) C: 2/102 (1.96) RR (95%CI): 1.03 (0.14-7.46) P= 1 Mortality (15 day), n/N (%) I:0/0 (0) C: 2/102 (1.96) RR (95%CI): 0.98 (0.95-1.01) P= 0.4976 Duration of hospitalization Time to hospital discharge, days (95%CI) I: 7 (6-8) C: 7 (6-8) HR (95%CI): 0.903 (0.68-1.21) P= 0.4623 ICU admission Day 15 I: 7/99 (7.1) C: 10/102 (9.8) RR (95%CI): 0.70 (0.25-1.91) P=0.4863 Day 28	Definitions: • Treatment Emergent Adverse Events were defined as CTCAE grade 3 or higher; • Adverse events included following disorders: blood and lymphatic system, Gastro-intestinal, Hepatobiliary, infections, injury, investigations, metabolism and nutrition, musculoskeletal and connective tissue, nervous system, psychiatric, renal and urinary, respiratory, thoracic and mediastinal, skin and subcutaneous tissue and vascular. Remarks: • The largest part of the participants was recruited in one tertiary centre (n=132). • Study was funded by Sanofi, which had however no role in study's design, data collection, management, analysis and interpretation nor in writing the report. • Study might have been underpowered. • Patients in the control group progressing to • Brescia-COVID ≥ 2 plus inflammatory parameters were given the option to

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	<p>the report for publication.</p> <p><u>Conflicts of interest:</u> Authors declared that they have nothing to disclose.</p>	<ul style="list-style-type: none"> Received immunosuppressive monoclonal antibody therapy within past 5 months; AST/ALT values >10 x ULN; Neutropenia (<0.5 x 10⁹/L); Severe thrombocytopenia (<50 x 10⁹/L); Sepsis caused by an alternative pathogen; Diverticulitis with risk of perforation; Ongoing infectious dermatitis. <p><u>N total at baseline:</u> N = 201 Intervention: 99 Control: 102</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 60.12 y (11.54) C: 59.85 y (11.77)</p> <p>Sex, n/N (%) male: I: 71/99 (71.72%) C: 70/102 (68.63%)</p> <p>Disease severity, mean (SD): I: NR C: NR</p> <p>Days from symptom onset to randomization, median (IQR) I: 9.0 (8.0-11.0) C: 10.0 (8.0-12.0)</p> <p>Ferritin, ng/mL I: 680.5 (405-1284) C: 908.5 (480-1717)</p> <p>IL-6, pg/mL I: 19.20 (6.0-46.0) C: 13.25 (3.85-43.35)</p>			<p>Intervention: NR Reasons NA</p> <p>Control: NR Reasons NA</p>	<p>I: 7/99 (7.07) C: 10/102 (9.8) RR (95%CI): 0.70 (0.25-1.91) P=0.4863</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> <i>Progression to IMV or death, n/N (%)</i> I: 4/99 (4) C: 9/102 (8.8) HR (95%CI): 0.4481 (0.14-1.46) P=0.1673 <i>Brescia-COVID score ≥3, day 15, n/N (%)</i> I: 16/99 (16.16) C: 16/102 (15.69) RR (95%CI): 1.03 (0.48-2.20) P=0.8874 <i>Brescia-COVID score ≥3, day 28, n/N (%)</i> I: 16/99 (16.16) C: 16/102 (15.69) RR (95%CI): 1.03 (0.48-2.20) P=0.8874 <i>Time to BRESCIA COVID score = 0</i> I: 86/99 (86.9) C: 88/102 (86.3) HR (95%CI): 0.9488 (0.70-1.28) P= 0.6381 <i>Time to respiratory failure</i> I: 16/99 (16.2) C: 16/102 (15.7)</p>	<p>be rescued with sarilumab at the same weight-adjusted doses (n=18). Patients randomly assigned to sarilumab therapy at baseline progressing to Brescia- COVID ≥ 2 were rescued according to local clinical practice protocol (n=27).</p> <p><u>Authors conclusion:</u> Our clinical trial failed to demonstrate any benefits of an early therapeutic intervention with sarilumab when added to an optimized SOC regimen that includes CS in the treatment of hospitalized patients with COVID-19 pneumonia with inflammatory parameters, who were under standard oxygen therapy. No new safety issues were identified.</p>

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		<p><i>Also available: coexisting conditions and other laboratory values</i></p> <p>Groups comparable at baseline? Unclear, patients in the control group had higher ferritin levels and higher serum IL-6 levels.</p>				<p>HR (95%CI): 1.059 (0.51-2.03) P= 0.9638 <i>Time to reduction of supplemental oxygen requirements</i> I: 91/99 (91.9) C: 96/102 (94.1) HR (95%CI): 0.9742 (0.73-1.30) P=0.7975</p> <p>Safety <u>Treatment Emergent Adverse events, n/N (%)</u> I: 4/99 (4.04) C: 6/102 (5.88) Effect (95%CI): NR P=NR <u>Adverse events, n/N (%)</u> I: 18/99 (18.2) C: 16/102 (15.7) Effect (95%CI): NR P=NR</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p> <p><i>Also available: (other) Brescia-COVID scores at other days than 15 and 28, subgroup analyses for the group BRESCIA COVID score ≥ 3 by age, sex, sarilumab dose and CRP-level.</i></p>	
Lescure, 2021	<p><u>Type of study:</u> RCT; double-blind, placebo-controlled</p> <p><u>Setting:</u></p>	<p>Hospitalized COVID-19 patients with severe or critical illness</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> ≥18 years admitted to hospital 	<p>I: sarilumab 200 mg II: sarilumab 400 mg</p> <p>The hospital pharmacist added the contents of prefilled syringes of</p>	<p>Placebo</p> <p>The hospital pharmacist prepared the</p>	<p><u>Length of follow up:</u> 60 days</p> <p><u>Loss to follow-up:</u> I: 2/161 (1.2%)</p>	<p>Clinical outcomes <u>Mortality</u> Patients alive at day 29</p> <p>I: 143 (90%) II: 159 (92%)</p>	<p><u>Definitions:</u> <i>7-point ordinal scale:</i> (1) death; (2) admitted to hospital, on invasive mechanical ventilation or extracorporeal membrane oxygenation; (3) admitted to hospital, on non-</p>

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	<p>multinational phase 3 trial; 45 hospitals</p> <p><u>Country:</u> Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain</p> <p><u>Source of funding:</u> 'This study was funded by Sanofi (Paris, France) and Regeneron Pharmaceuticals (Tarrytown, USA). Medical writing assistance was provided by Richard J Hogan, and Vojislav Pejović of Eloquent Scientific Solutions, a division of Envision Pharma Group, and editorial and graphics assistance was provided by Eloquent Scientific Solutions. This support was funded by Sanofi.'</p>	<ul style="list-style-type: none"> laboratory-confirmed SARS-CoV-2 infection in any specimen within 2 weeks before random assignment evidence of pneumonia by chest imaging or chest auscultation no alternative explanation for clinical presentation severe disease (<i>defined as administration of supplemental oxygen by nasal cannula, simple face mask, or another similar device</i>) or critical disease (<i>defined as need for supplemental oxygen delivered by non-rebreather mask or high-flow nasal cannula, use of invasive or non-invasive ventilation, or treatment in ICU</i>). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> low probability of surviving 48h or remaining at the investigational site > 48h, dysfunction ≥ 2 organ systems, need for extracorporeal life support, or renal replacement therapy at screening; absolute neutrophil count < 2000 cells per mm³; aspartate aminotransferase or alanine aminotransferase (ALT) exceeding 5x upper limit of normal at screening; < 50 000 platelets per mm³ at screening; known active, incompletely treated, suspected or known extrapulmonary tuberculosis; previous or concurrent use of immunosuppressant drugs at 	<p>sarilumab 200 mg solution for subcutaneous injection supplied by the sponsor into a specified volume of locally sourced 0.9% sodium chloride solution for IV infusion (two syringes for the 400 mg dose, one syringe for the 200mg dose).</p> <p>An option for a second dose existed (within the assigned treatment group) within 24–48 h of the first dose, based on the investigator's benefit-risk assessment (amended protocol 02; April 8, 2020).</p>	<p>volume of locally sourced 0.9% sodium chloride solution for IV infusion.</p> <p>An option for a second dose existed (within the assigned treatment group) within 24–48 h of the first dose, based on the investigator's benefit-risk assessment (amended protocol 02; April 8, 2020).</p> <p>Number of doses received 1 dose: 79 (94.0%) 2 doses: 5 (6.0%)</p>	<p>Reasons: 2 did not start treatment (randomised twice, n=1; suspected bacterial infection, n=1) II: 0/173 (0%) C: 2/86 (2.3%) Reasons: 2 did not start treatment (improved, n=1; withdrew consent, n=1)</p> <p>Number of doses received 1 dose: 79 (94.0%) 2 doses: 5 (6.0%)</p>	<p>C: 77 (92%) Difference vs placebo I: -1.7 (-9.3 to 5.8) II: 0.2 (-6.9 to 7.4)</p> <p>Patients alive at day 60, n (%) I: 142 (89.3) II: 155 (89.6) C: 75 (89.3) Difference vs placebo (95% CI) I: 0.0 (-8.2 to 8.2) II: 0.3 (-7.7 to 8.3)</p> <p><i>Results also reported for severe vs. critically ill patients separately</i></p> <p><u>Duration of hospitalization</u> Proportion of patients with need for ICU care during study (among patients not in ICU at baseline), n (%) I: 11 (11.2) II: 17 (14.9) C: 7 (12.5) Difference vs placebo (95% CI) I: -1.3 (-12.0 to 9.4) II: 2.4 (-8.4 to 13.3)</p> <p>Number of days of hospitalisation among patients alive at day 60, least squares mean (SE), days I: 15.6 (1.0) II: 16.1 (0.9) C: 15.9 (1.3) Difference vs placebo (95% CI) I: -0.2 (-3.5 to 3.0)</p>	<p>invasive ventilation or high-flow oxygen devices; (4) admitted to hospital, requiring supplemental oxygen; (5) admitted to hospital, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19-related or otherwise); (6) admitted to hospital, not requiring supplemental oxygen, no longer requiring ongoing medical care; and (7) discharged from hospital.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In this multinational, randomised, placebo-controlled trial of patients with severe or critical COVID-19 who were receiving the local standard of care, there was no observed benefit of intravenous sarilumab over placebo. The treatment groups had similar rates of serious infections and adverse events leading to death, and types of adverse events were consistent with previous clinical trial data for sarilumab. No new safety signals for sarilumab were observed in these patients with COVID-19. Adequately powered trials of targeted immunomodulatory therapies assessing survival as a primary endpoint are suggested in patients with critical COVID-19.</p>

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		<p>screening, including, but not limited to, IL-6 inhibitors or Janus kinase inhibitors within 30 days of baseline;</p> <ul style="list-style-type: none"> • anti-CD20 agents without evidence of B-cell recovery to baseline concentrations or IL-1 receptor antagonist within 1 week of baseline; • abatacept within 8 weeks of baseline; tumour necrosis factor α inhibitors within 2–8 weeks of baseline; • alkylating agents, including cyclophosphamide, within 6 months of baseline; • cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, or methotrexate < 4 weeks of baseline; • or intravenous immunoglobulin < 5 months of baseline; • use of systemic chronic (eg, oral) corticosteroids for a condition not related to COVID-19 at doses higher than prednisone 10 mg/day or equivalent at screening; • suspected or known active systemic bacterial or fungal infections < 4 weeks of screening <p><u>N total at baseline:</u> Randomized: N = 420 Intervention-I: 161 Intervention-II: 173 Control: 86 Included in mITT analysis: N = 416 Intervention-I: 159 Intervention-II: 173</p>				<p>II: 0.2 (-3.0 to 3.5)</p> <p>Time from first dose to discharge due to recovery, Kaplan-Meier estimates, days Median (95% CI) C: 14.0 (11.0–16.0) I: 11.0 (10.0–15.0) II: 13.0 (10.0–15.0) Hazard ratio vs placebo (95% CI) I: 1.05 (0.79 to 1.40) II: 1.00 (0.76 to 1.33)</p> <p><u>Symptom resolution</u> Time to ≥ 2-point improvement on seven-point clinical status scale, median Kaplan Meier estimate, days: I: 10.0 (9.0 to 12.0) II: 10.0 (9.0 to 13.0) C: 12.0 (9.0 to 15.0) Hazard ratio vs placebo I: 1.03 (0.75 to 1.40) II: 1.14 (0.84 to 1.54) <i>Results also reported for severe vs. critically ill patients separately</i></p> <p>Time to NEWS2 of <2 and maintained for 24 hours; Kaplan-Meier estimates, days, Median (95% CI) I: 9.0 (7.0–10.0) II: 9.0 (8.0–11.0) C: 11.0 (8.0–14.0) Hazard ratio vs placebo (95% CI) I: 1.05 (0.77–1.44) II: 1.09 (0.80–1.48)</p>	

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		<p>Control: 84</p> <p><u>Important characteristics:</u> <u>Age, median (IQR):</u> I: 58·0 (51·0–67·0) II: 58·0 (48·0–67·0) C: 60·0 (53·0–69·5) <u>Sex, n/N (%) male:</u> I: 108/159 (68%) II: 99/173 (57%) C: 54/84 (64%)</p> <p><u>Severity of illness</u> <u>Severe</u> I: 92/159 (58%) II: 105/173 (61%) C: 55/84 (65%) <u>Critical</u> I: 65/159 (41%) II: 68/173 (39%) C: 29/84 (35%) <u>Multisystem organ dysfunction</u> I: 2/159 (1%) II: 0/173 C: 0/84 <u>Clinical status, 7-point scale</u> 2 I: 17/159 (11%) II: 24/173 (14%) C: 9/84 (11%) 3 I: 28/159 (18%) II: 21/173 (12%) C: 11/84 (13%) 4 I: 112/159 (70%) II: 128/173 (74%) C: 64/84 (76%) 5 I: 2/159 (1%) II: 0/173 C: 0/84</p>				<p>Analysis of time to resolution of fever Kaplan-Meier estimates, days Median (95% CI)§ I: 8·0 (7·0–9·0) II: 9·0 (7·0–10·0) C: 7·0 (6·0–12·0) Hazard ratio vs placebo (95% CI) I: 0·91 (0·59–1·40) II: 0·92 (0·60–1·40)</p> <p><u>Need for respiratory support</u> Time to improvement in oxygenation (defined as increase in SpO₂/FiO₂ of ≥50 compared with the nadir SpO₂/FiO₂ for ≥48 hours), Kaplan-Meier estimates, days, median (95% CI)§ I: 6·0 (5·0–7·0) II: 6·0 (5·0–7·0) C: 7·0 (5·0–8·0) Hazard ratio vs placebo (95% CI) I: 1·17 (0·86–1·58) II: 1·11 (0·83–1·50)</p> <p>Initiation of mechanical ventilation, non-invasive ventilation, or use of high-flow nasal cannula, n (%) C: 13 (19·1) I: 26 (20·5) II: 33 (23·4) Difference vs placebo (95% CI) I: 1·4 (–10·3 to 13·0) II: 4·3 (–7·4 to 16·0)</p>	

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		<p><u>Time from dyspnoea onset to baseline</u>, days I: 5.0 (2.0–10.0) II: 4.0 (2.0–9.0) C: 7.0 (3.0–10.0)</p> <p><u>Duration of hospital stay before dosing</u>, days I: 3.0 (1.0–4.0) II: 2.0 (2.0–4.0) C: 4.0 (2.0–6.0)</p> <p><u>Admitted to ICU before dosing</u> I: 61 (38%) II: 59 (34%) C: 28 (33%)</p> <p><u>Duration of ICU stay before dosing</u>, days I: 2.0 (1.0–3.0) II: 2.0 (1.0–3.0)C: 1.0 (1.0–3.5)</p> <p>Groups comparable at baseline?</p>				<p>Patients alive off supplemental oxygen at day 29, n (%) I: 135/159 (84.9%) II: 145/173 (83.8%) C: 73/84 (86.9%) Difference vs placebo (95% CI I: -2.0 (-11.1 to 7.1) II -3.1 (-12.2 to 6.0)</p> <p>Percent of ventilator-free days in the first 28 days, least squares mean (SE) I: 74.8 (2.2) II: 75.7 (2.1) C: 77.3 (3.0) Difference vs placebo (95% CI) I: -2.4 (-10.2 to 5.3) II: -1.6 (-9.2 to 6.1)</p> <p><i>Also reported: Percent of days with hypoxaemia / supplemental oxygen / resting respiratory rate >24 breaths/min, time to saturation ≥94% on room air</i></p> <p>Safety <u>Adverse events</u> Any treatment-emergent adverse event I: 103 (65%) II: 121 (70%) C: 55 (65%) Any serious treatment-emergent adverse event I: 42 (26%) II: 51 (29%) C: 20 (24%) of which:</p>	

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						<p>Any serious infection</p> <p>I: 18 (11%) II: 22 (13%) C: 10 (12%)</p> <p>Pneumonia</p> <p>I: 1 (1%) II: 6 (3%) C: 0</p> <p>COVID-19 pneumonia</p> <p>I: 11 (7%) II: 4 (2%) C: 2 (2%)</p> <p>Bacterial pneumonia</p> <p>I: 1 (1%) II: 3 (2%) C: 1 (1%)</p> <p>Any treatment-emergent adverse event leading to death</p> <p>I: 17 (11%) II: 18 (10%) C: 9 (11%)</p> <p>Any adverse event of special interest</p> <p>I: 53 (33%) II: 76 (44%) C: 18 (21%)</p> <p>Of which</p> <p>Alanine aminotransferase increase</p> <p>I: 48 (30%) II: 55 (32%) C: 16 (19%)</p> <p>Invasive bacterial or fungal infection</p> <p>I: 8 (5%) II: 15 (9%) C: 3 (4%)</p> <p>Grade ≥ 2 hypersensitivity reaction</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						I: 1 (1%) II: 7 (4%) C: 0 Grade 4 neutropenia I: 3 (2%) II: 6 (3%) C: 0 Grade ≥2 infusion-related reaction I: 1 (1%) II: 6 (3%) C: 0 Virological outcomes <u>Viral clearance</u> not reported <i>Also reported: Sarilumab concentration, pharmacodynamic markers, and laboratory findings potentially related to COVID-19 severity, over time</i>	
The REMAP-CAP Investigators, 2020	<p><u>Type of study:</u> RCT Open-label design</p> <p><u>Setting:</u> Hospitals up to November 19, 2020</p> <p><u>Country:</u> International trial.</p> <p><u>Source of funding:</u> The trial has multiple international funders. Roche Products and</p>	<p>Critically ill patients with COVID-19 admitted to ICU and receiving respiratory or cardiovascular organ support</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • 18 years of age or older • either clinically suspected or microbiologically confirmed Covid-19 • severe disease state: admitted to ICU and receiving respiratory or cardiovascular organ support* • enrolled within 24 hours after starting organ support in the ICU 	<p>1) tocilizumab or 2) sarilumab</p> <p><u>Tocilizumab</u>, at a dose of 8 mg per kilogram of actual body weight (up to a maximum of 800 mg), was administered as an intravenous infusion over a period of 1 hour; this dose could be repeated 12 to 24 hours later at the discretion of the treating clinician if clinical improvement was judged insufficient.</p>	standard care (no immune modulation)	<p><u>Length of follow up:</u> 90 days</p> <p><u>Loss to follow-up:</u> Tocilizumab: 16/366 (4.4%) Reasons: -13 Withdrew consent -3 Had outcome that was not available</p> <p>Sarilumab: 3/48 (6.3%) Reasons: -3 Had outcome that was not available</p>	<p>Clinical outcomes <u>In-hospital death, n/N (%)</u> I_toci: 98/350 (28) I_sari: 10/45 (22) C: 142/397 (36)</p> <p><u>Primary in-hospital survival</u> Adjusted odds ratio Mean I_toci: 1.66±0.31 I_sari: 2.25±0.96 C: 1 Median (95% credible interval) I_toci: 1.64 (1.14 to 2.35) I_sari: 2.01 (1.18 to 4.71) C: 1</p>	<p><u>Definitions:</u> Respiratory organ support was defined as invasive or noninvasive mechanical ventilation, including through high-flow nasal cannulae if the flow rate was more than 30 liters per minute and the fraction of inspired oxygen was more than 0.4.</p> <p>Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope.</p> <p>The primary outcome was respiratory and cardiovascular organ support– free days, on an ordinal scale combining in-hospital death (assigned a value</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Sanofi supported the trial through provision of tocilizumab and sarilumab in the United Kingdom. The funders as well as Roche and Sanofi had no role in designing the trial, analyzing the data, writing the manuscript, or making the decision to submit the manuscript for publication.</p>	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> presumption that death was imminent with a lack of commitment to full support previously participated in REMAP-CAP within 90 days Additional exclusion criteria, specific to the Immune Modulation Therapy domain, are listed in a Supplementary Appendix. <p><u>N total at baseline:</u> N = 803 Tocilizumab: 353 Sarilumab: 48 Control: 402</p> <p><u>Important characteristics:</u> Age, mean±SD: I_toci: 61.5±12.5 I_sari: 63.4±13.4 C: 61.1±12.8 Sex, n/N (%) male: I_toci: 261/353 (74) I_sari: 39/48 (81) C: 283/402 (70) Acute respiratory support: None or supplemental oxygen only, n/N (%) I_toci: 1/353 (<1) I_sari: 0/48 C: 2/402 (<1) High-flow nasal cannulae I_toci: 101/353 (29) I_sari: 17/48 (35) C: 110/402 (27) Noninvasive ventilation only I_toci: 147/353 (42) I_sari: 23/48 (48) C: 169/402 (42) Invasive mechanical ventilation I_toci: 104/353 (29)</p>	<p>Sarilumab, at a dose of 400 mg, was administered as an intravenous infusion once only. All investigational drugs were dispensed by local pharmacies and were open label.</p>		<p>C: 15/412 (3.6%) Reasons: -10 Withdrew consent -5 Had outcome that was not available</p>	<p>Probability of superiority to control — % I_toci: 99.6 I_sari: 99.5 C: -</p> <p><u>Time to ICU discharge</u> Adjusted HR - mean (SD) I_toci: 1.43 (0.13) I_sari: 1.69 (0.32) C: 1 median (95% CrI) I_toci: 1.42 (1.18 to 1.70) I_sari: 1.64 (1.21 to 2.45) C: 1 Probability of superiority to control, % I_toci: >99.9 I_sari: 99.9 C: -</p> <p><u>Time to hospital discharge</u> Adjusted HR - mean (SD) I_toci: 1.42 (0.13) I_sari: 1.65 (0.31) C: 1 median (95% CrI) I_toci: 1.41 (1.18 to 1.70) I_sari: 1.60 (1.17 to 2.40) C: 1 Probability of superiority to control, % I_toci: >99.9 I_sari: 99.8 C: -</p> <p><u>Symptom resolution</u> Not reported.</p> <p><u>Number of respiratory and cardiovascular organ support*—free days up to day 21 (primary outcome)</u></p>	<p>of -1) and days free of organ support to day 21.</p> <p><u>Remarks:</u> -The trial uses an open-label design. -Because this is an early, preliminary report, some data are missing, including 11 outcomes.</p> <p><u>Authors conclusion:</u> In critically ill patients with Covid-19 receiving organ support in ICUs, were both effective as compared with the current standard of care, which included glucocorticoids in the majority of patients (>80%). The benefit was consistent across primary and secondary outcomes and across subgroups and secondary analyses, including survival.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I_sari: 8/48 (17) C: 121/402 (30)</p> <p>Groups comparable at baseline? Baseline characteristics were balanced across intervention groups and typical of a critically ill population with Covid-19.</p>				<p>Median (IQR) I_toci: 10 (-1 to 16) I_sari: 11 (0 to 16) C: 0 (-1 to 15) Adjusted odds ratio Mean I_toci: 1.65±0.23 I_sari: 1.83±0.44 C: 1 Median (95% credible interval) I_toci: 1.64 (1.25 to 2.14) I_sari: 1.76 (1.17 to 2.91) C: 1 Probability of superiority to control — % I_toci: >99.9 I_sari: 99.5 C: -</p> <p>Safety <u>Serious adverse events</u> Patients with >1 serious adverse event, n (%) I_toci: 9/353 (2.5) I_sari: 0/48 (0.0) C: 11/402 (2.7) Adjusted OR - mean (SD) I_toci: 1.22 (0.55) I_sari: 2.99 (2.95) C: 1 median (95% CrI) I_toci: 1.10 (0.48 to 2.58) I_sari: 2.10 (0.51 to 10.77) C: 1 Probability of superiority to control, % I_toci: 59.3 I_sari: 84.0 C: -</p> <p>Virological outcomes <u>Viral clearance</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Not reported. Also reported (secondary outcomes): 90-day Survival (time to event); Respiratory support-free days; Cardiovascular support-free days; WHO scale at day 14; Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline	
16.5. Siltuximab							
Declercq (2021)	See evidence table of Declercq (2021) by Anakinra.						
16.6. Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor)							
Rosas, 2022	<p><u>Type of study:</u> Global, randomised, double-blind, placebo-controlled, phase 3 trial.</p> <p><u>Setting:</u> Hospital</p> <p><u>Country:</u> Europe and North America.</p> <p><u>Source of funding:</u> F. Hoffmann-La Roche Ltd and the US Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adults who had SARS-CoV-2 infection based on local polymerase chain reaction testing; Patients who were hospitalised because of COVID-19 pneumonia with blood oxygen saturation of <94% or partial pressure of oxygen/fraction of inspired oxygen of <300 mm Hg. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Not reported. <p><u>N total at baseline:</u> N = 438 Intervention: N = 294 Control: N = 144</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 60.9 y (14.6) C: 60.6 y (13.7)</p> <p>Sex, n/N (%) male:</p>	<p>Tocilizumab plus standard of care</p> <p>intravenous tocilizumab 8 mg/kg (maximum 800 mg) or placebo plus local standard care (could have included antiviral therapy or corticosteroids in addition to supportive care).</p> <p>A second dose of tocilizumab or placebo could be given within 8 to 24 h after the first dose if clinical signs and symptoms did not improve</p>	Placebo plus standard of care	<p><u>Length of follow-up:</u> Maximum length of follow-up was 60 days.</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: N (%) Reasons (describe)</p> <p>Control: N (%) Reasons (describe)</p>	<p><u>Clinical outcomes Mortality (60 days)</u> I: 72/295 (24.4%) C: 36/143 (25.2%)</p> <p><u>Duration of hospitalization Patients (cumulatively) discharged at 60 days follow-up, n//N (%)</u> I: 197/294 (67%) C: 92/144 (63.9%)</p> <p><u>Time to symptom resolution</u> <i>Time to clinical improvement</i></p> <p><u>Invasive respiratory support</u> <i>Patients who required supplemental oxygen at or after the time of hospital discharge at 60 days follow-up, n/N (%)</i> I: 36/197 (18.3%) C: 24/92 (26.1%)</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> Clinical status on a 7-category ordinal scale at day 28. <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> Time to clinical improvement to day 28. <p><u>Definitions:</u></p> <ul style="list-style-type: none"> Standard of care was not further specified. Ready for discharge was defined as normal body temperature and respiratory rate and stable oxygen saturation on ambient air or <3 L supplemental oxygen. Time to clinical improvement up to day 28 was defined as time from initial treatment to a National Early Warning Score 2 (NEWS2) of <3 maintained for 24 hours. <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Research and Development Authority, under OT number HHSO1002018000 36C.</p> <p><u>Conflicts of interest:</u> Transparently reported.</p>	<p>I: 205/294 (69.7%) C: 101/144 (70.1%)</p> <p>Disease severity, mean (SD): <i>Defined by NEWS2 ordinal scale score for clinical status, n/N (%)</i></p> <p>2: hospitalization in a non-intensive care unit (ICU) without supplemental oxygen I: 9/294 (3.1%) C: 6/144 (4.2%)</p> <p>3: non-ICU hospitalization with supplemental oxygen I: 78/294 (26.5%) C: 44/144 (30.6%)</p> <p>4: ICU or non-ICU hospitalization with noninvasive ventilation or high-flow oxygen I: 94/294 (32%) C: 39/144 (27.1%)</p> <p>5: ICU hospitalization with mechanical ventilation I: 45/294 (15.3%) C: 15/144 (10.4%)</p> <p>6: ICU hospitalization with extracorporeal membrane oxygenation or mechanical ventilation and additional organ support I: 68/294 (23.1%) C: 40/144 (27.8%)</p> <p>Groups comparable at baseline.</p>				<p><i>Duration of supplemental oxygen through 28 days follow-up, median (95% CI)</i> I: 26.5 (19.0 to 28.0) days C: 28.0 (26.0 to 28.0) days</p> <p><u>Non-invasive respiratory support</u> not reported</p> <p>Safety <u>(Serious) adverse events</u> <i>≥1 adverse event, n/N (%)</i> I: 240/295 (81.4%) C: 118/143 (82.5%)</p> <p><i>≥1 serious adverse event, n/N (%)</i> I: 116/295 (39.3%) C: 64/143 (44.8%)</p> <p>Virological outcomes <u>Viral clearance</u> <i>Median time to negative RT-qPCR</i> I: 15.0 (95% CI 14.0 to 21.0) days. C: 21.0 (95% CI 14.0 to 28.0) days. HR 1.13 (95% CI 0.83 to 1.53)</p> <p><i>Negative RT-qPCR at day 28, n/N (%)</i> I: 139/240 (57.9%) C: 67/111 (60.4%)</p> <p><i>Neutralising anti-SARS-CoV-2 antibodies at day 28, %</i> I: 100% C: 98.3%</p>	<p>There was no mortality benefit with tocilizumab through day 60. Tocilizumab did not impair viral clearance or host immune response, and no new safety signals were observed. Future investigations may explore potential biomarkers to optimize patient selection for tocilizumab treatment and combination therapy with other treatments.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Neutralising anti-SARS-CoV-2 antibodies at day 60, % I: 100% C: 100%	
Broman, 2022	<p>Type of study: A randomized, single center, open label study</p> <p>Setting: Hospitalized patients, between August 12, 2020 and June 16, 2021 (COVIDSTORM study)</p> <p>Country: Finland</p> <p>Source of funding: No external funding was received for this study.</p> <p>Conflicts of interest: None to declare</p>	<p>Hospitalized patients with hypoxemia</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Written consent • Hospitalized with COVID-19 • Age ≥18 years • SARS-CoV-2 PCR positive • SpO2 ≤93% on ambient air or respiratory rate >30/min • At least 2 out of 4 <ul style="list-style-type: none"> - IL-6 >11.8 ng/L (2x ULN) - Ferritin >300 µg/L in women or >800 µg/L in men (2x ULN) - D-Dimer >1.5 mg/L - CRP >40 mg/L <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Previous severe allergic reaction to monoclonal • Concurrent infection (other than COVID-19) • Imminent and inevitable progression to death <24h • Long-term immunomodulatory drugs • Pregnant or breastfeeding • Participating in other clinical drug trials • Neutrophil count <1.0 x 10⁹/L • Platelet count <50 x 10⁹/L • ALT >350 IU/L in women or >500 IU/L in men (10x ULN) • antibody therapy 	<p>Tocilizumab: single infusion of TCZ over 60 minutes immediately after randomization (Day 1). Doses were dependent on the body weight; 400mg for <60kg, 600mg for 60-90kg and 800mg for >90kg</p> <p>+</p> <p>Standard care</p>	<p>Standard of care: not described</p> <p><i>“SoC did not include antivirals (e.g., remdesivir), nor hydroxychloroquine or other 82 experimental treatments, but could include LMWH subcutaneously and glucocorticoids.”</i></p>	<p>Length of follow-up: 28 days</p> <p>Incomplete outcome data & loss-to-follow-up: Intervention: N=2 (3.4%) Reasons: ignored exclusion criteria (n=1), immediate withdrawal of consent (n=1)</p> <p>No lost to follow-up</p> <p>Control: No incomplete data or lost to follow-up</p>	<p>Clinical outcomes</p> <p>Mortality (28 day): Mortality, n/N (%): I: 1/57 (1.8%) C: 0/29 (0%)</p> <p>Duration of hospitalization Median (IQR), days I: 9 (7-12) C: 12 (9-15) P=0.014</p> <p>Time to symptom resolution Not reported</p> <p>Invasive respiratory support Incidence of IMV in patients not on IMV at baseline, n (%) I: 5/57 (8.8%) C: 3/28 (10.7%)</p> <p>Safety</p> <p>Serious adverse events Not reported</p> <p>Virological outcomes</p> <p>Viral clearance</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Clinical status at day 28 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> • Incidence of IMV • Duration of respiratory support other than supplemental oxygen • Incidence and duration of ICU stay • Mortality rate at day 28 • Time to hospital discharge or ready for discharge • Duration of supplemental oxygen <p>Definitions: Clinical status was assessed using a 7-category ordinal scale, where 1: at home, normal daily activities; 2: at home, assistance needed; 3: hospitalized, no supplemental oxygen; 4: hospitalized (non-ICU), receiving supplemental oxygen; 5: in ICU, no invasive mechanical ventilation (IMV); 6: in ICU receiving IMV and/or extracorporeal membrane oxygenation (ECMO); 7: dead.</p> <p>Remarks: Standard of care was not described</p> <p>Authors conclusion: In hospitalized COVID-19 patients with hypoxemia and elevated inflammation markers, administration of tocilizumab in addition to standard of care was associated with significantly better clinical recovery by day 28 and a</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p><u>N total at baseline:</u> N = 86 Intervention: N=59 Control: N=29</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 58.4 y (14.1) C: 58.8 y (13.7)</p> <p>Sex, n/N (%) male: I: 34/57 (59.6%) C: 14/29 (48.3%)</p> <p>Disease severity: Illness severity by National Early Warning Score, mean (SD) I: 5.9 (2.4) C: 6 (2)</p> <p>Groups are comparable at baseline</p>					shorter hospitalization compared to standard of care alone.
Hermine, 2022 (TOCI-2 and SARI-2 trial, embedded in the CORIMUNO-19 cohort)	<p><u>Type of study:</u> Two cohort-embedded, investigator-initiated, multicenter, open-label, Bayesian randomised controlled clinical trials</p> <p><u>Setting:</u> hospital-based, between March 31 to April 18, 2020 (TOCI-2) and from March 27 to April, 2020 (SARI-2)</p>	<p><u>Hospital based COVID-19 patients with moderate, severe pneumonia or critical pneumonia</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Positive on RT-PCR and/or typical chest CT-scan with moderate to severe, or critical pneumonia ($O_2 > 3 \text{ L} \cdot \text{min}^{-1}$) WHO-CPS score > 5 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Exclusion criteria to the CORIMUNO-19 cohort Known hypersensitivity to the intervention Pregnancy Current documented bacterial infection 	<p>TOCI-2 Tocilizumab was administered intravenously (IV) at 8 mg kg⁻¹ on day 1.</p> <p>+</p> <p>Usual care</p> <p>SARI-2 Sarilumab was administered IV at a fixed dose of 400 mg on day 1</p> <p>+</p> <p>Usual care</p>	Usual care: antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the clinicians since, at that time, no standard of care (SOC) was defined, including the use of corticosteroids.	<p><u>Length of follow-up:</u> 90 days</p> <p>TOCI-2 <u>Loss-to-follow-up or incomplete data:</u> I: 2/51 (3.9%) <i>Reason</i> • <i>withdrew consent (n = 2)</i></p> <p>C: 3/46 (6.5%) <i>Reasons</i> • <i>withdrew consent (n = 3)</i></p> <p>No loss-to-follow up</p> <p>SARI-2</p>	<p>Clinical outcomes <u>Mortality</u> not reported</p> <p><u>Overall survival at D14, estimate (95% CI)</u></p> <p>TOCI-2 I: 90% (82 to 99) C: 79% (68 to 92) HR: 0.37 (0.12 to 1.15)</p> <p>SARI-2 I: 75% (64 to 88) C: 73% (59 to 90) HR: 0.95 (0.40 to 2.25)</p> <p><u>Overall survival at D28, estimate (95% CI)</u></p> <p>TOCI-2 I: 84% (74 to 95) C: 77% (65 to 90)</p>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> No improvement in WHO score at day 4 Extubation or removal of NIV $> 48 \text{ h}$ at day 14 <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> Overall survival, day 14, 28, 90 WHO-CPS score at day 4, 7 and 14 Day-28 ventilator-free days Oxygen supply independency at day 28 and 90 Discharge at day 28 and day 90 ICU discharge at day 28 and day 90 <p><u>Definitions:</u> -</p> <p><u>Remarks:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> France (12 sites, TOCI-2; 8 sites, SARI-2)</p> <p><u>Source of funding:</u> This trial was publicly funded (Ministry of Health, Programme Hospitalier de Recherche Clinique [PHRC COVID-19-20-0143, PHRC COVID-19-20-0029], Foundation for Medical Research (FRM), AP-HP Foundation, and the Reacting program).</p> <p><u>Conflicts of interest:</u> Roche and Sanofi donated TCZ and SARI.</p> <p>Transparently reported.</p>	<ul style="list-style-type: none"> Patients with any out of ranges laboratory results on ANC, haemoglobin levels, PLT, SGOT or SGPT <p>TOCI-2 <u>N total at baseline:</u> N = 97 Intervention: 51 Control: 46</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 63.2 y (59.4-70.9) C: 65.4 y (57.6-70.5)</p> <p>Sex, n/N (%) male: I: 33/49 (67%) C: 33/43 (77%)</p> <p>Disease severity, n/N (%) <i>Defined by WHO-CPS score ≥7,</i> n/N (%) I: 36/49 (74%) C: 31/43 (71%)</p> <p>Groups comparable at baseline.</p> <p>SARI-2 <u>N total at baseline:</u> N = 91 Intervention: 50 Control: 41</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 61.9 y (53.8-66.2) C: 61.2 y (55.3-68.5)</p> <p>Sex, n/N (%) male: I: 36/48 (75%) C: 26/33 (79%)</p>			<p><u>Loss-to-follow-up or incomplete data:</u> I: 2/50 (4.0%) <i>Reason</i></p> <ul style="list-style-type: none"> withdrew consent (n = 2) <p>C: 8/41 (19.5%) <i>Reasons</i></p> <ul style="list-style-type: none"> withdrew consent (n = 8) <p>No loss-to-follow up</p>	<p>HR: 0.56 (0.22 to 1.46)</p> <p>SARI-2 I: 71% (59 to 85) C: 67% (52 to 85) HR: 0.89 (0.40 to 1.96)</p> <p><u>Overall survival at D90, estimate (95% CI)</u> TOCI-2 I: 76% (64 to 89) C: 70% (57 to 85) HR: 0.67 (0.30 to 1.49)</p> <p>SARI-2 I: 71% (59 to 85) C: 61% (46 to 80) HR: 0.74 (0.35 to 1.58)</p> <p><u>Duration of hospitalization</u> not reported</p> <p><u>Discharge at D28, estimate (95%CI)</u> TOCI-2 I: 55% (40 to 68) C: 42% (27 to 56) HR: 1.45 (0.80 to 2.63)</p> <p>SARI-2 I: 35% (22 to 49) C: 30% (16 to 46) HR: 1.21 (0.55 to 2.66)</p> <p><u>Discharge at D90, estimate (95%CI)</u> TOCI-2 I: 70% (54 to 82) C: 60% (44 to 74) HR: 1.35 (0.84 to 2.17)</p> <p>SARI-2 I: 65% (48 to 77) C: 52% (33 to 68) HR: 1.30 (0.71 to 2.37)</p>	<p>Results on secondary outcomes should be regarded as exploratory (stated by the authors)</p> <p><u>Authors conclusion:</u> In critically ill patients with COVID-19, anti-IL-6 Receptors did not significantly increase the number of patients alive without any NIV, MV by D14.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Disease severity, n/N (%) Defined by WHO-CPS score ≥ 7, n/N (%) I: 32/48 (67%) C: 24/33 (41%)</p> <p>Groups comparable at baseline.</p>				<p><u>ICU discharge at D28, estimate (95%CI)</u> TOCI-2 I: 72% (55 to 84) C: 60% (42 to 74) HR: 1.28 (0.73 to 2.24) SARI-2 I: 60% (43 to 74) C: 71% (50 to 85) HR: 0.78 (0.42 to 1.44)</p> <p><u>ICU discharge at D90, estimate (95%CI)</u> TOCI-2 I: 84% (66 to 93) C: 83% (63 to 93) HR: 1.15 (0.73 to 1.18) SARI-2 I: 79% (61 to 89) C: 82% (57 to 93) HR: 0.84 (0.49 to 1.47)</p> <p><u>Time to symptom resolution</u> not reported</p> <p><u>No improvement in WHO score at D4, n/N (90% CI)</u> TOCI-2 I: 35/49 (71%) C: 30/43 (70%) Median posterior absolute risk difference +1.7% (-13.6+17.1) SARI-2 I: 34/48 (71%) C: 26/33 (79%) Median posterior absolute risk difference -7.3% (-22.5 to +8.7)</p> <p><u>WHO-CPS score, D2-D14 (longitudinal analysis)</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>TOCI-2 aOR: 0.76 (0.27 to 2.13)</p> <p>SARI-2 aOR: 0.72 (0.21 to 2.41)</p> <p><u>Extubation or removal of HIV at D14 (95%CI)</u></p> <p>TOCI-2 I: 47% (32 to 60) C: 42% (27 to 56) HR: 1.19 (0.71 to 2.04)</p> <p>SARI-2 I: 38% (24 to 51) C: 33% (18 to 50) HR: 1.05 (0.55 to 2.07)</p> <p><u>Oxygen supply independency, estimate at D28 (95% CI)</u></p> <p>TOCI-2 I: 59% (44 to 72) C: 49% (33 to 63) HR: 1.44 (0.82 to 2.52)</p> <p>SARI-2 I: 44% (29 to 57) C: 36% (20 to 53) HR: 1.20 (0.59 to 2.44)</p> <p><u>Oxygen supply independency, estimate at D90 (95% CI)</u></p> <p>TOCI-2 I: 69% (53 to 80) C: 64% (47 to 77) HR: 1.28 (0.80 to 2.03)</p> <p>SARI-2 I: 71% (52 to 83) C: 56% (35 to 68) HR: 1.29 (0.74 to 2.25)</p> <p><u>Invasive respiratory support</u> not reported</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>Non-invasive respiratory support</u> not reported</p> <p>Safety <u>Serious adverse events</u> Patients with at least one AE</p> <p>TOCI-2 I: 33/49 (67%) C: 30/43 (70%)</p> <p>SARI-2 I: 32/48 (68%) C: 22/33 (68%)</p> <p>Virological outcomes <u>Viral clearance</u> not reported</p>	
Declercq (2021)	See evidence table of Declercq (2021) by Anakinra.						
Rosas, 2021b	<p><u>Type of study:</u> Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial.</p> <p><u>Setting:</u> Hospital, June 2020-March 2021</p> <p><u>Country:</u> Not stated.</p> <p><u>Source of funding:</u> This trial was supported by F. Hofmann-La Roche Ltd.</p>	<p><u>Hospitalized COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Positive SARS-CoV-2 polymerase chain reactive test result within 7 days of randomization; Pneumonia confirmed by chest x-ray or computed tomography; Hypoxemia requiring >6 L/min supplemental oxygen. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Estimated glomerular filtration rate was <30 mL/min; Alanine aminotransferase or aspartate aminotransferase levels were >5 x the upper limit of normal within 24 hours of screening. 	<p>Remdesivir plus tocilizumab</p> <p>Remdesivir was administered intravenously, followed by a single intravenous dose of tocilizumab 8 mg/kg (maximum, 800 mg)</p>	<p>Remdesivir plus placebo</p> <p>Remdesivir was administered intravenously, followed by a single intravenous dose of placebo 9 mg/kg (maximum, 800 mg).</p>	<p><u>Length of follow-up:</u> 60 days.</p> <p><u>Loss-to-follow-up:</u> Intervention: N = 9</p> <p>Control: N = 4</p> <p><u>Incomplete outcome data:</u> Intervention: N = 98</p> <p>Control: N = 50</p>	<p>Clinical outcomes <u>Mortality at day 28, n/N (%)</u> I: 78/430 (18.1%) (95% CI 14.5 to 21.8) C: 41/210 (19.5%) (95% CI 14.2 to 24.9) Weighted difference: -1.3 (-7.8 to 5.2) P=0.69</p> <p><u>Mortality at day 60, n/N (%)</u> I: 97/430 (22.6%) (95% CI 18.6 to 26.5) C: 54/210 (25.7%) (95% CI 19.8 to 31.6) Weighted difference -3 (-10.1 to 4) P=0.39</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In this randomized, double-blind, placebo-controlled trial, tocilizumab plus remdesivir did not shorten time to hospital discharge or “ready for discharge” to day 28 compared with placebo plus remdesivir in patients with severe COVID-19 pneumonia, most of whom received systemic corticosteroids. Serious infections were not more frequent with tocilizumab treatment, and no new safety signals were identified.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> IOR Grant from Roche/Genentech related to the submitted work and grant from Genentech and personal fees from Genentech, Boehringer, and Bristol Myers Squibb outside the submitted work. GD: Grants from Gilead Sciences, Regeneron Inc., Roche, Boehringer Ingelheim, and Edasa Biotech outside the submitted work. Gilead Medical Affairs sentinel panel and Scientific Advisory Board for Safeology Inc. RLG: Personal fees from Eli Lilly, Gilead Sciences Inc., GlaxoSmithKline, Johnson and Johnson, and Roivant Sciences Inc. and non- financial support from Gilead Sciences Inc. outside the submitted work. SML: Investigator fees from</p>	<ul style="list-style-type: none"> Patients with suspected active bacterial, fungal, viral, or other infection except COVID-19. <p><u>N total at baseline:</u> N = 640 Intervention: N = 430 Control: N = 210</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 60.1 y (13.3) C: 58.2 y (13.3)</p> <p>Sex, n/N (%) male: I: 266/434 (61.9%) C: 139/210 (66.2%)</p> <p>Disease severity, mean (SD): <i>Defined by ordinal scale for clinical status</i></p> <p><u>3 (Non-ICU hospital ward or ready for hospital ward requiring supplemental oxygen)</u> I: 29/434 (6.7%) C: 13/210 (6.2%)</p> <p><u>4 (ICU or non-ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen)</u> I: 336/434 (78.1%) C: 175 (210 (83.3%)</p> <p><u>5 (ICU, requiring intubation and mechanical ventilation)</u> I: 30/434 (9.1%) C: 9/210 (4.3%)</p> <p><u>6 ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support)</u></p>				<p><i>Time to death to day 28, median (IQR)</i> I: non evaluable C: non evaluable P=0.79 HR 0.95 (95% CI 0.65 to 1.39)</p> <p><u>Duration of hospitalization</u> <i>Time to hospital discharge or ready for discharge to day 28, median (IQR)</i> I: 14 (12-15) days C: 14 (11-16) days P=0.74 HR 0.97 (95% CI 0.78 to 1.19)</p> <p><u>Time to symptom resolution</u> <i>Clinical status at day 14 assessed on the 7-category ordinal scale, n/N (%)</i></p> <p>1 I: 231/430 (54.0%) C: 110/210 (52.4%)</p> <p>2 I: 11/430 (2.6%) C: 4/210 (1.9%)</p> <p>3 I: 38/430 (8.9%) C: 24/210 (11.4%)</p> <p>4 I: 41/430 (9.6%) C: 14/210 (6.7%)</p> <p>5 I: 21/430 (4.9%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Roche/Genentech during the conduct of the trial. PR: Nothing to disclose. BDH: Personal fees from Kite Pharma and Novartis outside the submitted work. AWC: Nothing to disclose. JSO: Institutional funding from Roche during conduct of the trial. NAH: Grants from GlaxoSmithKline, Sanof, AstraZeneca, Genentech, Boehringer Ingelheim, Novartis, and Gossamer Bio; personal fees from GlaxoSmithKline, Sanof, AstraZeneca, Genentech, Novartis, Regeneron, Teva, and Amgen outside the submitted work. AS: Personal fees from Genentech, AbbVie, Pharmacyclics, Janssen, Kite Pharma, Celgene, Ver- astem,	I: 26/434 (6.0%) C: 13/210 (6.2%) Groups comparable at baseline? Yes.				C: 14/210 (6.7%) 6 I: 43/430 (10%) C: 24/210 (11.4%) 7 I: 43/430 (10%) C: 20/210 (9.5%) <u>Respiratory support</u> <i>Time to mechanical ventilation or death to day 28, median (IQR)</i> I: non evaluable C: non evaluable P=0.9 HR 0.98 (95% CI 0.72 to 1.34) Safety <u>Adverse events, N</u> I: N = 1094 C: N = 530 <i>Patients with 1 or more than 1 event, n/N (%)</i> I: 320 (429 (74.6%) C: 147/213 (69.0%) <i>Patients with 1 or more than 1 serious adverse event, n/N (%)</i> I: 128/429 (29.8%) C: 72/213 (33.8%) Virological outcomes <u>Viral clearance</u> Not reported	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>BeiGene, Novartis, TG Therapeutics, Seattle Genetics, Morphosys, Jazz Pharmaceuticals, and Gilead Sciences and nonfinancial support from Bristol Myers Squibb outside the submitted work. JG-D: Nothing to disclose. IG: Nothing to disclose. JC: Grant provided to institution from Roche/Genentech during conduct of the trial. Grants and personal fees from Gilead Sciences Inc. outside the submitted work. OG: Employee of Roche and shareholder of Roche Holding AG. EG: Employee of Roche. NL-K: Employee of Roche/Genentech. LT: Employee of Roche/Genentech and has an unpublished patent pending, "Tocilizumab and Remdesivir Combination Therapy for COVID-</p>						

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	19 Pneumonia.” KT: Former employee of Roche/Genentech and owns stock in Roche/Genentech. HC: Employee of Gilead Sciences Inc. DB: Former employee of and holds stock in Gilead Sciences Inc. JKO: Employee of Roche/Genentech.						
Horby, 2021a Recovery Collaborative Group	<u>Type of study:</u> RCT (open-label), part of the RECOVERY trial. <u>Setting:</u> 131 National Health Service Hospitals participating in the RECOVERY trial, enrolment between April 23, 2020 until Jan 24, 2021; This study was part of the RECOVERY trial, in which patients were randomized to one	Hospitalized, adult patients with clinical evidence of progressive COVID-19. <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Adult patients Clinical evidence of progressive COVID-19 (oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Tocilizumab not available at the hospital/time of enrolment Tocilizumab was definitely contra-indicated or definitely indicated Patients with known hypersensitivity to tocilizumab, evidence of active tuberculosis 	Usual care + Tocilizumab (A single intravenous infusion over 60 min was provided. The dose was established by bodyweight (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). A second dose could be given 12–24 h later if the patient’s condition had not improved.)	Usual care	<u>Length of follow up:</u> Until discharge, death or at day 28 after randomisation. <u>Loss to follow-up:</u> I: 1964/2022 (97%) completed follow-up Reasons: not reported C: 2049/2094 (98%) completed follow-up Reasons: not reported (for the outcome 28-day mortality 99% completed follow-up)	Clinical outcomes <u>Mortality (28-30 day), n/N (%)</u> <u>28-day mortality, n/N (%)</u> I: 621/2022 (31%) C: 729/729 (35%) RR (95%CI): 0.85 (0.76–0.94) P= 0.0028 Subgroup analyses are available, based on e.g. days since symptom onset, corticosteroid treatment and respiratory support. <u>Duration of hospitalization</u> <u>Median time to discharge, days</u> I: 19 C: >28	<u>Definitions:</u> Receipt of invasive mechanical ventilation or death/receipt of ventilation included only those on no ventilator support or non-invasive ventilation at second randomisation (of tocilizumab). Successful cessation of invasive mechanical ventilation included only those on invasive mechanical ventilation at second randomisation <u>Remarks:</u> 16% of patients in the tocilizumab group reportedly did not receive treatment and reasons were not recorded. Furthermore, 77 patients in the usual care group did receive tocilizumab.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>of the following groups: Part A: 542 dexamethasone, 557 lopinavir-ritonavir, 383 hydroxy-chloroquine, 2041 azithromycin, 3083 colchicine, 8107 usual care; Part B: 5285 convalescent plasma, 2416 REGN-COV2, 6301 usual care; Part C: 4450 aspirin, 4594 usual care; After 21 days, eligible patients were randomised to either tocilizumab + usual care versus usual care alone.</p> <p><u>Country:</u> United Kingdom</p> <p><u>Source of funding:</u> UK Research and Innovation, National Institute of Health Research, Roche (provision of tocilizumab and reviewed draft publication for factual accuracy on tocilizumab).</p>	<p>infection or clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)</p> <p><u>N total at baseline:</u> N = 4116 Intervention: 2022 Control: 2094</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 63.3 y (13.7) C: 63.9 y (13.6) Sex, n/N (%) male: I: 1337/2022 (66%) C: 1437/2094 (69%) Number of days since symptom onset, median (IQR): I: 9 (7–13) C: 10 (7–14) Number of days since hospitalisation, median (IQR): I: 2 (1–5) C: 2 (1–5)</p> <p>Disease severity <u>Respiratory support at second randomisation</u> No ventilator support, n/N (%): <i>Defined as patients not receiving any oxygen and patients receiving low-flow oxygen</i> I: 935/2022 (46%) C: 933/2094 (45%) Non-invasive ventilation, n/N (%): <i>Defined as patients receiving high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation</i> I: 819/2022 (41%)</p>				<p><i>Discharged from hospital <28 days, n/N (%)</i> I: 1150/2022 (57%) C: 1044/2094 (50%) RR (95%CI): 1.22 (1.12–1.33) P<0.0001</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support Receipt of invasive mechanical ventilation or death</u> <i>Invasive mechanical ventilation, n/N (%)</i> I: 265/1754 (15%) C: 343/1800 (19%) RR (95%CI): 0.79 (0.69–0.92) P= 0.0019</p> <p><i>Death, n/N (%)</i> I: 490/1754 (28%) C: 580/1800 (32%) RR (95%CI): 0.87 (0.78–0.96) P=0.0055</p> <p><u>Receipt of ventilation</u> <i>Non-invasive ventilation, n/N (%)</i> I: 281/935 (30%) C: 309/933 (33%) RR (95%CI): 0.91 (0.79–1.04) P= 0.15 <i>Invasive mechanical ventilation, n/N (%)</i> I: 67/935 (7%) C: 86/933 (9%)</p>	<p>There is high risk of bias, since participants and local study staff were not blinded.</p> <p>Roche Products supported the study through the supply of tocilizumab and reviewed the draft publication for factual accuracy relating to tocilizumab.</p> <p><u>Authors conclusion:</u> The RECOVERY trial has shown that for patients hospitalised with severe COVID-19, treatment with tocilizumab reduces mortality, increases the chances of successful hospital discharge, and reduces the chances of requiring invasive mechanical ventilation. These benefits are additional to those previously reported for dexamethasone. These findings require an update to clinical guidelines, which has already begun, and efforts to increase the global availability and affordability of tocilizumab.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> The authors have no conflict of interest or financial relationships relevant to the submitted work.</p>	<p>C: 867/2094 (41%) Invasive mechanical ventilation, n/N (%): <i>Defined as patients receiving invasive mechanical ventilation or extracorporeal membranous oxygenation</i> I: 268/2022 (13%) C: 294/2094 (14%)</p> <p><i>Oxygen saturation, median (IQR):</i> I: 94% (92–96) C: 94% (91–95)</p> <p>Groups comparable at baseline? Yes</p>				<p>RR (95%CI): 0.78 (0.57–1.06) P= 0.11</p> <p><i>Successful cessation of invasive mechanical ventilation, n/N (%)</i> I: 95/268 (35%) C: 98/294 (33%) RR (95%CI): 1.08 (0.81–1.43) P=0.60</p> <p>Safety <u>Adverse events</u> <i>Any major cardiac arrhythmia</i> I: 108/2022 (6%) C: 133/2094 (7%)</p> <p>Authors stated that there were three reports of serious adverse reactions believed to be related to tocilizumab: one each of otitis externa, Staphylococcus aureus bacteraemia, and lung abscess, all of which resolved with standard treatment.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p> <p>Also reported: Use of haemodialysis or Hemofiltration</p>	
Wang, 2021	<p><u>Type of study:</u> open-label multicenter RCT</p>	patients with moderate or severe COVID-19	tocilizumab + standard care	standard care	<p><u>Length of follow-up:</u> Not specified.</p>	<p>Subgroup analyses were performed for patients with moderate or severe</p>	<p><u>Definitions:</u> * The diagnosis of moderate or severe disease was defined according to the</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Setting</u> hospital-based, between February 13 and March 13, 2020</p> <p><u>Country:</u> 6 hospitals in Anhui and Hubei, China</p> <p><u>Source of funding:</u> This work was supported by the Department of Science and Technology of Anhui Province and Health Commission of Anhui Province (No. 202004a07020001) and the China National Center for Biotechnology Development (No. 2020YFC0843800). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • PCR confirmed COVID-19 • age 18-85 years • elevated plasma IL-6 levels • moderate (with bilateral pulmonary lesions) or severe disease* • patient or authorized family member voluntarily participated in the study and signed the informed consent form <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • participation in other drug clinical trials • pregnant or breast-feeding women; • ALT or AST > 5 ULN (neutropenia < 0.5 x 10⁹/L; platelet < 50 x 10⁹/L) • rheumatism- and immunity-related diseases, cancer, and other related diseases • use of antirejection or immunomodulatory drugs • allergy to tocilizumab or any of the excipients • active hepatitis and tuberculosis, associated with specific bacterial and fungal infections • history of organ transplantation • mental disorders <p><u>N total at baseline:</u> Randomized: N = 65</p> <p>Intervention: N = 33 Control: N = 32</p>	(The first dose of tocilizumab was 400 mg, diluted in 100 mL of 0.9% saline, and administered intravenously for more than 1 h. A second dose was given if a patient remained febrile for 24 h after the first dose.)		<p><u>Loss-to-follow-up:</u> None.</p> <p><u>Incomplete outcome data:</u> None.</p>	<p>COVID-19 for primary and secondary outcomes. The primary outcome was the cure rate.</p> <p>Clinical outcomes <u>Mortality</u> Not reported.</p> <p><u>Cure rate**</u> I: 32/34 (94.14%) C: 27/31 (87.10%) rate difference 7,02 (95%CI: -7.19-21.23)</p> <p><u>Recovery rate of hypoxia at day 14</u> I: 22/24 (91.67%) C: 12/20 (60.00%) rate difference 31.67 (95%CI: 7.52-55.82)</p> <p><u>Worsening rate of hypoxia during hospitalization</u> Not reported.</p> <p><u>Duration of hospitalization</u> Median (IQR) I: 26 (17-27) C: 24 (15-28) median difference 2 (95%CI: -4-2)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> Not reported.</p> <p>Safety <u>Serious adverse events</u> I: 0/34 (0%)</p>	<p>Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or updated version) as follows: moderate disease, fever or other respiratory symptoms, bilateral pulmonary lesions confirmed by chest imaging; severe disease was defined if any of the following conditions was met: (1) respiratory rate ≥ 30 breaths/min; (2) SpO₂ $\leq 93\%$ while breathing room air; (3) PaO₂/FiO₂ ≤ 300 mmHg.</p> <p>**The definition for cure followed the standard given by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or updated version): (1) fever attenuated continuously for 7 days, (2) twice negative SARS-CoV-2 nucleic acid detections, (3) CT scan demonstrating chest effusion improved more than 50%.</p> <p>when the patient is discharged from the hospital.</p> <p><u>Remarks:</u> The authors did not enrol enough eligible patients in accordance with the previously designed protocol. The time between the onset of disease and randomization was relatively long in some patients.</p> <p><u>Authors conclusion:</u> This study showed that tocilizumab treatment is not associated with a significantly higher cure rate among COVID-19 patients. However, it can improve oxygenation, symptoms, and reduce disease worsening with an acceptable side effect profile. Tocilizumab had no significant influence on the time needed for negative viral</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Conflicts of interest:</u> The authors declare that they have no conflicts of interest.</p>	<p>One patient in the control group, who worsened severely 3 days after randomization, was crossed over to the tocilizumab group in accordance with the study protocol. However, this patient was erroneously included in the intervention group for the ITT analyses.</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 63.5 y (58-71) C: 63 y (54-69)</p> <p>Sex, n/N (%) male: I: 18/34 (52.94%) C: 15/31 (48.39%)</p> <p>Groups were comparable at baseline.</p>				<p>C: 1/31 (3.23%)</p> <p><u>Non-serious adverse events</u> I: 20/34 (58.82%) C: 4/31 (12.90%)</p> <p>Also reported are specific treatment-related adverse events.</p> <p>Virological outcomes <u>Viral clearance (i.e. time to negative virus load)</u> Median (IQR) I: 17 (12-20) C: 16 (12-21.5) median difference 1.5 (95%CI: -4-5)</p>	load. For COVID-19 patients with bilateral pulmonary lesions and elevated IL-6 levels, tocilizumab is recommended for better disease management.
Soin, 2020 COVINTOC trial	<p><u>Type of study:</u> RCT; open-label, multicentre</p> <p><u>Setting:</u> Public and private hospitals; recruited between May 30, 2020, and Aug 31, 2020.</p> <p><u>Country:</u> India</p> <p><u>Source of funding:</u> Medanta Institute of Education and Research, Roche India, Cipla India, and Action COVID-19 India; The funder of the study</p>	<p><u>Hospitalized COVID-19 patients with moderate to severe illness</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Age ≥ 18 years • admitted to hospital • SARS-CoV-2 infection confirmed by WHO criteria (positive PCR test on any specimen) • moderate to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-1920 (moderate: defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO₂] 90–94%; severe: respiratory rate ≥30 per min or SpO₂ <90% in ambient air, or ARDS or septic shock) 	<p>Tocilizumab</p> <p>Tocilizumab 6 mg/kg plus standard care</p> <p>Tocilizumab was administered as a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. An additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days after administration of the first dose. The dosing regimen was selected on the</p>	Standard care	<p><u>Length of follow up:</u> 28 days</p> <p><u>Loss to follow-up:</u> I: 16/91 (17.6%) (died, n=11; withdrawn consent, n=2; withdrew because of no efficacy, n=2; not willing to visit hospital, n=1)</p> <p>C: 20/88 (22.7%) (died, n=15; withdrew consent, n=3, discharged against medical advice, n=1; chose to receive tocilizumab, n=1)</p>	<p>Clinical outcomes</p> <p>Mortality</p> <p>Day 7 I: 2 (2%) C: 2 (2%) Diff -0.1 (-4.4 to 4.3), p=0.97</p> <p>Day 14 I: 8 (9%) C: 9 (10%) Diff -1.4 (-10.0 to 7.2), p=0.74</p> <p>Day 21 I: 10 (11%) C: 14 (16%) Diff -4.9 (-14.9 to 5.1), p=0.33</p> <p>Day 28 I: 11 (12%) C: 15 (17%) Diff -5.0 (-15.3 to 5.4), p=0.35</p>	<p><u>Authors conclusion:</u> Routine use of tocilizumab in patients admitted to hospital with moderate to severe COVID-19 is not supported. However, post-hoc evidence from this study suggests tocilizumab might still be effective in patients with severe COVID-19 and so should be investigated further in future studies.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	had a role in study design, data collection, data analysis, data interpretation, and writing of the report.	<p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • known severe allergic reaction to tocilizumab or other monoclonal antibodies • active tuberculosis infection • suspected or active bacterial, fungal, or viral infection (except treated hepatitis C or B), or any other infection except COVID-19 • if death was imminent and inevitable within 24 h • imminent and inevitable within 24 h • received any oral anti-rejection or immuno-modulatory drugs in the previous 6 months or treatment with any investigational agent (including antivirals, cell-depleting therapies, biologics, and Janus kinase inhibitors) within five half-lives or 30 days before randomisation, whichever was longer. • diagnosis of immunerelated rheumatic disease or be receiving corticosteroids equivalent to methylprednisolone at a dose of more than 1 mg/kg per day at screening or baseline. • absolute neutrophil count < 500 cells per μL, platelet count < 50000 cells per μL, and alanine aminotransferase or aspartate aminotransferase concentrations > 10 x upper limit of normal within 24 h of screening or baseline <p><u>N total at baseline:</u> N = 180</p>	basis of the cost and supply considerations in India and because a single dose between 4 mg/kg and 8 mg/kg plus an additional dose to a maximum of 800 mg, if required, has been recommended on the basis of initial reports on the use of tocilizumab in the treatment of COVID-19 in China [ref 21].		143 (79%) of 180 patients completed 28 days of follow-up, 75 (82%) in the tocilizumab group and 68 (76%) in the standard care group	<p><u>Duration of hospitalization ICU admission</u> I: 71 (78%) C: 64 (73%) Diff 5.3 (-7.3 to 17.9), p= 0.41</p> <p><u>Duration of ICU stay, days</u> Mean (SD) I: 8.2 (6.2) C: 8.4 (6.5), p= 0.91 Median (IQR) I: 7.0 (3.0 to 10.0) C: 6.0 (3.5 to 11.0)</p> <p><u>Symptom resolution</u> <u>Progression of COVID-19, day 14; defined as progression from moderate to severe or from severe to death up to</u> I: 8 (9%) C: 11 (13%) diff -3.7 (-18.2 to 11.2)*</p> <p><u>At least a one-grade improvement in cytokine release syndrome up to day 28 [American Society for Transplantation and Cellular Therapy cytokine release syndrome grade ref 22]</u> I: 58 (64%) C: 59 (67%) diff -3.3 (-17.9 to 11.3), p= 0.64</p> <p><u>Time to clinical improvement (defined</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Randomized: 90 vs. 90 Analyzed: Intervention: 91 Control: 88</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 56 (47–63) y C: 54 (43–63) y Sex, n/N (%) male: I: 76/91 (84%) C: 76 (86%) Disease severity Moderate I: 41 (45%) C: 47 (53%) Severe I: 50 (55%) C: 41 (47%) Respiratory support Supplemental oxygen I: 81 (89%) C: 80 (91%) Non-invasive bilevel positive airway pressure ventilation I: 28 (31%) C: 20 (23%) Mechanical ventilation I: 5 (5%) C: 4 (5%) Intensive care unit I: 64 (70%) C: 54 (61%)</p> <p>Groups comparable at baseline.</p>				<p>as National Early Warning Score 2 [NEWS2] ≤ 2 maintained for 24 h)</p> <p><u>Organ failure-free days</u> Mean (SD) I: 24·6 (9·2) C: 23·2 (10·6), p= 0·35 Median (IQR) I: 28·0 (28·0 to 28·0) C: 28·0 (28·0 to 28·0)</p> <p>Time to clinical improvement, median time (days) <i>based on NEWS2 score</i> I: 9·0 (95% CI 8·0–21·0) C: 8·0 (95% CI 6·0–10·0) Log rank p=0·43 <i>Based on COVID-19 grade</i> I: 7·0 (95% CI 5·0–8·0) C: 7·0 (95% CI 5·0–9·0) Log rank p=0·93</p> <p><u>Need for respiratory support</u> <u>Ventilator-free days</u> Mean (SD) I: 24·3 (9·2) C: 23·2 (10·6), p= 0·45 Median (IQR) I: 28·0 (28·0 to 28·0) C: 28·0 (28·0 to 28·0)</p> <p><u>Duration of supplemental oxygen-free days</u> Mean (SD) I: 17·1 (9·4) C: 18·3 (9·9), p= 0·41 Median (IQR) I: 20·0 (12·0 to 24·0)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 22·0 (16·0 to 25·0)</p> <p><u>Incidence of mechanical ventilation up to day 28</u> I: 14 (15%) C: 13 (15%) Diff 0·6 (-9·9 to 11·1), p= 0·91</p> <p>Safety <u>Adverse events, 28 days</u> Adverse events, patients with at least one event I: 33 (36%) patients, 54 events C: 22 (25%) patients, 55 events Infections I: 6 (7%) C: 5 (6%) Serious adverse events* I: 18 (20%) patients, 23 events C: 15 (17%) patients, 24 events Deaths I: 13 (14%) C: 15 (17%) Grade 3 or worse adverse events I: 2 (2%) C: 5 (6%)</p> <p>Virological outcomes <u>Viral clearance</u> time to negative result on RT-PCR</p> <p><i>Also reported: Serum concentrations of IL-6, ferritin, and C-reactive protein (CRP), requirement for renal</i></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<i>replacement therapy</i>	
Rosas, 2021a	<p>Type of study: A phase 3, international, randomized, double-blind placebo-controlled trial</p> <p>Setting: 62 hospitals</p> <p>Country: Nine countries in Europe and North America (Canada, Denmark, France, Germany, Italy, the Netherlands, the United Kingdom, and the United States).</p> <p>Source of funding: Supported F. Hoffmann–La Roche and by a grant (HHSO1002018000 36C) from the Biomedical Advanced Research and Development Authority of the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services. Drs. Cooper and</p>	<p><u>hospitalized patients with severe COVID-19 pneumonia.</u></p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Patients with confirmed positive polymerase-chain-reaction (PCR) assay of any body fluid and evidenced by bilateral chest infiltrates on chest radiography or computed tomography; Patients with blood oxygen saturation of 93% or less or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen of less than 300 mm Hg. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Patients were the treating physician determined that death was imminent and inevitable within 24 hours; Patients with tuberculosis or a bacterial, fungal, or viral infection other than SARS-CoV-2. <p>N total at baseline: N = 438 Intervention: 294 Control: 144</p> <p>Important characteristics: Age, mean (SD): I: 60.9 y (14.6) C: 60.6 y (13.7)</p> <p>Distribution (age) n/N (%): 18-64: I: 163/297 (55.4%) C: 81/144 (56.2%)</p>	Single intravenous infusion of <u>tocilizumab at a dose of 8 mg per kilogram of bodyweight, with a maximum dose of 800 mg plus standard care.</u>	Placebo plus standard care	<p>Length of follow up: The primary analysis was performed at day 28, and the final trial visit occurred at day 60.</p> <p>Loss to follow-up: Intervention group: - N= 70 (24%) discontinued trial on or before day 28; - N=57 (19%) died; - N=7 (2%) were lost to follow-up; - N=6 (2%) withdrew</p> <p>The 28 day follow-up evaluation completed in 224/294 (76.2%) patients.</p> <p>Control group: - N=36 discontinued trial on or before day 28; - N=27 (19%) died; - N=5 (3%) were lost to follow-up; - N=2 (1%) withdrew; - N=2 (1%) were withdrawn by physician.</p> <p>The 28 day follow-up evaluation completed in 108/144 (75%) patients.</p>	<p>Clinical outcomes <u>Mortality at day 28, n/N (%)</u>: I: 58/294 (19.7%) C: 28/144 (19.4%) Difference: 0.3 (95% CI= - 7.6 to 8.2) P=0.94</p> <p><u>Clinical status on 7- category ordinal scale at day 28, median value (95% CI)</u> I: 1.0 (95% CI= 1.0 to 1.0) C: 2.0 (95% CI= 1.0 to 4.0) Difference: -1.0 (95% CI= - 2.5 to 0.00) P=0.31</p> <p><u>Clinical status on 7- category ordinal scale at day 14, median value (95% CI)</u> I: 3.0 (95% CI= 2.0 to 4.0) C: 4.0 (95% CI= 3.0 to 5.0) Difference: -1.0 (95% CI= - 2.0 to 0.5)</p> <p><u>Days until hospital discharge or readiness for discharge, median number (95% CI)</u> I: 20.0 (95% CI= 17.0 to 27.0) C: 28.0 (95% CI= 20.0 to 'not evaluable')</p> <p><u>Symptom resolution – days until improvement by ≥2 categories on 7-category ordinal scale in clinical</u></p>	<p>Definitions: - National Early Warning Score 2: a standardized assessment for identifying acutely ill patients on the basis of respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness, and temperature. Values on this instrument range from 0 to 20, with higher scores indicating greater clinical risk.</p> <p>- Standard of care: according to local practice (anti-viral treatment, low-dose glucocorticoids, convalescent plasma, and supportive care).</p> <p>- Opportunistic infections were reported in one patient with candida sepsis in the intervention group and in one patient with respiratory moniliasis in the control group.</p> <p>Remarks: -</p> <p>Authors conclusion: Results of this trial must be interpreted in the context of therapies for severe Covid-19 pneumonia. Among the treatments for hospitalized patients with Covid-19 that have been investigated in randomized, controlled trials, dexamethasone was found to reduce mortality only among patients who were receiving mechanical ventilation or supplemental oxygen at randomization.28 Remdesivir shortened the time until recovery but did not have a significant effect on 14-day mortality.27 Clinical trials are under way to investigate many potential treatments, including other antiviral</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Youngstein were supported in part by the Biomedical Research Centre of the United Kingdom National Institute for Health Research. Dr. Malhotra is supported by the National Institutes of Health.	<p>65-84: I: 117/294 (39.8%) C: 60/144 (41.7%)</p> <p>>84: I: 14/294 (4.8%) C: 3/144 (2.1%)</p> <p>Sex, n/N (%) male: I: 205/294 (69.7%) C: 101/144 (70.1%)</p> <p>Illness severity on National Early Warming Score 2, mean (SD): I: 7.1 (3.0) C: 7.0 (3.0)</p> <p>Ordinal scale for clinical status, n/N (%):</p> <p><u>2</u> I: 9/294 (3.1%) C: 6/144 (4.2%)</p> <p><u>3</u> I: 78/297 (26.5%) C: 44/144 (30.6%)</p> <p><u>4</u> I: 94/294 (32.0%) C: 39/144 (27.1%)</p> <p><u>5</u>: I: 45/294 (15.3%) C: 15/144 (10.4%)</p> <p><u>6</u> I: 68/294 (23.1%) C: 40/144 (27.8%)</p> <p>Groups comparable at baseline?</p>				<p><u>status, median number of days (95% CI)</u> I: 14.0 (95% CI= 12.0 to 17.0) C: 18.0 (95% CI= 15.0 to 28.0) HR= 1.26 (95% CI= 0.97 to 1.64)</p> <p><u>Day in ICU, median number of days (95% CI)</u> I: 9.8 (95% CI= 7.0 to 15.7) C: 15.5 (95% CI= 8.7 to 25.5) Difference: -5.8 (95% CI= -15.0 to 2.9)</p> <p><u>Incidence of ICU stay among patients not in ICU at baseline, n/N (%)</u> I: 27/127 (21.3%) C: 23/64 (35.9%) Difference: -14.8 (95% CI= -28.6 to -1.0)</p> <p><u>Ventilator-free days at day 28, median number (95% CI)</u> I: 22.0 (95% CI= 18.0 to 28.0) C: 16.5 (95% CI= 11.0 to 26.0) Difference: 5.5 (95% CI= -2.8 to 13.0)</p> <p>Subgroup analysis</p> <p><u>Incidence of mechanical ventilation among patients not receiving mechanical ventilation at randomization, n/N (%)</u> I: 51/183 (27.9%)</p>	and antiinflammatory drugs, other targeted immunomodulators (e.g., sarilumab, anakinra, baricitinib, and canakinumab), anticoagulants, and antifibrotics (tyrosine kinase inhibitors). ²⁹ However, the need for effective treatments for patients with severe Covid-19 pneumonia continues to be a major challenge at this point in the pandemic

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 33/90 (36.7%) Difference: -8.9% (95% CI= -20.7 to 3.0)</p> <p><u>Clinical failure among patients not receiving mechanical ventilation at randomization, n/N (%)</u> I: 53/183 (29.0%) C: 38/90 (42.2%) HR= 0.61 (95% CI= 0.40 to 0.94)</p> <p><u>Clinical status on the ordinal scale at day 28 among patients who were receiving mechanical ventilation at randomization, median value (95% CI)</u> I: 5.0 (95% CI= 3.0 to 5.0) C: 5.0 (95% CI= 4.0 to 6.0)</p> <p><u>Clinical status on the ordinal scale at day 28 among patients who were not receiving mechanical ventilation at randomization, median value (95% CI)</u> I: 1.0 (95% CI= 1.0 to 1.0) C: 1.0 (95% CI= 1.0 to 1.0)</p> <p>Safety population I: N = 295 C: N = 143</p> <p><u>Any adverse event</u> <i>Patients with ≥1 event, N (%)</i> I: 228/295 (77.3%) C: 116 (81.1)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Total number of events, N</i> I: N = 778 C: N = 360</p> <p><u>Any serious adverse event</u> <i>Patients with ≥1 event, N (%)</i> I: 103/295 (34.9%) C: 55/143 (38.5%)</p> <p><i>Total number of events, N</i> I: N = 160 C: N = 101</p> <p><u>Death N (%)</u> I: 58/295 (19.7%) C: 28/143 (19.6)</p> <p><u>Patients with adverse events of special interest, n/N (%)</u> <i>Infection</i> I: 113/295 (38.3%) C: 58/143 (40.6%)</p> <p><i>Serious infection</i> I: 62/295 (21.0%) C: 37/143 (25.9%)</p> <p><i>Opportunistic infection</i> I: 1/295 (0.3%) C: 1/143 (0.7%)</p> <p>Virological outcomes Not reported</p>	
The REMAP-CAP Investigators, 2020	See the evidence table of the REMAP-CAP Investigators (2020) by sarilumab.						
Veiga, 2021	<u>Type of study:</u>	<u>Inclusion criteria:</u> • Hospital in-patients (aged 18 years or older) with confirmed	Tocilizumab (a single intravenous infusion at a dose of 8 mg/kg	Standard care The	<u>Length of follow up:</u> 15 day follow-up	<u>Clinical outcomes</u> <u>Mortality at day 15:</u> I: 11 / 65 (17)	<u>Definitions:</u>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>RCT (open label trial)</p> <p><u>Setting:</u> Nine hospitals in Brazil, 8 May to 17 July 2020. Follow-up for the last patient was completed on August 11, 2020.</p> <p><u>Country:</u> Brazil</p> <p><u>Source of funding:</u> Trial was funded by the hospitals and research institutes participating in the Coalition covid-19 Brazil. Exploratory laboratory analysis was conducted and funded by Fleury Laboratory in São Paulo, Brazil. Instituto Votorantim provided a donation for tocilizumab. It has no role in the design of the trial, the conduct, the analysis, or the decision to submit the manuscript for publication.</p>	<p>severe or critical covid-19 and symptoms for more than three days;</p> <ul style="list-style-type: none"> receiving supplemental oxygen or mechanical ventilation; and abnormal levels of at least two serum biomarkers (D dimer, C reactive protein, ferritin or lactate dehydrogenase). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Active uncontrolled infection; raised aspartate aminotransferase or alanine aminotransferase levels greater than five times the upper limit of normal; renal disease with an estimated glomerular filtration of <30 mL/min/1.72 m². <p><u>N total at baseline:</u> N = 129 patients Intervention: 65 patients Control: 64 patients (two patients received tocilizumab at discretion of the doctor)</p> <p><u>Important characteristics:</u> <u>Age, mean (SD):</u> I: 57.4 years (15.7) C: 57.3 years (13.5)</p> <p><u>Sex, n/N (%) male:</u> I: 44/65 (68%) C: 44/64 (69%)</p> <p><u>Disease severity, n/N (%):</u> <i>Based on a seven level ordinal clinical status scale (see comments)</i></p>	(maximum 800 mg) plus standard care. The concomitant use of hydroxychloroquine, azithromycin, corticosteroids, and antibiotics was allowed according to standard care per local institutional guidelines for patients with covid-19. Remdesivir was not available in Brazil.	concomitant use of hydroxychloroquine, azithromycin, corticosteroids, and antibiotics was allowed according to standard care per local institutional guidelines for patients with covid-19. Remdesivir was not available in Brazil.	<u>Loss to follow-up:</u> "The 15 day follow-up was completed for all patients." However, it is unclear if the 28/29 days follow-up also was completed for all patients.	<p>C: 2 / 64 (3)</p> <p><u>Mortality up to 28 days (n/N (%)):</u> I: 14 / 65 (21) C: 6 / 64 (9) Effect size (OR, 95% CI): 2.70 (0.97 to 8.35) P-value = 0.07</p> <p><u>Duration of hospitalization (days, mean (SD)):</u> I: 11.3 (8.0) C: 14.7 (8.2) Effect size (RR, 95% CI): 0.70 (0.55 to 0.87) P-value = 0.001</p> <p><u>Clinical status (6 level ordinal scale) at day 8:</u> 1: I: 23/65 (35) C: 16/64 (25)</p> <p>2: I: 7/65 (11) C: 7/64 (11)</p> <p>3: I: 10/65 (5) C: 12/64 (19)</p> <p>4: I: 1/65 (1) C: 4/64 (6)</p> <p>5: I: 19/65 (29) C: 24/64 (37)</p> <p>6: I: 5/65 (8) C: 1/64 (2)</p>	<p><i>Seven level ordinal clinical status scale:</i> 1 – not admitted to hospital and with no limitation in activities 2 – not admitted to hospital but with limitation in activities 3 – admitted to hospital and not receiving supplemental oxygen 4 – admitted to hospital and receiving supplemental oxygen 5 – admitted to hospital and receiving non-invasive positive pressure ventilation or high flow oxygen through a nasal cannula 6 – admitted to hospital and receiving mechanical ventilation 7 – death</p> <p><i>Six level ordinal clinical status scale:</i> 1: admitted to hospital 2: admitted to hospital, not receiving supplemental oxygen 3: admitted to hospital, receiving supplemental oxygen 4: admitted to hospital, receiving non-invasive ventilation or high flow oxygen through nasal cannula 5: admitted to hospital, receiving mechanical ventilation 6: death</p> <p><i>Clinical status (7 level ordinal scale) at day 29, in-hospital mortality, SOFA score at day 8 and day 15,ventilator-free days within 29 days, time to supplemental oxygen independence within 29 days, duration of hospital stay, secondary infections, thromboembolic events and non-severe adverse events were also reported in the article. In the appendix also additional characteristics of the population at baseline, use of other medications in the first 15 days,</i></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 4: 39/65 (60%) 5: 15/65 (23%) 6: 11/65 (17%)</p> <p>C: 4: 28 (44%) 5: 26 (41%) 6: 10 (16%)</p> <p>Groups comparable at baseline? Not for respiratory support, baseline clinical status and use of azithromycin.</p> <p>Post hoc analysis adjusted for baseline levels of respiratory support were consistent with the main analysis.</p> <p>Post hoc sensitivity analysis for the primary outcome adjusted for baseline clinical status on the seven level ordinal scale was also not indicative of treatment benefit.</p> <p>Azithromycin has proven to be ineffective for patients admitted to hospital with covid-19.</p>				<p>Effect measure (OR, 95% CI; 1-4 vs 5-6): 0.91 (0.44 to 1.89) p-value = 0.79</p> <p><u>Clinical status (7 level ordinal scale) at day 15:</u></p> <p><u>1:</u> I: 32/65 (49) C: 26/64 (41)</p> <p><u>2:</u> I: 3/65 (5) C: 5/64 (8)</p> <p><u>3:</u> I: 6/65 (9) C: 6/64 (9)</p> <p><u>4:</u> I: 6/65 (9) C: 10/64 (16)</p> <p><u>5:</u> I: 0/65 (0) C: 4/64 (6)</p> <p><u>6:</u> I: 7/65 (11) C: 11/64 (17)</p> <p><u>7:</u> I: 11/65 (17) C: 2/64 (3)</p> <p>Effect measure (OR, 95% CI; 1-5 vs 6-7): 1.54 (0.66 to 3.66) p-value = 0.32</p> <p><u>Any adverse events</u> I: 29 / 67 (43)</p>	<p>cumulative proportions of 7-level ordinal scale at day 15 to the primary outcome, main analysis and sensitivity analysis for the primary outcome, subgroup analysis for the primary outcome, adjudicated causes of in-hospital deaths, adjudicated causes of death at day 28 compared with treatment group, age and clinical status on 7-level ordinal scale, biomarker measurements analyses, effect of tocilizumab on the primary outcome, length of hospital stay and 15-day death according to duration of symptoms at randomization, relative distribution of patient status at day 15 (stratified by group), and serum-inflammatory markers and cytokines at baseline, D5 and D8 in the tocilizumab and control group published.</p> <p><u>Remarks:</u></p> <ul style="list-style-type: none"> - Groups were not comparable at baseline for respiratory support, baseline clinical status and use of Azithromycin. - Open label trial - "The 15 day follow-up was completed for all patients." However, it is unclear if the 28/29 days follow-up also was completed for all patients. <p><u>Authors conclusion:</u> In patients with severe or critical covid-19 tocilizumab plus standard care was not superior to standard care alone in improving clinical outcomes at 15 days, and might increase mortality.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>C: 21 / 62 (34) P-value = 0.26</p> <p><u>Reported severe adverse event, according to classification:</u> Any severe adverse event I: 11/ 67 (16) C: 7 / 62 (11) P-value: 0.45</p> <p>Raised ALT, AST, or bilirubin level I: 7/67 (10) C: 3/62 (5) P-value: 0.33</p> <p>Anaemia I:3/67 (4) C: 3/62 (5) P-value: 1.00</p> <p>Pneumothorax: I:0/67 (0) C: 1/62 (2) P-value: 0.48</p> <p>Neutropenia I:1/67 (1) C: 0/62 (0) P-value: 1.00</p> <p>Bleeding I: 1/67 (1) C: 0/62 (0) P-value: 1.00</p> <p>Intracranial bleeding I: 0/67 (0) C: 1/62 (2) P-value: 1.00</p> <p>Sudden cardiorespiratory</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						collapse I: 4/67 (6) C: 1/62 (2) P-value: 0.37	
Salama, 2020 EMPACTA trial	<p><u>Type of study:</u> RCT; double-blind, placebo-controlled, phase 3 trial</p> <p><u>Setting:</u> EMPACTA trial; multi-center</p> <p><u>Country:</u> International; United States 45 sites, Mexico 2 sites, Kenya 2 sites, South Africa 3 sites, Peru 5 sites, and Brazil 6 sites</p> <p><u>Source of funding:</u> Funded by Genentech; EMPACTA ClinicalTrials.gov number, NCT04372186. "The sponsor designed the trial, conducted it according to the protocol, collected the data, and performed analyses; a contract research organization paid by the sponsor managed and</p>	<p>Hospitalized patients with COVID-19 pneumonia</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Age ≥ 18 years Hospitalized with Covid-19 pneumonia COVID-19 confirmed by a positive polymerase-chain-reaction test and radiographic imaging Patients had a blood oxygen saturation < 94% while breathing ambient air <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> receiving continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation progression of illness to death was imminent and inevitable within 24 hours, as determined by treating physician suspected active tuberculosis or (other than SARS-CoV-2 infection or well controlled 	<p>Tocilizumab + standard care</p> <p>Tocilizumab: one or two doses of intravenous tocilizumab (8 mg per kilogram of body weight, to a maximum of 800 mg per dose)</p>	<p>Standard care + placebo</p> <p>Standard care: according to local practice, which could include antiviral treatment, the limited use of systemic glucocorticoids (recommended dose, ≤1 mg per kilogram of body weight of methylprednisolone or equivalent), and supportive care.</p> <p>Placebo: one or two doses of placebo</p>	<p><u>Length of follow up:</u> 60 days; "Efficacy was evaluated by day 28, and patients were followed for a total of 60 days. Patients who were discharged before day 28 were considered to have completed the trial and were followed weekly up to day 28, with a safety follow-up visit conducted by day 60."</p> <p><u>Loss to follow-up:</u> I: 10/259 (3.9%) Reasons: withdrew, n = 8; withdrawn by physician, n = 1; site unable to confirm administration of study drug, n = 1. C: 1/129 (0.8%) Reasons: withdraw, n = 1.</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality, day 28:</u> I: 26/ (10.4 [7.2 to 14.9]) C: 11 (8.6 [4.9 to 14.7]) HR 1.04 (95% CI 0.51 to 2.12) Weighted difference, percentage points: 2.0 (95% CI -5.2 to 7.8)</p> <p><u>Mechanical ventilation (invasive mechanical ventilation or ECMO) or death by day 28:</u> I: 12.0% (95% CI 8.5 to 16.9) C: 19.3% (95% CI 13.3 to 27.4) HR 0.56 (0.33 to 0.97) <u>Sub group - age ≤60:</u> I: 9/151 events C: 7/76 events HR 0.63 (95% CI 0.23 – 1.71) <u>Subgroup - age >60:</u> I: 20/98 events C: 17/52 events HR 0.53 (95% CI 0.28 to 1.03) <u>Time to hospital discharge or readiness for discharge, day 28; score of 1 on ordinal scale</u> I: 6.0 (6.0 to 7.0) days C: 7.5 (7.0 to 9.0) days HR 1.16 (0.91 to 1.48)</p>	<p><u>Definitions:</u> <u>Clinical status - 7-category ordinal scale</u> 1 - discharged (or ready for discharge as evidenced by normal body temp. and respiratory rate + stable oxygen saturation while breathing ambient air or ≤2 liters of suppl. oxygen); 2, hospitalized in non-intensive care unit (ICU) hospital ward (or ready for a hospital ward) and not receiving suppl. oxygen; 3, hospitalized in non-ICU hospital ward (or ready for hospital ward) and receiving suppl. oxygen; 4, hospitalized in ICU or non-ICU hospital ward and receiving noninvasive ventilation or high-flow oxygen; 5, hospitalized in ICU and receiving intubation and mechanical ventilation; 6, hospitalized in ICU and receiving ECMO or mechanical ventilation and additional organ support; 7, died.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it</p>

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	<i>monitored the trial under the direction and supervision of the sponsor."</i>	<p>HIV infection)</p> <ul style="list-style-type: none"> coexisting condition only in case when investigator determined that the condition would preclude safe participation in the trial. <p><u>N total at baseline:</u> N = 389</p> <p><u>Modified intention-to-treat:</u> Intervention: 249 (259 assigned to this arm; 10 dropped out) Control: 128 (129 assigned to this arm, 1 dropped out)</p> <p><u>Important characteristics:</u> Age, mean±SD: I: 56.0±14.3 C: 55.6±14.9 Sex, n/N (%) male: I: 150/249 (60.2%) C: 73/128 (57.0%) BMI, mean±SD: I: 32.0±7.9 C: 33.1±7.2 Days from first Covid-19 symptom at baseline, median (range) I: 8.0 (0.0-31.0; n=248) C: 8.0 (0.0-36.0, n=127) Disease severity, mean (SD): <i>Defined by ordinal scale; see right column for definitions</i> I: 2: 24/249 (9.6%) 3: 161/249 (64.7%) 4: 64/249 (25.7%) C: 2: 11/128 (8.6%) 3: 81/128 (63.3%) 4: 36/128 (28.1%)</p>				<p><u>Time to clinical improvement, day 28; at least a two-category improvement in clinical status relative to baseline score (for category 2 at baseline, clinical status of category 1 was considered to have met threshold), median:</u> I: 6.0 (6.0 to 7.0) days C: 7.0 (6.0 to 9.0) days HR 1.15 (95% CI 0.90 to 1.48)</p> <p><u>Time to clinical failure, day 28; time to death, mechanical ventilation, admission to ICU, or, in patients who were already in ICU at enrollment, worsening by two categories from baseline on the seven-category ordinal scale), or withdrawal [whichever occurred first]; median:</u> HR 0.55 (95% CI 0.33 to 0.93)</p> <p>Safety <i>Incidence and severity of adverse events [according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0]</i> <u>Total adverse events</u> I: 357 C: 187 <u>Patients with ≥1 adverse event, no. (%)</u></p>	did not improve survival. No new safety signals were identified.

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		<p>ICU admission at baseline, no. (%)</p> <p>I: 36 (14.5%) C: 22 (17.2%)</p> <p>Groups comparable at baseline.</p> <p>Other drugs - within 7 days prior to first dose study drug or during study</p> <p>Systemic corticosteroid</p> <p>I: 200/249 (80.3%) C: 112/128 (87.5%)</p> <p>Antiviral</p> <p>I: 196/249 (78.7%) C: 101/128 (78.9%)</p> <p>Dexamethasone</p> <p>I: 138/249 (55.4%) C: 86/128 (67.2%)</p> <p>Remdesivir</p> <p>I: 131/249 (52.6%) C: 75/128 (58.6%)</p>				<p>I: 127/250 (50.8%) C: 67/127 (52.8%)</p> <p>Serious event</p> <p>I: 38/250 (15.2%) C: 25/127 (19.7%)</p> <p><u>of which events related to tocilizumab or placebo, as determined by the investigator</u></p> <p>I: 3/250 (1.2%) C: 0/127 (0.0%)</p>	
Stone, 2020	<p><u>Type of study:</u></p> <p><u>Setting:</u> Hospital</p> <p><u>Country:</u> Boston, USA</p> <p><u>Source of funding:</u> Not mentioned</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> 19-85 years old; Confirmed SARS-CoV-2 infection by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay; At least two of the following signs: fever (body temp >38 degrees Celsius) within 72 hours before enrolment, pulmonary infiltrates, or a need for supplemental oxygen in order to maintain an oxygen saturation higher than 92%; 	Standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight administered intravenously, not to exceed 800 mg)	Placebo	28 days	<p><u>TIME-TO-EVENT OUTCOMES IN THE MODIFIED INTENTION-TO-TREAT POPULATION</u></p> <p><u>Mechanical ventilation or death</u></p> <p><u>N patients with event within 28 days</u></p> <p>I: N = 17 C: N = 10</p> <p><u>Percentage of patients with event (95 CI) at day 14</u></p> <p>I: 9.9 (95% CI= 6.2 to 15.7) C: 10.0 (95% CI= 5.1 to 18.9)</p>	<p><u>Remarks:</u></p> <p>-</p> <p><u>Authors conclusion:</u></p> <p>In this randomized, double-blind, placebocontrolled trial, we did not find any efficacy of interleukin-6 receptor blockade for the treatment of hospitalized patients with Covid-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • A C-reactive protein level higher than 50 mg liter; • A ferritin level higher than 500 ng per millilitre; • A d-dimer level higher than 1000 ng per millilitre; • A lactate dehydrogenase level higher than 250 U per liter. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Receiving supplemental oxygen at a rate that exceeded 10 liters per minute; • A recent history of treatment with biologic agents or smallmolecule immunosuppressive therapy; • Receiving other immunosuppressive therapy that the investigator believed placed them at higher risk for an infection; • Diverticulitis. <p><u>N total at baseline:</u> N = Intervention: Control:</p> <p><u>Important characteristics:</u> Age, mean (SD): I: C:</p>				<p><u>Percentage of patients with event (95 CI) at day 28</u> I: 10.6 (95% CI= 6.7 to 16.6) C: 12.5 (95% CI= 6.9 to 22.0)</p> <p><u>Hazard ratio (95% CI)</u> HR= 0.83 (95% CI= 0.38 to 1.81)</p> <p><u>Log rank value</u> 0.64</p> <p><u>Clinical worsening on ordinal scale</u></p> <p><u>N patients with event within 28 days</u> I: N = 31 C: N = 14</p> <p><u>Percentage of patients with event (95 CI) at day 14</u> I: 18.0 (95% CI= 12.9 to 24.9) C: 14.9 (95% CI= 8.7 to 24.7)</p> <p><u>Percentage of patients with event (95 CI) at day 28</u> I: 19.3 (95% CI= 14.0 to 26.2) C: 17.4 (95% CI= 10.7 to 27.7)</p> <p><u>Hazard ratio (95% CI)</u> HR= 1.11 (95% CI= 0.59 to 2.10)</p>	

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		<p>P=0 Sex, n/N (%) male: I: C:</p> <p>Groups comparable at baseline?</p>				<p><u>Log rank value</u> 0.73</p> <p><u>Mechanical ventilation</u></p> <p><u>N patients with event within 28 days</u> I: N = 11 C: N = 8</p> <p><u>Percentage of patients with event (95 CI) at day 14</u> I: 6.8 (95% CI= 3.6 to 11.4) C: 10.0 (95% CI= 4.6 to 17.7)</p> <p><u>Percentage of patients with event (95 CI) at day 28</u> I: 6.8 (95% CI= 3.6 to 11.4) C: 10.0 (95% CI= 4.6 to 17.7)</p> <p><u>Hazard ratio (95% CI)</u> HR= 0.65 (95% CI= 0.26 to 1.62)</p> <p><u>Death</u></p> <p><u>N patients with event within 28 days</u> I: N = 9 C: N = 3</p> <p><u>Percentage of patients with event (95 CI) at day 14</u> I: 4.4 (95% CI= 2.1 to 8.9) C: 1.3 (95% CI= 0.2 to 8.7)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><u>Percentage of patients with event (95 CI) at day 28</u> I: 5.6 (95% CI= 3.0 to 10.5) C: 3.8 (95% CI= 1.2 to 11.3)</p> <p><u>Hazard ratio (95% CI)</u> HR= 1.52 (95% CI= 0.41 to 5.61)</p> <p><u>Discontinuation of supplemental oxygen among patients receiving it at baseline</u></p> <p><u>N patients with event within 28 days</u> I: N = 114 C: N = 56</p> <p><u>Percentage of patients with event (95 CI) at day 14</u> I: 75.4 (95% CI= 67.9 to 82.2) C: 78.8 (95% CI= 68.3 to 87.7)</p> <p><u>Percentage of patients with event (95 CI) at day 28</u> I: 82.6 (95% CI= 75.9 to 88.4) C: 84.9 (95% CI= 75.2 to 92.2)</p> <p><u>Median N of days to event (95% CI)</u> I: 5.0 (95% CI= 3.8 to 7.6) C: 4.9 (95% CI= 3.8 to 7.8)</p> <p><u>Hazard ratio (95% CI)</u></p>	

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						<p>HR= 0.94 (95% CI= 0.67 to 1.30)</p> <p><u>Log rank value</u> 0.69</p> <p><u>Clinical improvement on ordinal scale</u></p> <p><u>N patients with event within 28 days</u> I: N = 147 C: N = 72</p> <p><u>Percentage of patients with event (95 CI) at day 14</u> I: 86.3 (95% CI= 80.6 to 91.1) C: 81.5 (95% CI= 72.4 to 89.0)</p> <p><u>Percentage of patients with event (95 CI) at day 28</u> I: 91.3 (95% CI= 86.3 to 95.1) C: 88.9 (95% CI= 81.0 to 94.5)</p> <p><u>Median N of days to event (95% CI)</u> I: 6.0 (95% CI= 5.0 to 6.0) C: 5.0 (95% CI= 4.0 to 7.0)</p> <p><u>Hazard ratio (95% CI)</u> HR= 1.06 (95% CI= 0.80 to 1.41)</p> <p><u>Initial discharge</u></p> <p><u>N patients with event within 28 days</u></p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>I: N = 147 C: N = 72</p> <p><u>Percentage of patients with event (95 CI) at day 14</u> I: 86.3 (95% CI= 80.6 to 91.1) C: 81.5 (95% CI= 72.4 to 89.0)</p> <p><u>Percentage of patients with event (95 CI) at day 28</u> I: 91.3 (95% CI= 86.3 to 95.0) C: 88.9 (95% CI= 81.0 to 94.5)</p> <p><u>Median N of days to event (95% CI)</u> I: 6.0 (95% CI= 4.0 to 7.0) C: 6.0 (95% CI= 5.0 to 6.0)</p> <p><u>Hazard ratio (95% CI)</u> HR= 1.08 (95% CI= 0.81 to 1.43)</p> <p><u>DURATION OUTCOMES AND ADMISSION TO THE ICU OR DEATH IN THE MODIFIED INTENTION-TO-TREAT POPULATION</u></p> <p><u>Median duration of receipt of supplemental oxygen (IQR) in days</u> I: 4.0 (1.8 to 11.6) C: 3.9 (1.1 to 9.2)</p> <p><u>Median duration of mechanical ventilation (IQR) in days</u></p>	

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						I: 15.0 (12.6 to NR) C: 27.9 (16.3 to NR) <u>Admission to ICU or death (%)</u> I: 15.9% C: 15.8% Relative risk: 0.97 (0.50 to 1.88)	
Salvarani, 2020	<p>Type of study: RCT (prospective, open-label, randomized clinical trial)</p> <p>Setting: 24 hospitals; March 31 - June 11, 2020</p> <p>Country: Italy</p> <p>Source of funding: "The work at the IRCCS Sacro Cuore Don Calabria Hospital was partly funded by the Italian Ministry of Health "Fondi Ricerca Corrente – Linea 1, progetto 4". Roche provided the drug and its distribution to the centers."</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age ≥18 years • Instrumental diagnosis of COVID-19 pneumonia, RT-PCR confirmed respiratory tract specimen. • Acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (Pao2/Fio2) ratio between 200 and 300 mm/Hg • inflammatory phenotype defined by a temperature greater than 38 °C during the last 2 days, and/or serum C-reactive protein (CRP) levels of 10 mg/dL or greater and/or CRP level increased to at least twice the admission measurement. • allowed to receive oxygen therapy with Venturi mask or high-flow nasal cannula with recorded and preset Fio2 <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • ICU admission, • known hypersensitivity to tocilizumab, • any condition preventing future admission to ICU (e.g. advanced age with multiple comorbidities, will to avoid future intubation) 	<p>Tocilizumab + supportive care</p> <p>Tocilizumab intravenously within 8 hours from randomization at a dose of 8 mg/kg up to a maximum of 800 mg, followed by a second dose after 12 hours.</p> <ul style="list-style-type: none"> • 58/60 received treatment without prohibited drugs • 1/60 received tocilizumab + steroids • 1/60 did not receive tocilizumab due to SAE • 5/60 patients received steroids after clinical worsening 	<p>Supportive care</p> <p>Supportive care: following the treatment protocols of each center:</p> <ul style="list-style-type: none"> • Not allowed: IL-1 blockers, Jak inhibitors, tumor necrosis factor inhibitors. • Steroids were allowed if already taken before hospitalization. • Clinical worsening: patients in both arms could receive any therapy, including steroids, <u>and, for patients randomized in the control</u> 	<p>Length of follow-up: 30 days (primary endpoint 14 days)</p> <p>Loss to follow-up: 3/66 (4.5%) patients in the control group withdrew consent and were excluded from the analysis. Other patients were all included in the efficacy analysis.</p>	<p>Clinical worsening at 14 days: <i>Definition: see information at the right column</i> I: 17/60 (28.3%) C: 17/63 (27.0%) Rate ratio 1.05 (0.59 – 1.86) p=.87</p> <p>Admission to ICU with mechanical ventilation <i>14 days</i> I: 6/60 (10%) C: 5/63 (7.9%) Rate ratio 1.26 (0.41 – 3.91) <i>30 days</i> I: 6/60 (10%) C: 5/63 (7.9%) Rate ratio 1.26 (0.41 – 3.91)</p> <p>Death from any cause <i>14 days</i> I: 1/60 (1.7%) C: 1/63 (1.6%) Rate ratio 1.05 (0.07 – 16.4) <i>30 days</i> I: 2/60 (3.3%) C: 1/63 (1.6%) Rate ratio 2.10 (0.20 – 22.6)</p>	<p>Information: The primary outcome 'clinical worsening' was defined as occurrence of 1 of the 3 following events:</p> <ul style="list-style-type: none"> • admission to ICU with mechanical ventilation • death from any cause • Pao2/Fio2 ratio less than 150 mm Hg in 1 of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination <p>Remarks:</p> <ul style="list-style-type: none"> • This was an open label trial. • Analyses were performed according to an intention-to-treat protocol. • See columns of intervention en control treatment for information on the actual treatment that patients received <p>Authors conclusion: The administration of tocilizumab in patients with COVID-19 pneumonia and a Pao2/ Fio2 ratio between 200 and 300 mm Hg did not reduce the risk of clinical worsening. Further blinded, placebo-controlled randomized clinical trials are needed to confirm the results and to explore possible applications of</p>

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		<p>Patients at enrollment were allowed to receive oxygen therapy with Venturi mask or high-flow nasal cannula with recorded and preset Fio2, but not invasive or noninvasive mechanical ventilation. After randomization, patients were allowed to receive supplemental oxygen therapy, including noninvasive ventilation, according to clinical needs.</p> <p><u>N total at baseline:</u> N = 126 Intervention: 60 Control: 66</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 61.5y (51.5-73.5) C: 60.0y (54.0-69.0) Sex, n/N (%) male: I: 40/60 (66.7%) C: 37/66 (56.1%)</p> <p>Control group had lower CRP, IL-6, ferritin, and D-dimer levels and were more frequently treated with antivirals compared to intervention group.</p>		<p><u>arm, tocilizumab.</u></p> <ul style="list-style-type: none"> • 60/66 received standard care and no prohibited drugs • 6/60 received additional drug treatment (tocilizumab IV + steroids (n=2), tocilizumab subcut. (n=1), steroids (n=2), canakinumab (n=1)) <p>12/66 received 2 doses of tocilizumab IV after clinical worsening</p>		<p><u>Discharge from hospital</u> <i>14 days</i> I: 34/60 (56.7%) C: 36/63 (57.1%) Rate ratio 0.99 (0.73 – 1.35) <i>30 days</i> I: 54/60 (90%) C: 58/63 (92.1%) Rate ratio 0.98 (0.87 – 1.09)</p> <p><u>Adverse events, No (%)</u> I: 14/60 (23.3%) <i>1 patient had 2 events</i> C: 7/63 (11.1) <i>1 patient had 3 events</i> In publication, also data on 6 sub-categories of AE's</p>	<p>tocilizumab in different stages of the disease, such as in patients with a Pao2/Fio2 ratio less than 200 mm Hg.</p>
Hermine, 2020	<p><u>Type of study:</u> Cohort-embedded, investigator-initiated multicenter, open-label, Bayesian randomized clinical trial.</p> <p><u>Setting:</u> Nine university hospitals</p>	<p><u>Inclusion criteria group 1:</u></p> <ul style="list-style-type: none"> • Confirmed SARS-CoV-2 infection (positive on rRT-PCR and/or typical chest computed tomographic [CT] scan) with moderate, severe, or critical pneumonia (O2 >3 L/min, WHO clinical Progression Scale [WHO-CPS] score ≥5. 	<p>Tocilizumab in combination with usual care</p> <p>Intravenously administration of Tocilizumab of 8 mg/kg on day 1. Administration of an additional fixed doze of tocilizumab, 400 mg IV, on day 3 was recommended if oxygen requirement was not decreased by more</p>	<p>Usual care alone</p> <p>Usual care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at</p>	28 days	<p><i>The 2 primary outcomes were (1) the proportion of patients dead or needing non-invasive or mechanical ventilation on day 4 (>5 on the WHO-CPS); and (2) survival with no need for non-invasive or mechanical ventilation at day 14.</i></p> <p><u>Primary outcome by day 14; N</u> I: 15/63</p>	<p><u>Remarks:</u> TCZ (group 1): receiving tocilizumab UC (group 2): receiving usual care</p> <p><u>Authors conclusion:</u></p>

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	<p><u>Country:</u> France</p> <p><u>Source of funding:</u> This trial was publicly funded (Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research (FRM), AP-HP Foundation and the Reacting program).</p> <p>The funding agencies had no access to the trial data and had no role in the design, conduct or reporting of the trial. Roche donated TCZ in unrestricted grant, and had no role in the trial design or conduct; the collection, management, analysis, interpretation of the data; or in the preparation, review of the manuscript or the approval of the manuscript for submission.</p>	<p><u>Inclusion criteria group 2:</u></p> <ul style="list-style-type: none"> aWHO-CPS score of 5 with O2 levels of 3 L/min or higher but without noninvasive ventilation (NIV) or mechanical ventilation (MV). <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Known hypersensitivity to TCZ, pregnancy, current documented bacterial infection, patients with any of following laboratory results out of the ranges detailed below at screening: absolute neutrophil count (ANC) $1.0 \times 10^9 /L$ or less or platelets (PLT) less 50 G /L.. <p><u>N total at baseline:</u> N = 131 Intervention: N = 64 Control: N = 67</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 64.0 (57.1 to 74.3) C: 63.3 (57.1 to 72.3)</p> <p>Sex, n/N (%) male: I: 44/63 (70%) male C: 44/67 (66%) male</p> <p>BMI, median (IQR) I: 27.9 (23.3 to 30.8) C: 27.4 (24.5 to 31.3)</p>	than 50%, but decision was left to the treating physician.	the discretion of the clinicians.		<p>C: 24/67</p> <p><u>Mechanical ventilation or death by day 14; N (95% CI)</u> I: 17% (95% CI= 8 to 26) C: 27% (95% CI= 15 to 37) Difference -9 (95% CI= -24 to 5)</p> <p><u>Deaths day 14; N</u> I: 7/63 C: 6/67</p> <p><u>Survival day 14; % (95% CI)</u> I: 89% (95% CI= 81 to 97) C: 91% (95% CI= 84 to 98)</p> <p><u>Deaths day 28; N</u> I: 7/63 C: 8/67</p> <p><u>Survival day 28; % (95% CI)</u> I: 89% (81 to 97) C: 88% (80 to 96)</p> <p><u>Patients with at least 1 adverse event; N (%)</u> I: 28 (44%) C: 36 (54%)</p> <p><u>Patients with multiple adverse events; N (%)</u> I: 16 (25%) C: 19 (28%)</p> <p><u>Patients with at least 1 serious adverse event; N (%)</u> I: 20 (32%) C: 29 (43%) P = 0.21</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						Patients with multiple serious adverse events; N (%) I: 5 (8%) C: 10 (15%)	
17. Other immunomodulators							
17.1. Auxora (potent and selective small molecule inhibitor of calcium release-activated calcium (CRAC) channels)							
Bruen, 2022	<p><u>Type of study:</u> A phase 2, randomized, multicenter, double-blind, placebo-controlled trial (CARDEA)</p> <p><u>Setting:</u> Hospitalized patients, enrolled from September 08, 2020 to May 24, 2021</p> <p><u>Country:</u> 17 centers across the United States</p> <p><u>Source of funding:</u> This study was funded by CalciMedica, Inc. (La Jolla, CA, USA).</p> <p><u>Conflicts of interest:</u> Yes, transparently reported</p>	<p>Hospitalized patients with severe COVID-19 pneumonia</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adults with ≥ 1 symptom consistent with COVID-19 infection A diagnosis of COVID-19 confirmed by laboratory testing using polymerase chain reaction or other assay Pneumonia documented by chest imaging Receiving HFNC or low flow nasal canula Baseline imputed PaO₂/FiO₂ ratio > 75 and ≤ 300 <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients could not be receiving either non-invasive or invasive mechanical ventilation at the time of enrolment. <p><u>N total at baseline:</u> N = 284 Intervention: N=143 Control: N=141</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 59.4 y (12.1) C: 60.4 y (12.3)</p> <p>Sex, n/N (%) male:</p>	Auxora was administered by a 4-h IV infusion at 2.0 mg/kg (1.25 mL/kg) at 0-h and 1.6 mg/kg (1 mL/kg) at 24 and 48 h	Placebo for 5 days	<p><u>Length of follow-up:</u> 60 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: 13/143 (9.1%) patients with imputed PaO₂/FiO₂ >200</p> <p>Placebo: 10/141 (7.1%) patients with imputed PaO₂/FiO₂ >200</p> <p>One patient was lost to follow up (unknown to which treatment group the patient was allocated)</p>	<p><u>Clinical outcomes</u> <u>All-cause mortality at Day 60, n/N (%)</u> I: 18/130 (13.8%) C: 27/131 (20.6%) P=0.15</p> <p><u>All-cause mortality at Day 30, n/N (%)</u> I: 10/130 (7.7%) C: 23/131 (7.7%) P=0.02</p> <p><u>Duration of hospitalization</u> Not reported</p> <p><u>Time to symptom resolution</u> <u>Median Time to recovery, days (95%CI)</u> I: 7.0 (6.0-9.0) C: 10.0 (7.0-14.0) P=0.1</p> <p><u>Invasive respiratory support, proportion of patients day 60 (95%CI)</u> I: 0.19 (0.13-0.18) C: 0.28 (0.21-0.37) P=0.19</p> <p><u>Non-invasive respiratory support</u> Not reported</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> Time to recovery through Day 60 Symptoms resolved <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> All-cause mortality at Day 60 all-cause mortality at Day 30 Proportion of patients requiring invasive mechanical ventilation or death through Day 60 Proportion of patients requiring invasive mechanical ventilation through Day 60 Differences in outcomes measured by the 8-point ordinal scale through Day 60 Safety endpoints included the occurrence and severity of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs). <p><u>Definitions:</u> The primary endpoint was time to recovery through Day 60, defined as meeting the criteria for category 6 (Hospitalized, not requiring supplemental oxygen or ongoing medical care), category 7 (Discharged, requiring supplemental oxygen), or category 8 (Discharged, not requiring supplemental oxygen) using an 8-point ordinal scale.</p> <p><u>Remarks:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 84/130 (64.6%) C: 92/131 (70.2%)</p> <p>Disease severity Not reported</p> <p>Groups comparable at baseline? Yes</p>		administered to 8 patients after randomization, and 6 were determined to have received placebo after unblinding.		<p>Safety <u>Serious adverse events</u> I: 49/130 (35%) C: 34/131 (24.1%)</p> <p>A detailed list of SAE is provided in the article.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<p>The primary and key secondary endpoints were also evaluated in pre-specified subgroups of patients who required oxygen therapy via either HFNC or low flow nasal cannula at baseline or patients having a baseline imputed PaO₂/FIO₂ ≤ 100 or 101–200 at baseline, and in all randomized patients.</p> <p>Due to declining rates of COVID-19 hospitalizations and utilization of standard of care medications prohibited by regulatory guidance, the trial was stopped early.</p> <p><u>Authors conclusion:</u> Auxora was safe and well tolerated with strong signals in both time to recovery and all-cause mortality through Day 60 in patients with severe COVID-19 pneumonia. Further studies of Auxora in patients with severe COVID-19 pneumonia are warranted.</p>
Miller, 2020	<p><u>Type of study:</u> RCT, open-label</p> <p><u>Setting:</u> Multi-center; three centers in the USA</p> <p><u>Country:</u> USA</p> <p><u>Source of funding:</u> This study was funded by CalciMedica, Inc. (La Jolla, CA, USA).</p>	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> adults RT-PCR confirmed COVID-19 diagnosis pneumonia documented by chest imaging ≥ 1 symptom consistent with COVID-19 (e.g. fever, cough, sore throat, malaise, headache, muscle pain, dyspnea, confusion, or respiratory distress) ≥ 1 clinical sign suggesting respiratory compromise (e.g. respiratory rate ≥ 30 breaths/min, heart rate ≥ 125 bpm, SpO₂ < 93% on room air or 	<p>Auxora (CRAC channel inhibitor) + standard of care</p> <p>3 consecutive days as a 4-h continuous IV infusion</p> <p>Initial dose: 2.0 mg/kg (max 250 mg), Subsequent doses: 1.6 mg/kg (max 200 mg) at 24 and 48 h.</p> <p>At the discretion of investigators, patients were able to receive convalescent</p>	<p>Standard of care</p> <p>including antiviral agents and low flow supplemental oxygen, but investigational therapies and immunosuppressive medications were not permitted.</p>	<p><u>Length of follow-up:</u> 30 days</p> <p><u>Assessments:</u> Day 1 to 10: daily Day 11 to 28 or discharge: every 48 hours</p>	<p>Efficacy (study arm A) <u>Time to recovery</u>, median I: 5 days C: 12 days <u>Recovery</u> RR 1.87 (95% CI 0.72 to 4.89) Intubation required I: 3/17 (18%) C: 4/8 (50%) (95% CI, - 0.07 to 0.71) <u>Death or invasive mechanical ventilation</u> I: 18% C: 56% HR 0.23 (95% CI, 0.05 to 0.96)</p>	<p><u>Remarks:</u> “This study was funded by CalciMedica, Inc. (La Jolla, CA, USA). The study was designed by the funder with input from the lead investigators. The funder compiled and analyzed the study data and interpreted the data in collaboration with all authors. All authors had full access to all the data in the study...”</p> <p><u>Authors conclusion:</u> In this preliminary, phase 2 study of the novel CRAC inhibitor, Auxora, the observed favorable safety profile and efficacy signals when compared to standard of care support</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>requiring > 2 L oxygen by nasal cannula to maintain SpO2 ≥ 93%, or PaO2/FiO2 < 300, imputed from pulse oximetry or determined by arterial blood gas</p> <p><u>Study arm A:</u> N total at baseline: 26 Intervention: 17 Control: 9</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 59y ± 12 C: 61y ± 13 Sex, n/N (%) male: I: 7/17 (41%) C: 5/9 (56%)</p> <p>Groups were comparable at baseline, except for the rate of diabetes, which was higher in the intervention group.</p>	plasma if they required invasive mechanical ventilation	<p>At the discretion of investigators, patients were able to receive convalescent plasma if they required invasive mechanical ventilation</p> <p><i>NB: Study arm B received high flow supplemental oxygen; because small groups (n=3 and N=3) this comparison is left out of this table</i></p>		<p><u>Clinical improvement</u>, 8-point ordinal scale: greater in intervention group Day 4: OR 0.21 (95% CI, 0.04 to 0.098) Day 9-12: remained significant No additional data provided</p> <p>Safety (study arm A=B; I: n=3 and C: n=1 patients on low oxygen) ≥ 1 AE I: 15/20 (75%) C: 8/10 (80%) 3/15 related to treatment (episode of itching, increase in alkaline phosphate, and rash) <u>AE related to infection</u> I: 30% C: 30% ≥ 1 SAE I: 6/20 (30%) C: 5/10 (50%) None related to treatment</p> <p><u>Mortality</u> I: 2/20 (10%) C: 2/10 (20%) 10-17 days after randomization</p>	<p>the need for further investigation in a large, double-blind, placebo controlled trial in patients with severe COVID-19 pneumonia.</p> <p>In addition, these results suggest the potential for the clinical development of Auxora for the treatment of other etiologies of acute respiratory distress syndrome.</p>
17.2. Colchicine (anti-inflammatory and analgesic medication)							
Dorward, 2022	<u>Type of study:</u> Prospective, multicentre, open-label, multi-arm, randomised, controlled, adaptive platform trial	<p>Patients- ≥ 18 y with symptomatic COVID-19, regardless of their risk factors for disease progression or vaccination status</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> adults aged ≥ 65 y or ≥ 18 y with comorbidities* or shortness of 	<p>Colchicine + usual care</p> <p>Colchicine 500 µg daily for 14 days</p> <p>Usual care in the UK NHS for suspected COVID-19 in the community is largely focused on managing</p>	<p>Usual care alone</p> <p>Usual care in the UK NHS for suspected COVID-19 in the community is largely focused</p>	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Incomplete outcome data & loss-to-follow-up for primary analysis:</u> The Bayesian primary analysis model</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> <u>Death at day 28:</u> I: 0/156 (0%) C: 1/120 (1%)</p> <p>Duration of hospitalization Days, median (IQR)</p>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> time to first-reported recovery defined as the first instance that a participant reports feeling recovered admission to hospital or death related to COVID-19 <p>Secondary outcomes:</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Setting: Community-based, primary care, enrolment started on April 2, 2020, and is ongoing; the colchicine arm was closed on May 26 2021</p> <p>Country: UK</p> <p>Source of funding: Funded by a grant to the University of Oxford from UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research (NIHR) as part of the UK Government's rapid research response fund. The funder had no role in the study design, data collection, analysis, interpretation, nor writing of the article, nor decision to submit for publication.</p> <p>Conflicts of interest:</p>	<p>breath, and unwell for ≤ 14 days with suspected COVID-19 in the community</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> people were ineligible to be randomised to colchicine if they were already taking colchicine or if colchicine was contraindicated according to the British National Formulary <p>N total at baseline: Randomized: N = 4997 Intervention: N = 212 Control: N = 2081 Other treatments: N = 2704</p> <p>Important characteristics: Age, mean (SD): I: .48.5 y (13.2) C: 61.7 y (9.0)</p> <p>Sex, n/N (%) male: I: 107/206 (51.9%) C: 932/2050 (45.5%)</p> <p>Baseline characteristics were similar between the comparison groups</p>	<p>symptoms with antipyretics, although previous results from PRINCIPLE led to the introduction of inhaled budesonide on an off-label, case-by- case basis for people aged ≥ 65 y or 50-65 y with comorbidities</p>	<p>on managing symptoms with antipyretics, although previous results from PRINCIPLE led to the introduction of inhaled budesonide on an off-label, case-by- case basis for people aged ≥ 65 y or 50-65 y with comorbidities</p>	<p>included data from 2755 of 2900 (95%) participants who were SARS-CoV-2 positive and who provided follow-up data and were randomised to colchicine (n = 156), usual care alone (n = 1145), and other treatment groups (n = 1454).</p>	<p>I: 6 (4-7) C: 28 (28-28)</p> <p>Time to symptom resolution <u>Time to first-reported recovery</u> Days, median (IQR) I: 15 (7-not reached) C: 14 (6-not reached) HR 0.92 (95%BI: 0.72-1.16)</p> <p>Invasive respiratory support <u>Mechanical ventilation</u> I: 0/155 (0%) C: 0/120 (0%)</p> <p>Non-invasive respiratory support Oxygen administration I: 5/155 (3%) C: 1/120 (1%)</p> <p>Other There was no clear evidence of benefit for any of the secondary outcomes.</p> <p>Safety Regarding serious adverse events, there was one hospital admission unrelated to COVID-19 in the colchicine group and one in usual care.</p> <p>Virological outcomes Not reported.</p>	<ul style="list-style-type: none"> early, sustained recovery (recovered by day 14 and remains recovered until day 28) time to sustained recovery (date participant first reports recovery and subsequently remains well until 28 days) daily rating from 1-10 of how well participants feel time to initial alleviation of symptoms (date symptoms first reported as minor or none), time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remain minor or none until 28 days) time to initial reduction of severity of symptoms (among people with symptom at baseline, date symptom severity reported at least one grade lower) worsening of symptoms (worsening symptom by one grade from mild to moderate/severe, or from moderate to severe, and excluding individuals reporting symptom severity as major at baseline), contacts with healthcare services hospital assessment without admission, duration of hospital admission, oxygen administration, intensive care unit admission mechanical ventilation WHO ordinal scale of clinical progression adherence to study treatment WHO-5 Well-Being Index serious adverse events

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	Transparently and extensively reported.						<ul style="list-style-type: none"> all-cause death or urgent, non-elective hospital admission reports of new household infections <p><u>Definitions:</u> * Comorbidities required for eligibility were: heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problems; weakened immune system (e.g. chemotherapy); and self-reported obesity or BMI \geq 35 kg/m².</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> Colchicine did not improve time to recovery in people at higher risk of complications with COVID- 19 in the community.</p>
Gorial, 2022	<p><u>Type of study:</u> Open label randomized clinical trial</p> <p><u>Setting:</u> Hospitalized patients, enrolled from April, 2021 to August, 2021</p> <p><u>Country:</u> Baghdad, Iraq</p> <p><u>Source of funding:</u> No sources of funding</p> <p><u>Conflicts of interest:</u> None to declare</p>	<p>Hospitalized patients with moderate to severe COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> ≤18 years Moderate to severe COVID-19 according to the WHO classification <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Patients with hypersensitivity to colchicine Chronic diseases Heart failure Cancer Pregnant and lactating women Those receiving immunosuppressive chemotherapy 	colchicine 0.5 mg tablet 1x2 for 1 week followed by 0.5 mg tablet 1x1 for another week + the standard therapy (total duration of colchicine 14 days).	only standard care which included all or some of the following, according to the clinical condition of each patient: - Acetaminophen 500mg on need - Vitamin C 1000mg twice/day - Zinc 75-125 mg/day - Vitamin D3 5000IU/day	<p><u>Length of follow-up:</u> 14 days</p> <p><u>Incomplete outcome data & loss-to-follow-up:</u> No loss to follow up reported.</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> No data available</p> <p>Reported by the authors: The mortality rate in the 4 treatment groups ranged between zero to 5%, with no important or statistically significant differences in the risk of death between groups</p> <p><u>Duration of hospitalization</u> Not reported</p> <p><u>Time to symptom resolution</u> Cymmylative incidence of cure with time (days) since the start of treatment,</p>	<p>Primary outcome:</p> <ul style="list-style-type: none"> Percentage cure/deaths of patients and evaluated by normalization of clinical evaluation, laboratory investigations, and imaging <p>Secondary outcome(s):</p> <ul style="list-style-type: none"> Time to recovery Proportion and nature of possible side effects seen during the trial <p><u>Definitions:</u></p> <p><u>Remarks:</u> No data was available on the primary outcome, it was presented in survival curves</p> <p><u>Authors conclusion:</u></p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<ul style="list-style-type: none"> • Digoxin, amiodarone, verapamil, or protease inhibitor use <p><u>N total at baseline:</u> N = 160 Intervention: N=80 Control: N=80</p> <p><u>Important characteristics:</u> Age, median (IQR) Not reported per group, the overall median age was 49 y [37-60.5)</p> <p>Sex, n/N (%) male: I: 46/80 (57.5%) C: 39/80 (48.8%)</p> <p>Disease severity Defined according to the WHO classification</p> <p>Moderate I: 40/80 (50%) C: 40/80 (50%)</p> <p>Severe I: 40/80 (50%) C: 40/80 (50%)</p> <p>Groups comparable at baseline? Yes</p>		<ul style="list-style-type: none"> - Azithromycin 250mg/day for 5 days - Oxygen therapy/ C-Pap if needed - - Dexamethasone 6 mg/day or methylprednisolone 40mg twice per day, if needed - Mechanical ventilation, if needed 		<p>median survival time (95% CI)</p> <p>Moderate severity of disease I: 4 (3.4-4.6) C: 7 (6.3-7.7)</p> <p>Severe disease I: 5 (3.7-6.3) C: 9 (7.8-10.2)</p> <p><u>Invasive and non-invasive respiratory support</u> Not reported</p> <p>Safety <u>Serious adverse events</u> Not reported</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	Colchicine in the current study reduced time to recovery by an average of 5 days less in severe and 2 days in moderate COVID19 cases. The association between this add on treatment and mortality was not established. Side effects were mild and confined to gastrointestinal upset and diarrhea. Hence, there seems a potential role for using Colchicine as an add on to treat severe COVID19 patients.
Pourdowlat, 2022	<p><u>Type of study:</u> Multicenter, randomized clinical trial</p> <p><u>Setting:</u> 5 hospital sites.</p> <p><u>Country:</u></p>	<p><u>Non-hospitalised patients with moderate to severe COVID-19</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • aged 18-80 y • confirmed COVID-19 according to PCR results or manifestations in CT scan 	<p><u>Colchicine:</u> Colchicine was administered at a dose of 0.5 mg for 3 days and then continued 1 mg/day for 12 days</p> <p>+</p>	<p><u>Standard of care included:</u> hydroxychloroquine, prophylactic dose of anticoagulant agents, vitamin D3, and</p>	<p><u>Length of follow-up:</u> 14 days</p> <p><u>Loss-to-follow-up:</u> I: 13/102 (12.7%)</p> <p><u>Reasons</u></p> <ul style="list-style-type: none"> • needed hospitalization and 	<p>Clinical outcomes <u>Mortality</u> Not reported.</p> <p><u>Duration of hospitalization</u> Not reported.</p>	<p><u>Definitions:</u> † New York Heart Association (NYHA) class (I-IV) is a system for evaluating the severity of limitation of physical activity: Class I: No functional limitations; Class II: Slight functional limitations;</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Iran</p> <p><u>Source of funding:</u> Not reported.</p> <p><u>Conflicts of interest:</u> No competing interests.</p>	<ul style="list-style-type: none"> evidence of moderate to severe lung involvement not taking colchicine <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> lactating, pregnant, or plans to become pregnant <30 days after end of study shock or hemodynamic instability history of Crohn's or ulcerative colitis, diarrhea or chronic malabsorption neuromuscular diseases eEGF <30 ml/min history of cirrhosis, hepatitis, or severe liver disease colchicine use for other conditions history of an allergic reactions to colchicine receiving chemotherapy <p><u>N total at baseline:</u> N = 202 Intervention: N = 102 Control: N = 100</p> <p><u>Important characteristics:</u> Age, median (IQR), year: I: 54.4 (19.2) C: 56.0 (18.5)</p> <p>Sex, n/N (%) male: I: 52/102 (61.2%) C: 41/63 (66.1%)</p> <p><u>Disease severity</u> CT score of lung involvement, M (SD) I: 10.2 (6.4) C: 9.8 (6.3)</p>	Standard of care	naproxen along with O2 therapy aiming for O2 Sat >93% on room air.	<p><i>other intervention (n = 5)</i></p> <ul style="list-style-type: none"> did not refer for follow-up CT scan because of feeling healthy (n=8) <p>C: 37/100 (37%)</p> <p><i>Reasons</i></p> <ul style="list-style-type: none"> needed other intervention in the outpatient setting (n = 19) needed hospitalization and additional intervention (n=18) <p><u>Incomplete outcome data:</u> Completed the trial: N=153 Intervention: N=89 Control: N=63</p>	<p><u>Time to symptom resolution</u> <u>Percentage change of lung improvement based on CT-score (difference from baseline, median (IQR))</u> I: 80.0 (55.84) C: 66.76 (74.58) p=0.048</p> <p><u>Percentage change of lung involvement based on percent of CT involvement (difference from baseline, median (IQR))</u> I: 85.7 (50.0) C: 75.0 (73.2) P=0.065</p> <p><u>Percentage change of dyspnea based on NHYA classification† (difference from baseline, mean (SD))</u> I:31.94 (29.1) C:20.0 (23.0) P=0.026</p> <p><u>Respiratory support:</u> Not reported.</p> <p>Safety <u>Adverse events</u> No severe adverse effects including thrombosis were recorded in patients in either group.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	<p>Class III: Marked functional limitations;</p> <p>Class IV: Unable to carry on any physical activity without discomfort</p> <p><u>Remarks:</u> High percentage lost to follow-up in the control group due to worsening clinical conditions.</p> <p><u>Authors conclusion:</u> In this clinical trial of patients with moderate to severe COVID-19, those who were randomized to the group receiving colchicine treatment for up to 15 days had significantly higher odds of having better chest CT findings and functional class on day 14 than those receiving standard care, but with an effect size of uncertain clinical importance.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups comparable at baseline? Yes.					
Diaz, 2021	<p><u>Type of study:</u> open-label, multicentre, randomized clinical trial</p> <p><u>Setting:</u> hospital-based, between April 17, 2020 and March 19, 2021</p> <p><u>Country:</u> 42 centres in Argentina</p> <p><u>Source of funding:</u> The Population Health Research Institute contributed fees to the investigators. Fundacion ECLA funded all other aspects of the trial.</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported.</p>	<p>hospitalized patients with COVID-19 symptoms and severe acute respiratory syndrome or oxygen desaturation</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • age ≥ 18 y • diagnosed with COVID-19 infection through an approved testing method • hospitalized • severe acute respiratory syndrome or oxygen desaturation ≤ 93% <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • clear contraindications for the use of colchicine • pregnant or lactating females • chronic kidney disease • negative RT-PCR test before randomization <p><u>N total at baseline:</u> Randomized: N = 1279</p> <p>Intervention: N = 640 Control: N = 639</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 62 y (14) C: 62 y (15)</p> <p>Sex, n/N (%) male: I: 421/640 (65.8%) C: 409/1279 (64%)</p> <p>Baseline characteristics were well balanced between the colchicine and usual care groups</p>	<p>Colchicine + usual care</p> <p>Colchicine was administered orally in a loading dose of 1.5mg immediately after randomization, followed by 0.5mg orally within 2 hours of the initial dose and 0.5mg orally twice a day for 14 days or discharge, whichever occurred first.</p>	Usual care (not defined)	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> I: 33/640 (5.2%) C: 5/639 (0.8%)</p> <p>Reasons for loss-to-follow-up or incomplete data is reported</p>	<p>Clinical outcomes</p> <p><u>Mortality</u> <u>Intubation for mechanical ventilation or 28-day mortality*</u> I: 160/640 (25%) C: 184/639 (28.8%) HR: 0.83 (0.67 – 1.02) p=0.08</p> <p><u>Mortality at day 28</u> I: 131/640 (20.5%) C: 142/639 (22.2%) HR 0.88 (0.70 – 1.12) p=0.30</p> <p><u>Duration of hospitalisation</u> Not reported</p> <p><u>Time to symptom resolution</u> Not reported</p> <p><u>Respiratory support</u> Not reported</p> <p><u>Safety</u> Not reported</p> <p><u>Virological outcomes</u> Not reported</p>	<p><u>Definitions:</u> * the first coprimary outcome was the composite of a new requirement for mechanical ventilation or death evaluated at 28 days after randomization. For this outcome, participants intubated at the time of randomization were only followed for death.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> This randomized clinical trial found that compared with usual care, colchicine did not significantly reduce mechanical ventilation or 28-day mortality in patients hospitalized with COVID-19 pneumonia.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Absalón-Aguilar , 2021	<p>Type of study: triple-blind, placebo-controlled clinical trial</p> <p>Setting: Hospital-based, between May 2020 and June 16, 2020</p> <p>Country: Mexico</p> <p>Source of funding: This study was funded with resources from Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.</p> <p>Conflicts of interest: The authors declare that they do not have a conflict of interest.</p>	<p>Hospitalized patients with severe COVID-19</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • age 18-70 y • tested positive for at least one of the following COVID-19 diagnostic assays <ul style="list-style-type: none"> ○ PCR for SARS-CoV-2 in nasopharyngeal swab ○ rapid antigen test ○ serum anti-SARS-CoV-2 IgG antibody • respiratory failure, respiratory rate ≥ 30, SpO₂ $\leq 93\%$ at rest, P_aO₂/F_iO₂ ≤ 300 mmHg <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • chronic liver or kidney failure • pregnancy • puerperium • receiving any drug with known interaction with colchicine • receiving antimalarial drugs, azithromycin, convalescent plasma, remdesivir, tocilizumab, or baricitinib <p>N total at baseline: Randomized: N = 116 ITT population: N = 116 Intervention: N = 56 Control: N = 60</p> <p>Important characteristics: Age, median (IQR): I: 55 y (43-62) C: 52 y (44-2)</p> <p>Sex, n/N (%) male: I: 37/56 (66%) C: 39/60 (65%)</p>	Colchicine (1.5 mg p.o. at baseline, followed by 0.5 mg p.o. for 10 days)	Placebo	<p>Length of follow-up: 10 days</p> <p>Loss-to-follow-up: none</p>	<p>Clinical outcomes</p> <p>Mortality Not reported.</p> <p>Duration of hospitalization Duration of ICU stay Days, median (IQR) 0 (0-1) vs. 0 (0-0.75); p = 0.29</p> <p>Total length of hospital admission Days, median (IQR) 8 (5-10.75) vs. 7.5 (6-11.5); p = 0.73</p> <p>Time to symptom resolution Not reported.</p> <p>Respiratory support Not reported.</p> <p>Other Death or progression to critical disease at 10 days (primary outcome) OR 0.83 (95%CI: 0.35-1.93)</p> <p>Safety Adverse events I: 15/56 (26.8%) C: 7/60 (11.7%) p = 0.057</p> <p>Virological outcomes Viral clearance Not reported.</p> <p>Also, changes in vital signs (temperature, respiratory and heart rate, SpO₂),</p>	<p>Definitions: *Critical disease was defined as multiple organ failure, shock, or need for invasive mechanical ventilation</p> <p>Remarks: -</p> <p>Authors conclusion: Colchicine treatment in hospitalized patients with severe COVID-19 is safe but not effective for the prevention of disease progression or death. After colchicine treatment, patients had a higher BUN but lower levels of IL-8, IL-12p70, and IL-17. Currently, guidelines for the management of hospitalized adults with COVID-19 recommend against the use of colchicine. Our study contributes to the reinforcement of this recommendation and will be useful for front-line physicians facing severe COVID-19.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		Groups were (statistically) comparable at baseline, except for hypertension (more prevalent in the control group) and dexamethasone use (more participants in the control group received dexamethasone).				inflammatory, and coagulation markers (leukocytes, neutrophil/lymphocyte ratio, C-reactive protein, lactate dehydrogenase, D-dimer and fibrinogen) were compared between treatment groups.	
RECOVERY Collaborative Group, 2021	<p><u>Type of study:</u> randomised, controlled, open-label, platform trial</p> <p><u>Setting:</u> hospital-based, between November 27 2020 and March 4 2021</p> <p><u>Country:</u> 177 hospitals in UK, 2 hospitals in Indonesia, and 2 hospitals in Nepal</p> <p><u>Source of funding:</u> UK Research and Innovation (Medical Research Council), National Institute of Health Research, and Wellcome Trust</p> <p><u>Conflicts of interest:</u> The authors declare no competing interests.</p>	<p>hospitalized patients with COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> admitted to hospital with clinically suspected or laboratory confirmed SARS-CoV-2 infection no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> children pregnant women severe liver impairment significant cytopaenia concomitant use of strong CYP3A4 or P-glycoprotein inhibitors hypersensitivity to lactose <p><u>N total at baseline:</u> Randomized: N = 11.340 ITT population: N = 11.340</p> <p>Intervention: N = 5610 Control: N = 5730</p> <p><u>Important characteristics:</u> Age, mean (SD):</p>	colchicine 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice a day by mouth or nasogastric tube for 10 days in total or until discharge + usual care	usual care	<p><u>Length of follow-up:</u> 28 days</p> <p><u>Loss-to-follow-up or incomplete data:</u> Intervention: N =19 (0.3%) <i>Reason</i></p> <ul style="list-style-type: none"> withdrew consent (n = 19) <p>Control: N =24 (0.4%) <i>Reason</i> withdrew consent (n = 24)</p>	<p>Clinical outcomes</p> <p>Mortality <u>All-cause mortality within 28 days (primary outcome)</u> I: 1173/5610 (21%) C: 1190/5730 (21%) RR 1.01 (95%-CI: 0.93-1.10)</p> <p>Duration of hospitalisation <u>Time to discharge from hospital alive within 28 days</u> Days, median (IQR) I: 10 (5 to >28) C: 10 (5 to >28)</p> <p><u>Discharged from hospital within 28 days</u> I: 3901/5610 (70%) C: 4032/5730 (70%) RR 0.98 (95%-CI: 0.94-1.03)</p> <p>Time to symptom resolution Not reported</p> <p>Respiratory support <u>Receipt of invasive mechanical ventilation or death (in patients not on invasive mechanical</u></p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In adults hospitalised with COVID-19, colchicine was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 63.3 y (13.8) C: 63.5 y (13.7)</p> <p>Sex, n/N (%) male: I: 3897/5610 (69%) C: 4012/5730 (70%)</p> <p>Groups were comparable at baseline.</p>				<p><u>ventilation at randomisation</u> I: 1344/5342 (25%) C: 1343/5469 (25%) RR 1.02 (95%-CI: 0.96-1.09)</p> <p><u>Receipt of ventilation (in patients not on any form of ventilation at randomisation)</u> I: 852/3815 (22%) C: 941/3962 (24%) RR 0.94 (95%-CI: 0.87-1.02)</p> <p><u>Receipt of non-invasive ventilation (in patients not on any form of ventilation at randomisation)</u> I: 818/3815 (21%) C: 904/3962 (23%) RR 0.94 (95%-CI: 0.86-1.02)</p> <p><u>Receipt of invasive mechanical ventilation (in patients not on any form of ventilation at randomisation)</u> I: 259/3815 (7%) C: 228/3962 (6%) RR 1.18 (95%-CI: 0.99-1.40)</p> <p><u>Successful cessation of invasive mechanical ventilation (in patients on invasive mechanical ventilation at randomisation)</u> I: 88/268 (33%) C: 81/261 (31%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p>RR 1.01 (95%-CI: 0.75-1.37)</p> <p>Other <u>Use of haemodialysis or haemofiltration (in patients not on haemodialysis or haemofiltration at randomisation)</u> I: 212/5570 (4%) C: 203/5683 (4%) RR 1.07 (95%-CI: 0.88-1.29)</p> <p>Safety <u>Serious adverse events</u> There were two reports of a serious adverse reaction believed related to colchicine: one patient had severe acute kidney injury and one had rhabdomyolysis.</p> <p>Virological outcomes Not reported</p> <p>Similar results were observed across all prespecified subgroups and in an exploratory analysis by baseline CRP concentration. In an exploratory analysis restricted to the 11.009 (97%) patients with a positive SARS-CoV-2 test result, the result for the primary outcome was virtually identical to the overall result.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Pascual-Figal, 2021	<p>Type of study: prospective, randomized, Phase III, controlled and open label clinical trial</p> <p>Setting: Mount Sinai Beth Israel, Mount Sinai Morningside, and Mount Sinai West Hospitals, between September 2020 and December 2020</p> <p>Country: USA</p> <p>Source of funding: funds from 1) "Cardiology Research group" at the IMIB-Arrixaca and the University of Murcia, Murcia, Spain; 2) Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain. Centro Nacional de Investigaciones Cardiovasculares (CNIC) is supported by the Spanish Ministry of Economy and Competitiveness (MINECO)</p>	<p>hospitalized patients with COVID-19 that do not need mechanical ventilatory support (non-ICU) and within the first 48 hours of hospital admission</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • males or females \geq 18y • SARS-CoV-2 infection confirmed by RT-PCR • admitted in hospital in the previous 48 hours with COVID-19 diagnosis • 7-points WHO clinical status of 3, 4 or 5 <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • invasive or noninvasive mechanical ventilation needed • established limitation of therapeutic effort • inflammatory bowel disease • chronic diarrhea or malabsorption • previous neuromuscular disease • any disease with an estimated vital prognosis under 1 year • severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²) • medical history of cirrhosis, active chronic hepatitis or severe hepatic disease defined by liver transaminases levels threefold above the normal upper limit • previous colchicine treatment for other diseases • history of allergic reaction or significant sensitivity to colchicine, immunosuppressive 	<p>Colchicine plus standard of care</p> <p>an initial load dose of 1.5 mg (1 mg and 0.5 mg two hours after), followed by 0.5 mg every 12 hours during the next 7 days and 0.5 mg every 24 hours until the completion of 28 days of total treatment</p>	<p>standard of care dexamethasone (6 mg once a day for 10 days)</p>	<p>Length of follow-up: 28 days</p> <p>Loss-to-follow-up or incomplete data:</p> <p>Intervention: N = 0</p> <p>Control: N = 0</p>	<p>Clinical outcomes</p> <p>clinical deterioration (+1 WHO scale at any time)</p> <p>I: 13.8% C: 5.8% p=0.303</p> <p>Mortality</p> <p>I: 0/52 (0.0%) C: 2/51 (3.9%) P= 0.47</p> <p>Duration of hospitalisation</p> <p>Length of hospitalization, mean (SD)</p> <p>I: 6.6 (3.9) C: 5.8 (4.9) P=0.34</p> <p>Days in ICU, mean (SD)</p> <p>I: 5.0 (0.0) C: 8.3 (8.1) P=0.62</p> <p>ICU admission</p> <p>I: 2/52 (3.8 %) C: 4/51 (7.8%) P=0.66</p> <p>Time to symptom resolution</p> <p>Days to 1-grade improvement WHO scale: Mean (SD)</p> <p>I: 5.7 (3.5) C: 5.0 (84.7) P=0.35</p>	<p>Definitions: WHO 7-points scale: 1. Not hospitalized, no limitation of activities; 2. Not hospitalized, limitation of activities; 3. Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen by mask or nasal prongs; 5. Hospitalized, non-invasive ventilation or high flow oxygen; 6. Hospitalized, intubation and mechanical ventilation or ECMO; 7. Death.</p> <p>Remarks: Among the limitations of our study are the small sample size and the limited number of adverse events that underpowered the ability to reach conclusions.</p> <p>Authors conclusion: In conclusion, in this randomized, open-label and controlled clinical trial in hospitalized COVID-19 patients (nonICU), oral colchicine administration within the first 48 hours of hospitalization did not significantly improve the patients clinical condition, or their inflammatory markers. However, colchicine seemed to prevent further clinical deterioration after considering concomitant therapies and baseline risk variables. Further powered trials and pooled analysis are necessary to define the role of colchicine in the prevention of clinical deterioration of COVID-19 patients.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>and Pro-CNIC Foundation</p> <p><u>Conflicts of interest:</u> None to declare.</p>	<p>agents, including corticoids, within the previous 6 months</p> <p><u>N total at baseline:</u> Total:= 103 Intervention: = 52 Control: N = 51</p> <p><u>Important characteristics:</u> Age, mean (SD): I: 51.8 y (11.7) C: 50.3 y (12.4)</p> <p>Sex, n/N (%) male: I: 27/52 (51.9%) C: 27/51 (52.9%)</p> <p>WHO clinical scale: 3: I: 17/52 (32.7) C: 17/51 (33.3) 4: I: 35/52 (67.3) C: 34/51 (66.7)</p> <p>Groups were comparable at baseline.</p>				<p>Respiratory support I: 2/52 (3.8 %) C: 4/51 (7.8%) P=0.66</p> <p>Safety <u>adverse effects</u> (Supplemental Table S1)</p> <p>Virological outcomes Not reported</p>	
Tardif, 2021	<p><u>Type of study:</u> phase 3, double-blinded, adaptive, placebo-controlled, multicentre trial</p> <p><u>Setting:</u> community-based in 6 countries, between March 23 and December 22, 2020</p> <p><u>Country:</u></p>	<p>Community-treated patients with COVID-19</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> age ≥ 40 y diagnosis of COVID-19 within 24 h of enrolment (confirmed by PCR, or an epidemiological link with a household member who had a positive nasopharyngeal test result for patients with symptoms compatible with COVID-19, or a clinical algorithm in a symptomatic 	Orally administered colchicine (0,5 mg twice per day for the first 3 days and then once per day for 27 days thereafter)	Placebo	<p><u>Length of follow-up:</u> 30 days</p> <p><u>Loss-to-follow-up:</u> I: 78/2235 (3.5%) <i>Reasons: 35 patients did not take colchicine, 33 withdrew consent, 5 died, 4 were lost to follow-up, and 1 was admitted to hospital and intubated</i></p>	<p>A pre-specified subgroup analysis was performed for patients with PCR confirmed COVID-19.</p> <p>Clinical outcomes Mortality <u>Composite of death or hospitalisation for COVID-19 within 30 days</u> I: 104/2235 (4.7%) C: 131/2253 (5.8%) OR 0.79 (95%CI: 0.61-1.03)</p> <p><u>Death within 30 days</u></p>	<p><u>Definitions:</u> * high-risk characteristics were defined as: age ≥ 70 y, BMI ≥ 30 kg/m², diabetes, uncontrolled hypertension (SBP ≥ 150 mm Hg), known respiratory disease, known heart failure, known coronary disease, fever ≥ 38.4°C within the last 48 h, dyspnoea at time of presentation, bicytopenia, pancytopenia, or combination of high neutrophil and low lymphocyte counts</p> <p><u>Remarks:</u> The study was stopped when 75% of the planned patients were recruited</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Brazil, Canada, Greece, South Africa, Spain, and the USA</p> <p><u>Source of funding:</u> The Government of Quebec, the Bill & Melinda Gates Foundation, the National Heart, Lung, and Blood Institute of the US National Institutes of Health, the Montreal Heart Institute Foundation, the NYU Grossman School of Medicine, the Rudin Family Foundation, and philanthropist Sophie Desmarais</p> <p><u>Conflicts of interest:</u> Conflicts of interest were transparently and extensively reported. Most importantly, one author's institution has submitted a pending patent for a method of treating a coronavirus infection using colchicine; the author has waived</p>	<p>patient without an obvious alternative cause)</p> <ul style="list-style-type: none"> not currently treated in hospital and not under immediate consideration for hospital treatment ≥ 1 high-risk characteristic* <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> inflammatory bowel disease or chronic diarrhoea or malabsorption pre-existent progressive neuromuscular disease eGFR < 30 mL/min per 1.73 m² severe liver disease current treatment with colchicine current chemotherapy for cancer history of substantial sensitivity to colchicine <p><u>N total at baseline:</u> Randomized: N = 4506 Included: N = 4488</p> <p>Intervention: N = 2235 Control: N = 2253</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 53 y (47-61) C: 54 y (47-61)</p> <p>Sex, n/N (%) male: I: 997/2235 (44.6%) C: 1070/2253 (47.5%)</p> <p>Groups were comparable at baseline.</p>			<p>Control: 85/2253 (3.8%) <i>Reasons: 21 patients did not take placebo, 47 withdrew consent, 9 died, and 8 were lost to follow-up</i></p>	<p>I: 5/2235 (0.2%) C: 9/2253 (0.4%) OR 0.56 (95%CI: 0.19-1.67)</p> <p>Duration of hospitalization <u>Hospitalisation for COVID-19 within 30 days</u> I: 101/2235 (4.5%) C: 128/2253 (5.7%) OR 0.79 (95%CI: 0.60-1.03)</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p>Respiratory support <u>Mechanical ventilation</u> I: 11/2235 (0.5%) C: 21/2253 (0.9%) OR 0.53 (95%CI: 0.25-1.09)</p> <p>Safety <u>Serious and non-serious adverse events</u> Any SAE: I: 108/2195 (4.9%); C: 139/2217 (6.3%)</p> <p>Pneumonia SAE: I: 63/2195 (2.9%); C: 92/2217 (4.1%)</p> <p>Pulmonary embolism: I: 11/2195 (0.5%); C: 2/2217 (0.1%)</p> <p>Deep venous thrombosis: I: 0/2195 (0%); C: 0/2217 (0%)</p> <p>Myocardial infarction: I: 0/2195 (0%); C: 1/2217 (< 0.1%)</p>	<p>and had completed the 30 day follow-up.</p> <p><u>Authors conclusion:</u> In community-treated patients including those without a mandatory diagnostic test, the effect of colchicine on COVID-19-related clinical events was not statistically significant. Among patients with PCR confirmed COVID-19, colchicine led to a lower rate of the composite of death or hospital admission than placebo.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	his rights and does not stand to benefit financially if colchicine becomes used as a treatment for COVID-19.					Dehydration SAE: I: 3/2195 (0.1%); C: 6/2217 (0.3%) Any trial medication-related AE: I: 532/2195 (24.2%); C: 344/2217 (15.5%) Gastrointestinal AE: I: 524/2195 (23.9%); C: 328/2217 (14.8%) Gastrointestinal SAE: I: 6/2195 (0.3%); C: 3/2217 (0.1%) Diarrhoea AE: I: 300/2195 (13.7%); C: 161/2217 (7.3%) Nausea AE: I: 43/2195 (2.0%); C: 47/2217 (2.1%) Gastrointestinal haemorrhage AE: I: 1/2195 (< 0.1%); C: 0/2217 (0%) Rash AE: I: 4/2195 (0.2%); C: 13/2217 (0.6%) Virological outcomes <u>Viral clearance</u> Not reported.	
Lopes, 2021	<u>Type of study:</u> Randomized, doubleblinded, placebo controlled clinical trial <u>Setting:</u> Single-center; April to 30 August 2020	Hospitalized patients with moderate or severe COVID-19 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> hospitalized with moderate or severe COVID-19 diagnosed by RT-PCR and lung CT scan involvement compatible with COVID-19 pneumonia; ≥ 18 years; 	Colchicine 0.5 mg thrice daily for 5 days, then 0.5 mg twice daily for 5 days. If body weight ≥ 80 kg, the first dose was 1.0 mg. Whether a patient had chronic kidney	The institutional treatment for COVID-19 (azithromycin 500 mg od for up to 7 days, hydroxychloroquine 400 mg td for 2 days,	<u>Length of follow up:</u> Until discharge, laboratory tests until day 7 if discharge did not happen before. <u>Loss to follow-up:</u> I: 1/36 (2.7%) Reason: ICU admission I: 1/36 (2.7%)	Mortality <u>Death:</u> I: 0 C: 2 (6%) Hospitalization <u>Incidence hospitalisation</u> Day 7 I: 42% C: 72%	<u>Definitions:</u> <ul style="list-style-type: none"> Requirement of oxygen supply: measure of SatO2 ≤92% at rest. Criteria for discharging patients from the hospital: absence of dyspnoea and SatO2 >92%, both for at least 48 consecutive hours.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Country:</u> Brazil</p> <p><u>Source of funding:</u> FAPESP grants, CNPq and CAPES grants</p>	<ul style="list-style-type: none"> • Body weight > 50 kg; • normal levels of serum Ca²⁺ and K⁺; • QT interval <450 ms at 12 derivations ECG (according to the Bazett formula) • Negative serum or urinary β-HCG if woman under 50. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Mild form of COVID-19 or in need for ICU admission; • diarrhoea resulting in dehydration; • known allergy to colchicine; • diagnosis of porphyria, myasthenia gravis or uncontrolled arrhythmia at enrolment; • pregnancy or lactation; • metastatic cancer or immunosuppressive chemotherapy; • regular use of digoxin, amiodarone, verapamil or protease inhibitors; • chronic liver disease with hepatic failure; • inability to understand the Consent Form. <p><u>N total at baseline:</u> N = 75 Intervention: 36 Control: 36</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 54.5 (42.5–64.5) C: 55.0 (42.0–67.0) Sex, n/N (%) male: I: 19/36 (53) C: 14/36 (39%)</p>	<p>disease dose was reduced to 0.25 mg thrice daily for 5 days, then 0.25 mg td for 5 days, no matter the body weight.</p> <p>All patients received institutional treatment for COVID-19 (see control).</p>	<p>then 400 mg od for up to 8 days and unfractionated heparin 5000 UI thrice daily until the end of hospitalization).</p> <p>Methylprednisolone 0.5 mg/kg/day for 5 days could be added if the need for supplemental oxygen was 6 L/min or more.</p>	<p>Reason: ICU admission</p>	<p>Day 10 I: 9% C: 39%</p> <p><u>Duration of hospitalization</u> (days, median (IQR)) I: 7.0 (5.0–9.0) C: 9.0 (7.0–12.0)</p> <p><u>ICU admission</u> (n/N) I: 2/36 C: 4/36</p> <p>Treatment was continued 1 patient in each group.</p> <p><u>Duration of treatment before ICU admission:</u> I: 2, C: 3 days</p> <p><u>Length of stay in ICU</u> (variable unclear) I: 12, C: 11 days</p> <p><u>Time of hospitalisation</u> (variable unclear) I: 23, C: 26 days</p> <p>Need for respiratory support</p> <p><u>Time to discontinuation of supplemental oxygen, median (IQR)</u> I: 4.0 days (2.0–6.0) C: 6.5 days (4.0–9.0).</p> <p><u>Need for supplemental oxygen</u> Day 2, I: 67% C: 86% Day 7 I: 9% C: 42%</p> <p>Adverse events AST transient elevation (n (%)) C: 4 (11) C: 3 (8)</p>	<p><u>Remarks:</u> Data on laboratory markers on day 2 and day 4 are also reported. A first interim analysis for the 30th randomized patient revealed significant differences between the groups for the primary endpoints, so they resumed the enrolment up to 38 patients instead of 60 patients. For this new interim analysis the difference resulted sustained.</p> <p><u>Authors conclusion:</u> Patients who received colchicine in this randomised, double-blinded, placebo-controlled clinical trial presented better evolution in terms of the need for supplemental oxygen and the length of hospitalisation. Serum CRP was a laboratory marker of clinical improvement. Colchicine was safe and well tolerated.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>Other Medication:</p> <p>Hydroxychloroquine (n (%)) I: 36 (100%) C: 36 (100%)</p> <p>Azithromycin (n (%)) I: 36 (100%) C: 36 (100%)</p> <p>Unfractionated heparin (n (%)) I: 36 (100%) C: 36 (100%)</p> <p>Methylprednisolone(n (%)) I: 25 (69%) C: 24 (67%)</p> <p>Respiratory support:</p> <p>Without supplemental oxygen I: 1 (3%) C: 4 (11%)</p> <p>On oxygen support (n (%)), (L/min; median (IQR)) I: 28 (78%), (3; 2.0–4.0) C: 24 (67%), (3; 2.0–3.5)</p> <p>On high flow I: 7 (19%) C: 8 (22%)</p> <p>Mechanical ventilation I: 0 C: 0</p> <p>Groups comparable at baseline.</p>				<p>ALT transient elevation (n (%)) I: 5 (14) C: 5 (14)</p> <p>Nausea/vomiting (n (%)) I: 2 (6) C: 4 (11)</p> <p>Abdominal pain (n (%)) I: 4 (11) C: 4 (11)</p> <p>New or worsened diarrhoea (n (%)) I: 6 (17) C: 2 (6)</p> <p>Nosocomial pneumonia (n (%)) I: 3 (8) C: 5 (14)</p> <p>Arrhythmia (n (%)) I: 0 C: 0</p> <p>QT interval at day 3 (ms; median (IQR)) I: 408 (392–415) C: 405 (388–406)</p> <p>QT interval variation (ms; median (IQR)) I: 22 (9–29) C: 28 (13–35)</p> <p>Also reported: laboratory parameters; Figure 4 and online supplemental figures 1 and 2 show the temporal variations of serum CRP and LDH and peripheral blood relation neutrophil to lymphocyte, respectively, from day 0 to day 7.</p>	
Deftereos, 2020	<p><u>Type of study:</u> RCT</p> <p><u>Setting:</u></p>	<p><u>Inclusion criteria:</u> - Patients ≥ 18 year, with SARS-CoV-2 infection (confirmed with</p>	<p><u>3 weeks of colchicine administration:</u> 1.5-mg loading dose followed by 0.5mg after 60 min,</p>	Standard medical treatment:	<p><u>Length of follow-up:</u> Not mentioned</p> <p><u>Loss-to-follow-up:</u></p>	<p><u>Primary end points:</u> <u>Biochemical phase:</u> <u>(1) Maximum high-sensitivity cardiac</u></p>	<p><u>Remarks:</u> - Concentrations of medication used as standard treatment are not mentioned - Length of follow up is not mentioned</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>105 COVID-19 patients were randomized: either standard medical treatment + Colchicine, or standard medical treatment</p> <p><u>Country:</u> 16 tertiary hospitals in Greece</p> <p><u>Source of funding:</u> ELPEN Pharmaceuticals, Acarpia Pharmaceuticals, and Karian Pharmaceuticals.</p>	<p>rPCR), ≥ 37.5 °C body temperature</p> <p>- 2 or more of the following: sustained coughing, sustained sore throat, anosmia and/or ageusia, fatigue and/or tiredness, and arterial oxygen partial pressure lower than 95mmHg on room air</p> <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> - Pregnancy or lactation - Known hypersensitivity to colchicine - Known hepatic failure, estimated glomerular filtration rate under 20 mL/min/1.73m², corrected QT interval of 450 milliseconds or higher - Clinical assessment indicating inevitable ventilatory support in next 24 hours <p><u>N total at baseline:</u> N = 105 Intervention: 55 Control: 50</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 63 (55 to 70) C: 65 (54 to 80) 95% CI: 1.5 (-5 to 8)</p> <p>Sex, n/N (%) male: I: 31/55 (56.4%) C: 30/50 (60.0%)</p> <p><u>Groups comparable at baseline?</u> Yes</p>	<p>maintenance doses of 0.5 mg twice daily</p> <p><u>Plus standard medical treatment:</u> Concentrations are not mentioned, only how many patients received which treatment:</p> <ul style="list-style-type: none"> - Chloroquine or Hydroxychloroquine: 55 (100%) - Azithromycin: 51 (92.7%) - Lopinavir or ritonavir: 14 (25.5%) - Tocilizumab: 2 (3.6%) 	<p>Concentrations are not mentioned, only how many patients received which treatment:</p> <ul style="list-style-type: none"> - Chloroquine or Hydroxychloroquine: 48 (96.0%) - Azithromycin: 46 (92.0%) - Lopinavir or ritonavir: 19 (38.0%) - Tocilizumab: 2 (4.0%) 	None	<p><u>troponin level, Median (IQR)</u> <u>Colchicine:</u> 0.0112 ng/mL <u>Control:</u> 0.008 ng/mL P = 0.38 95% CI: 0.0017 (-0.0015 to 0.0049)</p> <p><u>(2) Time for C-reactive protein to reach more than 3 times the upper reference limit</u> Not reported, as meaningful comparison was not possible, as 68,6% of patients already had CRP values higher than that at baseline</p> <p><u>Clinical phase:</u> <u>(1) Time to deterioration by 2 points on a 7-grade clinical status scale</u> <u>Colchicine:</u> 1/52 (1.8%) <u>Control:</u> 7/50 (14%) P = 0.02</p> <p><u>Secondary end points:</u> <u>(1) The percentage of participants requiring mechanical ventilation</u> <u>Colchicine:</u> 1/52 (1.8%) <u>Control:</u> 6/50 (12%)</p> <p><u>(2) All-cause mortality 10 day survival is reported:</u> <u>Colchicine:</u> 51/52 97% <u>Control:</u> 42/50 83% P = 0.03</p>	<p>- Not all outcomes are reported</p> <p><u>Authors conclusion:</u></p> <ul style="list-style-type: none"> - Authors state that patients with colchicine showed significantly improved time to clinical deterioration. - However, results should be treated with caution due to open-label design of the study and relatively small number of events

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						(3) <u>Number, type, severity, and seriousness of adverse events.</u> Vomiting, Diarrhoea requiring study drug stop, nausea, abdominal pain, muscle spasm and headache were reported, but similar over groups. Only diarrhoea was significantly different: <u>Colchicine: 25/55 (45,5%)</u> <u>Control: 9/50 (18%)</u> P= 0,003	
17.3. Fostamatinib							
NA	NA	NA	NA	NA	NA	NA	NA
17.4. Imatinib							
Aman, 2021	<p><u>Type of study:</u> Randomised, double-blind, placebo-controlled, clinical trial.</p> <p><u>Setting:</u> 13 large academic and non-academic teaching hospitals.</p> <p><u>Country:</u> The Netherlands.</p> <p><u>Source of funding:</u> Amsterdam Medical Center Foundation, Nederlandse Organisatie voor Wetenschappelijk Onderzoek/ ZonMW, and the European Union Innovative</p>	<p><u>Hospitalized patients with SARS-CoV-2 infection</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients 18 years or older; • Admitted to hospital with SARS-CoV-2 infection (confirmed with an RT-PCR test); • Required supplemental oxygen to maintain a peripheral oxygen saturation or greater than 94%. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Pre-existing severe pulmonary disease; • Pre-existing heart failure (a left ventricular ejection fraction of <40%); • Active treatment of a haematological or non-haematological malignancy within 12 months before enrolment; • Presence of cytopenia; 	<p>Imatinib</p> <p>A loading dose of 800 mg imatinib on day 0, followed by 400 mg once daily on days 1–9.</p>	<p>Placebo</p> <p>Patients in the placebo group received placebo tablets in a similar dosing scheme.</p> <p>*Standard of care not mentioned nor described.</p>	<p><u>Length of follow-up:</u> Up to 28 days.</p> <p><u>Loss-to-follow-up:</u> Intervention: N = 8 (4.1%)</p> <p>Reasons: N = 5 withdrew consent; N = 1 transferred to another hospital; N = 2 due to medication error.</p> <p>Control: N = 7 (3.4%)</p> <p>Reasons: N = 6 withdrew before first dose; N = 1 transferred to another hospital</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality (28 days)</u> I: 15/197 (8%) C: 27/188 (14%) Unadj. HR 0.51 (95% CI 0.27 to 0.95) P=0.034 Adj. HR 0.52 (95% CI 0.26 to 1.05) P=0.068 OR 0.49 (95% CI 0.25 to 0.96)</p> <p><u>Duration of hospitalization</u> <i>Admission to ICU during 28-day study period</i> I: 30/197 (20%) C: 33/188 (18%)</p> <p><i>Duration of ICU stay, median (IQR)</i> I: 8 days (5 to 13) C: 15 days (7 to 21) P=0.025</p>	<p><u>Definitions:</u> Grade 3 adverse events: not specified. Grade 4 adverse events: not specified.</p> <p><u>Remarks:</u> -</p> <p><u>Authors conclusion:</u> In conclusion, this randomised, placebo-controlled trial showed that imatinib does not reduce the time to discontinuation of supplemental oxygen and mechanical ventilation in hospitalised patients with COVID-19. However, the reduction in mortality (even if attenuated after correction for baseline imbalances) and duration of mechanical ventilation indicates that imatinib might confer clinical benefit in patients with COVID-19, and provide a rationale for further studies.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>Medicines Initiative 2.</p> <p>The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.</p> <p><u>Conflicts of interest:</u> JA and AVN are inventors on a patent (WO2012150857A 1; 2011) covering protection against endothelial barrier dysfunction through inhibition of the tyrosine kinase abl-related gene (arg). JA reports serving as a non-compensated scientific advisor for Exvastat. All other authors declare no competing interests.</p>	<ul style="list-style-type: none"> Concomitant treatments with medication known to strongly interact with imatinib. <p><u>N total at baseline:</u> N = 385 Intervention: 197 Control: 188</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 64 y (57-73) C: 64 y (55-74)</p> <p>Sex, n/N (%) male: I: 146/197 (74%) C: 118/188 (63%)</p> <p>Disease severity, mean (SD): Not reported > No differences in baseline laboratory measurements were observed between the two groups, suggesting similar disease severity at presentation.</p> <p>Groups comparable at baseline? Yes.</p>			<p><u>Incomplete outcome data:</u> None.</p>	<p><i>Duration of hospital admission, median (IQR)</i> I: 7 days (4 to 11) C: 6 days (3 to 11) P=0.51</p> <p><u>Time to symptom resolution</u> Not reported.</p> <p><u>Respiratory support</u> <i>Duration of mechanical ventilation, median (IQR)</i> I: 7 days (3 to 13) C: 12 days (6 to 20) P=0.0080</p> <p><i>Duration of mechanical ventilation for survivors only (post-hoc analysis), median (IQR)</i> I: 7 days (3 to 12) C: 12 days (6 to 25)</p> <p><i>Duration of oxygen supplementation, median (IQR)</i> I: 7 days (3 to 12) C: 5 days (3 to 11) P=0.23</p> <p><i>Intubated and mechanically ventilated patients who were admitted to ICU</i> I: 30/39 (77%) C: 26/33 (79%) Unadj. HR 1.07 (95% CI 0.63 to 1.80) P=0.814</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						<p><i>Time to discontinuation of supplemental oxygen and mechanical ventilation</i> Unadj. HR 0.95 (95% CI 0.76 to 1.20) P=0.69</p> <p>Safety <u>Adverse events</u> <i>Any adverse event (grade 3)</i> I: 156/197 (79%) C: 218/188 (116%) Total: 374/385 (97%)</p> <p><i>Any adverse event (grade 4)</i> I: 32/197 (16%) C: 42/188 (22%) Total: 74/385 (19%)</p> <p>*The full list of adverse events can be consulted in the original publication of the study.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported.</p>	
17.5. Leflunomide (immunosuppressive disease-modifying antirheumatic drug, DMARD)							
Wang, 2021	<p><u>Type of study:</u> Non-randomized pilot study.</p> <p><u>Setting:</u> Hu Bei Renmin Hospital in Wu han City.</p> <p><u>Country:</u> China.</p>	<p><u>Hospitalized adult patients.</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Patients 18 years or older; • Patients with radiologically confirmed COVID-19 pneumonia; • Patients who were transcriptase-polymerase chain reaction positive for SARS-CoV-2 for more than 28 days despite standard care; 	<p><u>Leflunomide</u></p> <p>Leflunomide was given at 30 mg/day to patients who were less than 64 years old, and 20 mg/ day to patients who were ≥65 years old. The treatment lasted for 14 days during the first phase. All patients who continued to be RTPCR-positive for SARS-</p>	<p><u>Standard of care</u></p> <p>Standard care was provided to all patients according to the guideline (National Health Commission of the People's</p>	<p><u>Length of follow-up:</u> 30 days.</p> <p><u>Loss-to-follow-up:</u> No loss to follow-up.</p> <p><u>Incomplete outcome data:</u> No incomplete outcome data.</p>	<p>Clinical outcomes <u>Mortality (28-30 day)</u> I: 0/15 (0%) C: 0/12 (0%)</p> <p><u>Discharge rate at day 14, n/N (%)</u> I: 11/15 (73.3%) C: 1/12 (8.3%) P=0.001</p>	<p><u>Definitions:</u> -</p> <p><u>Remarks:</u> - In order to further confirm the efficacy of leflunomide in enhancing the clearance of SARS-CoV-2, a sensitivity analysis was performed with the elimination of the patients whose viruses were cleared on day one after the enrollments. Based on this principle, four patients in the</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p><u>Source of funding:</u> This work was supported by the COVID-19 Emergency Tackling Research Project of Shandong University (Grant No. 2020XGA 01).</p> <p><u>Conflicts of interest:</u> The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest</p>	<ul style="list-style-type: none"> • Pneumonia confirmed by chest imaging; • Patients with an oxygen saturation of 94% or higher on room air PaO₂/FiO₂ ratio >300 mg Hg to the fraction of the inspired oxygen. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Pregnancy; • A history of liver disease; • An alanine aminotransferase level five times higher than the upper normal limit (50 U/L); • Stage 4 chronic kidney disease. <p><u>N total at baseline:</u> N = 27 Intervention: N=15 Control: N=12</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 65 y (43 to 70) C: 62 y (46 to 9.5) P=0.64</p> <p>Age <50, n/N (%): I: 4/15 (27%) C: 3/12 (25%) P=1.00</p> <p>Age 50 to 70, n/N (%): I: 6/15 (40%) C: 6/12 (50%) P=0.71</p> <p>Age >70, n/N (%): I: 5/15 (33%) C: 3/12 (25%) P=0.70</p> <p>Sex, n/N (%) male:</p>	CoV-2 by day 14 received leflunomide for 14 days as the second phase.	Republic of China, 2020) including supplemental oxygen and supportive care, as well as concurrent therapy with hydroxychloroquine, interferon- α , anti-human immunodeficiency virus drugs (lopinavir/ritonavir), or antiinfluenza drugs (arbidol, oseltamivir) was allowed		<p>Discharge rate at day 30, n/N (%) I: 15/15 (100%) C: 8/12 (66.7%)</p> <p><u>Median hospital stay, median (IQR)</u> I: 11 (7 to 19) days C: 24 (IQR not reported) days P<0.001</p> <p><u>Time to symptom resolution</u> not reported</p> <p><u>Respiratory support</u> not reported</p> <p>Safety <u>Adverse events, n/N (%)</u> I: 11/15 (73.3%) C: 10/12 (83.3%)</p> <p><u>Treatment Emergent Adverse Events, n/N (%)</u> I: 6/15 (40%) C: 3/12 (25%) *The most frequent TEAEs were hyperlipidaemia (20%), leukopenia (20%), and neutropenia (13.3%) in the intervention group, and hyperlipidaemia (16.7%) and hypoalbuminemia (8.3%) in the control group.</p> <p><u>Serious adverse events, n/N (%)</u> I: 0/15 (0%) C: 0/12 (0%)</p>	<p>leflunomide group (Grp 2) and one patient in standard care (grp 1) were eliminated. Therefore, 11 patients were left in each group for analysis. The results of the sensitivity analysis showed in Supplementary Figures S1–S3. The sensitivity analysis results are consistent with the overall primary endpoint results.</p> <p><u>Authors conclusion:</u> In conclusion, this pilot study has demonstrated that leflunomide has an acceptable safety profile and may be effective in enhancing SARS-CoV-2 clearance in refractory COVID-19 patients. Based on the efficacy and safety profiles of leflunomide on COVID-19 from this pilot study, a large sample size and randomized controlled trial is warranted.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		<p>I: 10/15 (67%) C: 4/12 (33%) P=0.13</p> <p>Mean duration of symptom onset or SARS-CoV-2 positivity before enrolment (IQR), days I: 47 (44 to 49) C: 42.5 (38 to 51.5) P=0.66</p> <p>Severe COVID-19 on admission, n/N (%): I: 6/15 (40%) 6/12 (50%) P=0.71</p> <p>Mild/common COVID-19 on admission, n/N (%): I: 9/15 (60%) C: 6/12 (50%) P=0.71</p> <p>Groups comparable at baseline? Yes.</p>				<p>Virological outcomes</p> <p><u>SARS-CoV-2 clearance rate at 14 days, n/N (%)</u> I: 12/15 (80%) C: 2/12 (16.7%) P=0.002</p> <p><u>Median time to SARS-CoV-2 clearance, median (IQR)</u> I: 6.0 (1 to 12) days C: 2/12 (16.7%)</p> <p><u>Median time to SARS-CoV-2 clearance after crossover, median (range; IQR)</u> 9 days (range 0 to 14; IQR 1 to 13)</p> <p><u>Virus clearance at day 30, n/N (%)</u> I: 15/15 (100%) C: 11/12 (91.7%)</p> <p>Three patients remained RT-PCR positive for SARS-CoV-2 despite 2 weeks of leflunomide therapy continued to receive leflunomide and they achieved SARS-CoV-2 clearance on days 15, 16, and 19, respectively.</p> <p>Nine patients receiving standard care remained RT-PCR positive for SARS-CoV-2 on day 14 postenrollment and were crossed over to receive leflunomide.</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Wang, 2020b	<p><u>Type of study:</u> Randomized Controlled Clinical Trial</p> <p><u>Setting:</u> Hospital</p> <p><u>Country:</u> China</p> <p><u>Source of funding:</u> Unclear (Funding agencies had no role in the study design and clinical medications; collection, analysis and interpretation of the data; preparation, written, review, or approval of the manuscript.)</p>	<p><u>Inclusion criteria:</u> (1) aged 18-70 years with a diagnosis of COVID-19 conforming to the Chinese Guidelines; (2) hospitalized for prolonged post-symptomatic viral shedding; (3) able to orally take medication; (4) non-pregnant women; (5) effective contraception for 7 days after taking the last medication.</p> <p><u>Exclusion criteria:</u> (1) presence of any condition that would not allow the protocol to be followed (eg known allergy to leflunomide, use of medications that are contraindicated with leflunomide and that could not be replaced or stopped during the trial period; (2) pregnant or breast-feeding; (3) known other serious comorbidities (eg liver, cardiovascular, cerebrovascular diseases, severe renal insufficiency or advanced cancer); (4) received interferon before enrolment; (5) unwilling to participate in the study.</p> <p><u>N total at baseline:</u> N = 50 Intervention: 26 Control: 24</p> <p><u>Important characteristics:</u> Age, mean (IQR): I: 56.0 (43.0 – 67.3) C: 55.5 (47.8 – 66.5) P=0.836</p> <p>Sex, 22/48 (46%) male: I (male:female): 13:11</p>	Leflunomide (50 mg, q12h, three consecutive times, orally; then 20 mg, once a day for 8 days; a total course of 10 days) plus nebulized IFN α -2a (3 million IU each time, adding 2 ml of sterilized water, atomization inhalation twice daily for 10 days)	Nebulized IFN α -2a alone for 10 days.	Patients were followed-up by primary health-care facilities and were re-tested for viral nucleic acid on days 7 and 14. After that, they stayed in their homes for a second isolation period of 14 days, and were then retested for viral nucleic acid by the end of this quarantine period.	<p><u>Conversion to severe case after enrolment (n (%)):</u> Intervention: 0 (0) Control: 0 (0)</p> <p><u>Death after enrolment (n (%)):</u> Intervention: 0 (0) Control: 0 (0)</p> <p><u>Duration of viral shedding after enrolment, day (median (IQR)):</u> Intervention: 8.0 (6 -15.5) Control: 11.5 (6.3 – 16.5)</p> <p><i>Patients with initial cough and expectoration, day:</i> Intervention: 11 (7.0 – 16.5) Control: 16 (7.5 – 38.8)</p> <p><u>Length of hospital stay, day (median (IQR)):</u> Intervention: 29.0 (19.3 – 47.3) Control: 33.0 (29.3 – 42.8)</p> <p><u>Side effects after enrolment, (n (%)):</u> Intervention: 10 (41.7) Control: 4 (16.7)</p> <p><u>The following outcomes were also described:</u> symptoms, laboratory results and abnormal laboratory results.</p>	<p><u>Remarks:</u> Due to few new COVID-19 patients in Wuhan, China since early March 2020, only convalescing patients with prolonged post-symptomatic viral shedding rather than those in the acute stage were enrolled in the study.</p> <p>Enrolled patients with five consecutively negative nucleic acid tests were considered as having “true negative” results (two times during hospitalization, two times during the first isolation, and one time at the end of the second quarantine).</p> <p>Definition of prolonged post-symptomatic viral shedding: laboratory confirmed patients with COVID-19 who continued to have nasopharyngeal RT-PCR positivity at least.</p> <p><u>Authors conclusion:</u> In COVID-19 patients with prolonged PCR positivity, no benefit in terms of the duration of viral shedding was observed with the combined treatment of leflunomide and IFN α-2a beyond IFN α-2a alone.</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
		C (male:female): 9:15 Groups comparable at baseline except for expectoration and cough.					
17.6. Mycobacterium W							
Sehgal, 2021	<p><u>Type of study:</u> Exploratory, multicentre, randomised, double-blind, two parallel arm, comparative controlled trial.</p> <p><u>Setting:</u> ICU's or high dependency units of four tertiary care centres in India.</p> <p><u>Country:</u> India</p> <p><u>Source of funding:</u> This study was supported by Council of Scientific and Industrial Research–New Millennium Indian Technology Leadership Initiative number 5/258/93/2020-NMITLI</p> <p><u>Conflicts of interest:</u> None declared.</p>	<p><u>Hospitalised critically COVID-19 patients</u></p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> >18 years old; Positive for SARS-CoV-2 RNA on RT-PCR; Saturation of <94% on ambient air and infiltrates on a chest radiograph; Subjects of childbearing age were included if they agreed to take effective contraception measures during the study period. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Pregnancy or breastfeeding subjects; Prior cardiorespiratory arrest; Chronic liver disease; Haemodialysis dependent chronic kidney disease; Enrolment in another trial; Active malignancy; Subjects unwilling to provide consent. <p><u>N total at baseline:</u></p>	Single daily dose of 0.3 mL Mw (in aliquots of 0.1 mL at three different sites) intradermally in the deltoid region for three consecutive days	Single daily dose of 0.3 mL matching placebo (in aliquots of 0.1 mL at three different sites) intradermally in the deltoid region for three consecutive days	<p><u>Length of follow up:</u> 28 days after randomisation</p> <p><u>Loss to follow-up:</u> N=2 withdrew consent. However, both of these subjects were included in the primary and safety analysis.</p>	<p><u>Clinical outcomes</u></p> <p><u>Mortality (28 days)</u> I: 4/22 (18.1%) C: 5/20 (25%)</p> <p><u>Duration of hospitalization</u> <i>ICU length of stay, median (IQR) days</i> I: 8 (4 to 11) days C: 8 (4 to 13) days P=0.84</p> <p><i>Hospital length of stay, median (IQR) days</i> I: 12 (9.5 to 16) days C: 12 (9 to 22) days P=0.92</p> <p><u>Time to symptom resolution</u> <i>Time to reduction by one-point on seven-point ordinal scale, median (IQR) days</i> I: 9 (5 to 10) days C: 7 (3 to 10) days P=0.52</p> <p><i>Time to reduction by two-point on seven-point ordinal scale, median (IQR) days</i> I: 12 (11 to 14) days C: 11 (8 to 24) days P=0.85</p> <p><u>Respiratory support</u></p>	<p><u>Definitions:</u> seven-point ordinal scale consisting of the following:</p> <ul style="list-style-type: none"> category 1: not hospitalised with the resumption of normal activities; category 2: not hospitalised but unable to resume normal activities; category 3: hospitalised but not requiring supplemental oxygen; category 4: hospitalised and requiring supplemental oxygen (nasal cannula, venturi mask, or non-rebreathing mask); category 5: hospitalised and requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; category 6: hospitalised and requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and category 7: death. <p><u>Remarks:</u> -</p> <p><u>Author's conclusion:</u> In conclusion, the use of immunomodulator Mw in addition to standard care resulted in early clinical improvement compared to standard care alone. Larger multicentre trials are required to confirm our findings</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	clinicaltrials.gov NCT04347174	<p>N = 42 Intervention: N = 22 Control: N = 20</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 59 (52 to 62.5) C: 51 (45 to 65) P=0.16</p> <p>Sex, n/N (%) male: I: 13/22 (59%) C: 16/20 (80%) P=0.19</p> <p>Disease severity, defined by score on the ordinal scale at baseline <i>4; hospitalized, requiring oxygen supplementation</i> I: 14/22 (63.6%) C: 15/20 (75%)</p> <p><i>5: hospitalized, requiring high-flow oxygen devices or NIV</i> I: 7/22 (31.8%) C: 5/20 (25%)</p> <p><i>6: hospitalized, receiving invasive MV or ECMO</i> I: 1/22 (4.5%) C: 0/20 (0%)</p> <p>Groups comparable at baseline? Yes.</p>				<p><i>Days on vasopressor drug, median (IQR) days</i> I: 0.7 (0.6 to 2.1) C: 1 (0.4 to 2.1) P=0.15</p> <p><u>Clinical status (7-point scale) on day 14</u> <i>1: not hospitalized with resumption of normal activities</i> I: 13/22 (59.1%) C: 8/20 (40%)</p> <p><i>2: not hospitalized, but unable to resume normal activities</i> No data.</p> <p><i>3: hospitalized, not requiring supplemental oxygen</i> I: 2/22 (9%) C: 4/20 (20%)</p> <p><i>4: hospitalized, requiring oxygen supplementation</i> I: 3/22 (13.6%) C: 3/20 (15%)</p> <p><i>5: hospitalized, requiring high-flow oxygen devices or NIV</i> I: 1/22 (4.5%) C: 0/20 (0%)</p> <p><i>6: hospitalized, receiving invasive MV or ECMO</i> I: 1/22 (4.5%) C: 1/20 (5%)</p> <p><i>7: death</i> I: 2/22 (9%)</p>	

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
						C: 4/20 (5%) Safety <u>Adverse events</u> The study found no safety concerns associated with the study drug, based on the assessments of organ dysfunction, vital signs, laboratory parameters, and local site reaction at the site of the injection. Virological outcomes <u>Viral clearance</u> <i>Time to PCR negativity, median (IQR) days</i> I: 9 (7 to 15.5) days C: 7.5 (5 to 14) days P=0.53	
17.7. Tractolimus							
Solanich, 2021	See evidence table of Solanich (2021) by Methylprednisolone.						
18. SSRI							
18.1. Fluvoxamine							
Seo, 2022	<u>Type of study:</u> single-blind, randomized, placebo-controlled trial <u>Setting:</u> Hospitalized patients, enrolled from January 15, 2021 to February 08, 2021 <u>Country:</u> Seoul, Korea <u>Source of funding:</u>	Hospitalized patients with mild to moderate COVID-19 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • ≤18 years • Laboratory-confirmed (RT-PCR) SARS-CoV-2 infection • Symptoms ,7 days consistent with COVID-19 and a positive RT-PCR within 3 days of randomization <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Patients with severe medical comorbidities • Patients who were immunocompromised 	Fluvoxamine at a dose of 50 mg of fluvoxamine or on day 1, then an increased dose of 100 mg twice daily, as tolerated, until discharge from the hospital (about 10 days). Dosing reduction was allowed for tolerability reasons. After discharge from the hospital, participants in the fluvoxamine group received a 1-day open-label course of 50 mg of	placebo (ursodeoxycholate) on the same regime as the intervention group	<u>Length of follow-up:</u> 30 days <u>Incomplete outcome data & loss-to-follow-up:</u> Intervention: 7/26 (26.9%) discontinued intervention due to adverse events Control: 1/26 (3.8%) discontinued due to consent withdrawal	Clinical outcomes <u>Mortality</u> Not reported <u>Duration of hospitalization</u> Not reported <u>Time to symptom resolution</u> Not reported <u>(Non) Invasive respiratory support</u> Requiring of oxygen therapy to maintain SpO2≥94% I: 1/26 (3.8%)	Primary outcome: <ul style="list-style-type: none"> • Clinical deterioration Secondary outcome(s): <ul style="list-style-type: none"> • Secondary endpoints included all the categories of clinical deterioration described above as primary endpoints, and days to clinical deterioration. <u>Definitions:</u> Clinical deterioration defined by any of the following: (1) decrease in oxygen saturation (<94.0%) in room air [19]; (2) supplemental oxygen required in order to

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
	<p>This study was supported by a grant (grant number: 2021IL0042) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea.</p> <p><u>Conflicts of interest:</u> None to declare</p>	<ul style="list-style-type: none"> Patients who were referred to a hospital within 24 h after admission with evidence of the primary endpoint at the time of randomization Those who were referred to a hospital for other reasons without aggravation of COVID-19 <p><u>N total at baseline:</u> N = 52 Intervention: N=26 Control: N=26</p> <p><u>Important characteristics:</u> Age, median (IQR): I: 54.0 y (44.0-60.3) C: 51.5 y (42.0-59.3)</p> <p>Sex, n/N (%) male: I: 18/26 (69.2%) C: 13/26 (50%)</p> <p>Disease severity Defined as having pneumonia at admission I: 5/26 (19.2%) C: 3/26 (11.5%)</p> <p>Groups comparable at baseline? Yes</p>	fluvoxamine twice daily to taper out.			<p>C: 1/26 (3.8%)</p> <p>Safety <u>Serious adverse events</u> There was no serious adverse event in either group</p> <p>A detailed list of Adverse Events is provided in the article.</p> <p>Virological outcomes <u>Viral clearance</u> Not reported</p>	<p>maintain an oxygen saturation of 94% or more; (3) aggravation of pneumonia with dyspnea and increased infiltrate on chest X-ray, or minute respiratory rate over 25; (4) WHO clinical progression scale 4 or greater</p> <p><u>Remarks:</u> Since the incidence and severity of COVID-19 in Korea decreased rapidly, and the transfer rate from the CTC to a hospital due to clinical deterioration was lower than anticipated, the study was underpowered</p> <p><u>Authors conclusion:</u> In conclusion, this randomized, single-blind, placebo-controlled trial did not show that fluvoxamine was effective in preventing patients with mild to moderate COVID-19 from clinical deterioration. However, due to its small sample size, larger randomized trials are needed.</p>

Risk of bias table for intervention studies (randomized controlled trials and non-randomized controlled trials) and comparative trials.

Deze tabel geeft een overzicht van de kwaliteit van de studies naar medicamenteuze behandeling bij COVID-19. Op gestandaardiseerde wijze worden studie-eigenschappen, die mogelijk de studieresultaten vertekenen, weergegeven. De studies staan gerangschikt op middel en datum van publicatie.

In de onderstaande tabel is de risk of bias weergegeven van de studies geïncludeerd vanaf 3/2/2022:

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
1. Remdesivir							
Pan, 2022	Definitely yes Reason: "Once a hospital has obtained approval, electronic entry of patients who have given informed consent takes only a few minutes. At the end of it, the randomly allocated treatment is displayed on the screen and confirmed by electronic messaging."	Definitely yes Reason: Allocation displayed on screen after entry of patient in the system	Probably yes Reason: Unblinded trial (mortality: unlikely)	Probably yes Reason: Low rate of lost-to follow-up and reasons comparable between groups	Definitely yes Reason: Outcomes in clinical trial record correspond with the outcomes reported in the study	Probably yes Reason: The study appears to be free of other sources of bias	Low
2. Corticosteroids							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
2.1. Dexamethasone							
2.2. Hydrocortisone							
2.3. Inhaled corticosteroids (budesonide, ciclesonide)							
Agustí, 2022	Definitely yes Reason: Randomization (1:1) was made by a permuted-block method with a block size of multiple of 2 elements and was stratified by centre with an interactive web service.	Definitely yes Reason: Central allocation	Probably no Reason: No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding	Definitely yes Reason: Reasons for missing outcome data unlikely to be related to outcome	Probably no Reason: The study protocol is available and not all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	Definitely no Reason: The funder of the study (i.e. pharmaceutical company) had no role in study design, data analysis, data interpretation, and writing of the report. The steering committee stopped the study prematurely in April 2021.	HIGH Open-label trial. Lack of blinding might have biased the results for the primary outcome disease progression. This RCTs lacks statistical power because it had to be terminated prematurely.
2.4. Methylprednisolone							
3. Hydroxychloroquine							
4. Immunoglobulin							
4.1. Hyperimmunoglobulin							
4.2. Intravenous immunoglobulin							
4.3. Normal immunoglobulin							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
5. Convalescent plasma							
Sullivan, 2022	Definitely yes Participants were randomly assigned in a 1:1 ratio with the use of a central web-based system and a permuted block sequence.	Definitely yes Participants were randomly assigned in a 1:1 ratio with the use of a central web-based system and a permuted block sequence.	Probably yes Double-blind trial. Unclear whether data collectors, outcome assessors and data analysts were blinded.	Definitely no Loss to follow-up was more than 10%, but similar in both groups.	Definitely yes The primary outcome reported in the study protocol was reported in the paper. No prespecified secondary outcomes are reported here. In the subgroup analysis, all the subgroups were prespecified.	Probably yes No other biases. The trial sponsors did not contribute to the trial design, to the collection, analysis, and interpretation of data, or to the decision to submit the manuscript for publication.	Some concerns Multicenter, double-blind, randomised, controlled trial with adequate allocation process. Loss to follow-up was frequent (> 10%) and similar in both groups.
Song, 2022	Definitely yes Reason: The randomization scheme used computer generated lists performed by the clinical research center, stratified by center, with blocks of various sizes and performed through a centralized	Definitely yes Reason: Allocation concealment was ensured	Definitely no Reason: It is an open label study.	Definitely yes Reason: None of the participants was lost to follow-up.	Probably yes Reason: the outcome measure adverse effects is not mentioned in the results section.	Probably yes Reason: Disease severity at baseline is not reported.	Some concerns Open label trial

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	internet service to ensure allocation concealment.						
De Santis, 2022	Definitely yes Reason: Using a computer random number generator	Definitely yes Reason: Central allocation	Definitely no Reason: Participants and key study personnel were not blinded, and the nonblinding of others likely to introduce bias (open label)	Definitely yes Reason: No missing outcome data	Definitely yes Reason: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way	Probably yes Reason: The possible conflict of interest are not reported.	Some concerns Open label trial. Lack of blinding might have biased the results for some of the outcome measures other than all-cause mortality.
Alemany, 2022	Definitely yes A central web-based randomisation system with allocation concealment and no stratification to randomly assign participants was used.	Definitely yes A central web-based randomisation system with allocation concealment and no stratification to randomly assign participants was used.	Definitely yes Double-blind trial. Blood bank staff masked the investigational products with opaque tubular bags that covered the entire unit of plasma or saline solution and the infusion catheter. Finally, an unmasked study nurse, who was not involved in patient follow-up, administered the investigational	Definitely yes Loss to follow-up was less than 10% and similar between the groups.	Definitely yes All outcomes reported in the study protocol were reported in the paper.	Probably yes No other biases.	LOW Multicenter, double-blind, randomised, placebo-controlled trial with adequate allocation and blinding process. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
Bajpai, 2022	Definitely yes Reason: Stratified block randomisation (each block of 10) was done in the ratio of 1:1 with 200 patients in each of the treatment groups (ie, CP with standard medical therapy (SMT) as the intervention arm vs SMT only as control arm)	Definitely yes Reason: Allocation concealment was done using the 'Sequentially Numbered Opaque Sealed Envelopes' method.	Definitely no Reason: Open label.	Definitely yes Reason: no lost to follow-up	Definitely no Reason: Not all outcome measures described in the method section are also reported (i.e. adverse events)	Definitely no Reason: Open-label trial. Some of the percentages are not calculated correctly. When looking at the percentages only (i.e., mortality), the numbers distort the picture to the extent that a misinterpretation of the treatment effect can occur.	HIGH
6. Monoclonal antibodies							
6.1. Adalimumab							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
6.2. Antibody JS016							
Dong (2022)	Probably yes Reason: <i>"Patients were randomly assigned in a 1:1 ratio to receive standard care (control group) or 101 standard care plus a single intravenous infusion of JS016, stratified by sites and disease severity 102 at randomization (i.e., moderate or severe disease)."</i>	No information reported regarding allocation concealment.	Definitely no Reason: <i>"Fourth, the trial was not blinded so that the potential Hawthorne effect might 273 have influenced clinical practice and decision makin."</i>	Probably yes Reason: both groups exluded one participant after randomization.	Probably yes Reason: all predefined outcome measures were reported.	Probably yes Reason: not mentioned	Some concerns Reason: no blinding and unclear concealment of allocation.
6.3. Anti-granulocyte-macrophage colony-stimulating-factor (GM-CSF)							
Criner, 2022	Probably yes Reason: Randomization was performed using a	Probably yes Reason: Not reported	Probably yes Reason: The study is double-blind. The study pharmacist (and/or qualified	Definitely yes Reason: Lost to follow-up was infrequent and almost similar in both groups	Probably no Reason: All outcomes reported in the study protocol were reported in the paper.	Probably no Reason: Enrollment was halted early for futility based on an interim analysis	Some concerns Reason: unclear concealment of allocation , enrollment was halted early for

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
	validated interactive voice/web response system and stratified based on two categories of patient clinical status at baseline: (1) mild ARDS or lesser extent of hypoxemia, and (2) moderate or severe ARDS.		pharmacy staff member), and the bioanalytical laboratory analysts was unblinded to study treatment.		The subgroup analyses are subjected to Type I errors.		futility based on an interim analysis
6.4. Bamlanivimab (INN, codenamed LY-CoV555, neutralizing monoclonal antibody)							
6.5. Bamlanivimab and Etesevimab (LY-CoV016; recombinant fully human monoclonal neutralizing antibody; together is combination of two monoclonal antibodies)							
Chen, 2022	Definitely yes Participants were centrally randomized using an interactive web response system.	Definitely yes Participants were centrally randomized using an interactive web response system.	Probably yes Double-blind (participant, investigator) trial. Unclear whether data collectors, outcome assessors and data analysts were blinded.	Unclear Not reported.	Probably yes All of the outcome measures mentioned in the method section were reported. However, it is unclear whether all endpoints related to symptom resolution and symptom improvement were reported.	Definitely no Patients were analyzed according to randomization, no ITT-analysis was performed. Large part of the authors is employee and shareholder at the funders.	HIGH Multicenter, double-blind, randomised, controlled trial with adequate allocation process. No ITT-analysis was performed. Large part of the authors is employee and shareholder at the funders.
6.6. Casirivimab and imdevimab (REGN-COV2; combination of two noncompeting, neutralizing human IgG1 antibodies)							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
RECOVERY Collaborative Group, 2022	Probably yes Eligible and consenting patients were assigned using web-based simple (unstratified) randomisation (appendix pp 32–34).	Probably yes Allocation was concealed until after randomisation	Definitely no Open-label trial. Lack of blinding is less worrisome for all-cause mortality.	Definitely yes Loss to follow-up was less than 10% and similar between the groups.	Definitely yes All outcomes reported in the study protocol were reported in the paper.	Probably yes No other biases.	Some concerns Large multicenter, open-label trial. Lack of blinding might have biased the results for some of the outcome measures other than all-cause mortality.
6.7. CERC-002							
6.8. Etanercept							
6.9. Gimsilumab							
6.10. Golimumab							
6.11. Infliximab							
6.12. Itolizumab (humanized monoclonal antibody (IgG1 kappa anti-CD6))							
6.13. Lenzilumab							
6.14. Mavrilimumab (human monoclonal antibody; anti-GM-CSF-Rα; human isoform IgG4)							
6.15. Namilumab							
6.16. Regdanvimab							
Streinu-Cercel, 2022	Probably yes	Probably yes	Definitely yes	Definitely yes	Definitely yes	Probably yes	Some concerns

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Reason: Randomization was performed using an interactive web response system, and a randomization schedule was prepared by unblinded biostatisticians. Randomization was stratified by age (≥60 vs <60 years), region (United States vs Asia vs Europe vs other), baseline comorbidities (yes vs no for having at least 1 of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, or pneumonia),	Reason: Unclear whether the randomization list was accessible before patient enrolment and whether allocation was concealed.	Reason: Participants, personnel, and outcome assessors were blinded to treatment allocation for the duration of the study	Reason: None of the participants was lost to follow-up.	Reason: All outcomes reported in the study protocol were reported in the paper.	Reason: ITTI and ITT analyses were performed. The funder of the study (i.e. pharmaceutical company) had a role in study design and data analysis.	LOW Some concerns HIGH Multicenter, double-blind, randomised, placebo-controlled trial with unclear allocation process. The funder of the study had an important role in study design and data analysis

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
	and participation in the pharmacokinetic substudy (yes vs no).						
6.17. Sotrovimab							
Gupta, 2022	Definitely yes Reason: Using an interactive web response system, eligible patients were randomized 1:1.	Definitely yes Reason: Allocation concealment was ensured. Participants and investigators (and treatment administrators) were all blinded to treatment allocation.	Definitely yes Reason: Patients and investigators remained blinded to randomization until the final analysis.	Definitely yes Reason: Reasons for missing outcome data unlikely to be related to outcome	Definitely yes Reason: Outcome measures described in the method section are also reported.	Probably no Reason: The funder of the study (i.e. pharmaceutical company) had a role in study design, data analysis, data interpretation, and writing of the report.	Some concerns Multicenter, double-blind, randomised, placebo-controlled trial with adequate allocation and blinding process. The funder of the study had an important role in study design, data analysis, data interpretation, or writing of the report.
6.18. Tixagevimab and cilgavimab (AZD7442)							
6.19. Vilobelimab (Anti-C5a antibody IFX-1; monoclonal anti-human complement factor C5a antibody)							
6.20. Secukinumab							
Resende, 2022	Probably yes Reason: "Enrolled patients were sequentially subjected to	No information Reason: -	Definitely no Reason: "This study had some limitations. It was open-label."	Definitely yes Reason: No patients were lost to follow-up.	Probably yes Reason: All predefined outcomes were reported.	Probably no Reason: small sample size	Some concerns

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
	<i>block randomisation (block size of 4) to receive 300mg of secukinumab subcutaneously at day-0 plus standard of care (SoC), hereinafter called group A, or SoC alone (group B) in a 1:1 ratio."</i>						
7. Polyclonal antibodies							
8. Supplements							
8.1. Vitamin C							
8.2. Vitamin D							
Cannata-Andía (2022)	Definitely yes Reason: Randomisation was performed individually in each centre using a computer-generated list with a 1:1 rati	Probably no Reason: Reason: not reported	Definitely no Reason: open-label study	Definitely yes Reason: Lost to follow-up was infrequent and almost similar in both groups	Definitely yes Reason: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way	Probably no Reason: The study cohort may be subject to bias because the population recruited for the study was heterogeneous, i.e., different countries with uneven socioeconomic issues	Some concerns Open label trial

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
						and health system coverage, and different latitudes that can influence calcidiol levels through different sun exposures	
Lakkireddy, 2021	Probably no Reason: Patients were randomised into two groups vis a vis alternatively as per their pre allotment serial numbers	Probably no Reason: Patients with were randomised into two groups vis a vis alternatively as per their pre allotment serial numbers.	Definitively no Reason: It is an open label study.	Probably no Reason: Reasons for dropping out of the study are different between the groups.	Probably yes Reason: In this publication only part of the predefined outcome measures are reported.	Definitely no Reason: No ITT protocol and total numbers in the treatment groups are not clear.	HIGH Unclear randomization and concealment, no ITT protocol, high dropout rates and no blinding (not for mortality, might also not induce high risk of bias in other objective outcomes)
8.3. Zinc							
9. Antiviral treatment							
9.1. Darunavir (antiretroviral treatment; also in combination with cobicistat)							
9.2. Favipiravir (be eventually used in combination with Baloxavir and/or marboxil)							
9.3. Lopinavir and ritonavir (brand name = Kaletra; fixed dose combination of antiretroviral treatment)							
9.4. Molnupiravir							
Jayk Bernal, 2022	Definitely yes	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Some concerns

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Reason: Eligible participants were randomly assigned in a 1:1 ratio through the use of a centralized, interactive-response technology system to receive either molnupiravir (800 mg delivered as four 200-mg capsules) or identical placebo, administered orally twice daily for 5 days. Randomization was stratified in blocks of four according to the time since onset of signs or symptoms (≤ 3 days vs. > 3 days).	Reason: Unclear whether the randomization list was accessible before patient enrolment and whether allocation was concealed.	Reason: Double-blind trial	Reason: Reasons for missing outcome data unlikely to be related to outcome	Reason: Outcomes in clinical trial record correspond with the outcomes reported in the study	ITT analysis was performed. The funder of the study (i.e. pharmaceutical company) had a role in study design and data analysis.	Multicenter, double-blind, randomised, placebo-controlled trial with adequate allocation and blinding process. The funder of the study had an important role in study design and data analysis
9.5. Nitazoxanide (brand name = Alinia; antiparasitic & broad-spectrum antiviral medication)							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
9.6. Novaferon (broad-spectrum antiviral drug)							
9.7. Oseltamivir (brand name = Tamiflu)							
9.8. Paxlovid							
9.9. Ribavirine (also known as tribavirin)							
9.10. Sofosbuvir (brand name = Sovaldi; has role as a prodrug, an antiviral drug and a hepatitis C protease inhibitor; only recommended with some combination of ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir)							
9.10.1. Sofosbuvir i.c.m. Daclatasvir (brand name = Daklinza; used in combination with sofosbuvir, ribavirin, and interferon)							
9.10.2. Sofosbuvir i.c.m. Ledipasvir (brand name = Harvoni; antiviral for hepatitis C-virus)							
9.10.3. Sofosbuvir i.c.m. Velpatasvir (NS5A inhibitor (by Gilead); fixed-dose combination medication with sofosbuvir for the treatment of hepatitis C)							
9.11. Umifenovir (brand name = Arbidol)							
10. Antibiotic treatment							
10.1. Azithromycin							
10.2. Doxycycline							
10.3. Lincomycine							
11. Antifungal treatment							
11.1. Intraconazole							
12. Antiparasitic treatment							
12.1. Ivermectin (broad spectrum anti-parasitic agent)							
Abbas, 2022	Definitely yes	Definitely yes	Definitely yes	No information	No information	Definitely no	HIGH

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Reason: Patients were divided into two groups according to a random list generated using the relevant software, using random blocks of 100 volumes.	Reason: The trial team, site staff, and patients were unaware of the randomized assignments.	Reason: The trial team, site staff, and patients were unaware of the randomized assignments	Reason: Not reported	Reason: The study appears to be not registered in the clinicaltrials.gov register	Reason: The study appears to be not registered in the clinicaltrials.gov register	
Reis, 2022	Definitely yes Reason: An independent pharmacist conducted the randomization at a central trial facility, from which the trial sites requested randomization by means of text message. Patients underwent randomization	Definitely yes Reason: The trial team, site staff, and patients were unaware of the randomized assignments. Only the pharmacist who was responsible for randomization was aware of which letter referred to which assignment.	Definitely yes Reason: The trial team, site staff, and patients were unaware of the randomized assignments	Definitely yes Reason: Reasons for missing outcome data unlikely to be related to outcome	Definitely yes All outcomes reported in the study protocol were reported in the paper.	Probably yes Reason: The study appears to be free of other sources of bias.	LOW

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	by means of a block randomization procedure for each participating site, with stratification according to age (≤ 50 years or > 50 years).						LOW Some concerns HIGH
Gonzalez, 2022	No information Method of randomisation not reported	No information Method of randomisation and concealment not reported	Definitely yes Reason: Patients and investigators remained blinded to randomization until the final analysis	No information Not reported	Definitely yes Reason: Outcome measures described in the method section are also reported	Definitely no Reason: Patient recruitment was stopped due to the therapeutic futility of hydroxychloroquine (one of the treatment arms in this RCT)	HIGH
Lim, 2022	Definitely yes Reason: The randomization (1:1) was based on an investigator-blinded randomization list uploaded to REDCap, which	Probably yes Reason: The randomization was based on an investigator-blinded randomization list uploaded to REDCap, which allocated the patients	Definitely no Reason: Open label	Probably yes Reason: 6 patients in the intervention arm withdrew consent before taking a dose of ivermectin. The modified intention-to-treat population for the primary analysis included 490 patients	Probably yes Reason: All outcome mentioned in the methods section were reported in the article. The trial register only mentions the co-primary outcomes, which are described in the article.	Probably no Reason: trials was underpowered for all-cause mortality outcome; no other problems reported	Some concerns open label design, underpowered for secondary outcome mortality

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	allocated the patients via a central, computer-generated randomization scheme across all study sites during enrollment. The randomization list was generated independently using random permuted block sizes 2 to 6. The randomization was not stratified by site.	via a central, computer-generated randomization scheme across all study sites during enrollment		(98% of those enrolled), with 241 in the intervention group and 249 in the control group			LOW Some concerns HIGH
13. Interferon							
13.1. Inhaled IFN-κ plus TFF2 (= Interferon kappa + Trefoil factor 2)							
13.2. Inhaled Interferon β-1b							
13.3. Interferon α-2b							
13.4. Interferon β-1a							
13.5. Interferon β-1b							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
13.6. Peginterferon Lambda							
13.7. Peginterferon Lambda-1a							
13.8. Pegylated Interferon-2b							
14. JAK-inhibitors							
14.1. Baricitinib (selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)							
Ely, 2022	Definitely yes Reason: Randomisation was facilitated by a computer-generated random sequence using an interactive web-response system and was performed by a study investigator or designee.	Definitely yes Reason: Central allocation	Definitely yes Reason: Blinding of participants and key study personnel ensured, and unlikely that blinding could have been broken	Definitely yes Reason: Reasons for missing outcome data unlikely to be related to outcome	Probably no Reason: As the cohort reported here was an addition to the parent trial study design, all endpoints are considered exploratory.	Definitely no Reason: The funder of the study (i.e. pharmaceutical company) had a role in study design, data analysis, data interpretation, and writing of the report.	Some concerns Multicenter, double-blind, randomised, placebo-controlled trial with adequate allocation and blinding process. The funder of the study had an important role in study design, data analysis, data interpretation, or writing of the report.
14.2. Fedratinib							
14.3. Filgotinib							
14.4. Nezulcitinib							
14.5. Oclacitinib							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
14.6. Peficitinib							
14.7. Ruxolitinib (Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)							
Han, 2022	Definitely yes Reason: Block randomisation, with a block size of 3, was used to decrease the risk of imbalance. Randomisation was stratified by geographical region (North America, western Europe, eastern Europe, Latin America, and other). Randomisation was done by interactive response technology.	Definitely yes Reason: Central allocation	Definitely yes Reason: Participants, investigator staff, persons performing the assessments, and the clinical trial team remained masked throughout the trial. Unmasking occurred in the case of participant emergencies and at the conclusion of the study.	Definitely yes Reason: Reasons for missing outcome data unlikely to be related to outcome	Definitely yes All outcomes reported in the study protocol were reported in the paper.	Probably no Reason: The overall therapeutic landscape and standard of care changed substantially during the study	Some concerns
14.8. Tofacitinib							
14.9. Upadacitinib							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
15. IL1-remmers							
15.1. Anakinra							
15.2. Canakinumab							
16. IL6-remmers							
16.1. Clazakisumab							
16.2. Levilimab (Monoclonal antibody- IL-6 inhibitor-BCD-089; IIsira)							
16.3. Olokizumab							
16.4. Sarilumab (human monoclonal antibody; against the interleukin-6 receptor; sold under the brand name Kevzara)							
García-Vicuña, 2022	Probably yes Central telephone randomization was performed by the Clinical Research and Clinical Trials Unit (CRCTU) at the HUP using the program www.randomization.com with a 2:1 proportion and	Probably yes Central allocation	Definitely no Open-label trial.	Definitely yes No lost to follow-up reported.	Probably yes All outcomes reported in the study protocol were reported in the paper.	Definitely no Assigned treatment groups were not well-balanced with several data that point to higher baseline severity in SAR arm patients. Patients on SAR were randomized earlier after disease onset compared to SC participants, suggesting a more advanced or poor prognostic disease leading to meeting the inclusion	HIGH Reason: no blinding, treatment groups not well-balanced with a high risk of bias

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
	5 blocks of 6 subjects.					criteria in a shorter time.	
Sivapalasingam, 2022	No information Method of randomisation is not reported.	No information Method of randomisation and concealment not reported.	No information Blinding is not described.	Probably no Reason: Reasons for missing outcome data unlikely to be related to outcome	Definitely yes Reason: Outcomes in clinical trial record correspond with the outcomes reported in the study	Probably yes ITT analysis was performed, disease severity was not reported at baseline.	Some concerns Multicenter, double-blind, randomised, placebo-controlled trial with unclear randomization and allocation concealment (might not induce high risk of bias in objective outcomes)
16.5. Siltuximab							
16.6. Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor)							
Rosas, 2022	Definitely yes Reason: "Patients were randomly assigned in a 2:1 ratio to receive intravenous tocilizumab 8 mg/kg (maximum 800 mg) or placebo plus local standard care	No information Reason: -	Definitely yes Reason: "COVACTA was a randomised, double-blind, placebocontrolled trial of tocilizumab in hospitalised patients with COVID-19."	Probably no Reason: Lost to follow-up was higher in the intervention group.	Probably yes Reason: all predefined outcomes were reported.	Probably yes	Some concerns

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	<i>(could have included antiviral therapy or corticosteroids in addition to supportive care) using an interactive voice or web-based response system and permuted-block randomisation."</i>						LOW Some concerns HIGH
Broman, 2022	Probably yes Random permuted blocks in a 2:1 ratio using block size of 6 and programmed by biostatistician with SAS Version 9.4 for Windows	Probably yes Not reported	Definitely no Open-label trial. Lack of blinding is less worrisome for all-cause mortality.	Definitely yes No lost to follow-up reported.	Definitely yes All outcomes reported in the study protocol were reported in the paper.	Probably yes No other biases.	Some concerns Reason: no blinding and unclear concealment of allocation.
Hermine, 2022	Definitely yes Reason: Using a web-based secure	Definitely yes Reason: Central allocation	Definitely no Reason: No blinding but the review authors judge that the	Definitely yes Reason: No missing outcome data	Definitely yes Reason: The study protocol is available and all of the study's	Definitely yes Reason: The study appears to be free of other sources of bias.	Some concerns Because of the design of the CORIMUNO platform,

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
	centralized system.		outcome and the outcome measurement are not likely influenced by lack of blinding (open label)		pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way		the sample size was small and not designed to show a difference in survival, credibility intervals were wide, and the treatment effect may be underestimated.
17. Other immunomodulators							
17.1. Auxora (potent and selective small molecule inhibitor of calcium release-activated calcium (CRAC) channels)							
Bruen, 2022	Definitely yes Reason: Randomization was stratified by the baseline imputed PaO2/FiO2 ratio of > 200 vs ≤ 200 through a central, concealed, webbased, automated system.	Definitely yes Reason: An independent statistician created the randomization schedule with stratified block randomization method using SAS proc plan procedure. Within each stratum, the treatment codes were assigned at a 1:1 ratio of Auxora and placebo with the block size of 4.	Definitely yes Reason: Participants, investigators, study teams, and the sponsor were all blinded to study drug assignment.	Definitely yes Reason: 1 patient dropped out	Definitely yes Reason: Outcome measures described in the method section are also reported.	Definitely no Reason: Due to declining rates of COVID-19 hospitalizations and utilization of standard of care medications prohibited by regulatory guidance, the trial was stopped early. The funder of the study had an important role in study design and data analysis	HIGH
17.2. Colchicine (anti-inflammatory and analgesic medication)							
Dorward, 2022	Definitely yes	Definitely yes	Definitely no	Definitely yes	Definitely yes	Probably no	Some concerns

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Eligible, consenting participants were randomised using a secure, in-house, webbased randomisation system (Sortition version 2.3).	Participants were randomised using a fully validated and compliant web-based randomisation system called Sortition.	PRINCIPLE is an open-label trial. The participant, legal representative if applicable, trial team and participant's GP were notified electronically of the treatment allocation. However, those managing the data were blinded to participant allocation.	The Bayesian primary analysis model included data from 2755 of 2900 (95%) participants who were SARS-CoV-2 positive and who provided follow-up data and were randomised to colchicine, usual care alone, and other treatment groups.	The primary and secondary outcomes reported in the study protocol were reported in the paper.	One of the primary outcomes, namely time to recovery, is a self-reported outcome.	Multicenter, open-label, randomised, controlled trial with adequate allocation process.
Gorial, 2022	Definitely yes Reason: Participants were randomized to fluvoxamine (Dumirox, JW Pharmaceutical, Korea) or placebo in a 1:1 ratio using alternating block sizes of 4	Definitely no Reason: Open-label trial.	Definitely no Reason: Open-label trial	Probably yes Reason: not mentioned by the authors	Definitely no Reason: The primary outcome (Percentage cure/deaths of patients) was not reported.	Definitely no Reason: Open-label trial.	HIGH
17.3. Fostamatinib							
17.4. Imatinib							
17.5. Leflunomide (immunosuppressive disease-modifying antirheumatic drug, DMARD)							

Study reference (first author, publication year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding: Was knowledge of the allocated interventions adequately prevented? Were patients blinded? Were healthcare providers blinded? Were data collectors blinded? Were outcome assessors blinded? Were data analysts blinded?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias If applicable/necessary, per outcome measure
	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	Definitely yes Probably yes Probably no Definitely no	LOW Some concerns HIGH
17.6. Mycobacterium W							
17.7. Tractolimus							
18. SSRI							
18.1. Fluvoxamine							
Seo, 2022	Definitely yes Reason: Participants were randomized to fluvoxamine (Dumirox, JW Pharmaceutical, Korea) or placebo in a 1:1 ratio using alternating block sizes of 4	Definitely no Reason: Open-label trial.	Definitely no Reason: Open-label trial	Definitely no Reason: Reasons for dropping out of the study are different between the groups.	Definitely yes Reason: All outcomes reported in the study protocol were reported in the paper.	Definitely no Reason: Open-label trial. Early termination of trial due to a decrease in COVID-19 patients. Trial is underpowered.	HIGH

In de onderstaande tabel is de risk of bias weergegeven van de studies geïncludeerd tot 3/2/2022:

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
1. Remdesivir								
Abd-Elsalam, 2021a	Eligible patients were randomly assigned at a 1:1 ratio by using computer random sequence generator.	Unlikely Treatment allocation was concealed from outcome assessors and patients using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely All predefined outcome measures were reported.	Unlikely Loss to follow-up almost equal in both groups. The reasons for loss to follow-up were also the same for both groups (transfer to another hospital).	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Ader et al., 2021	Computerized block randomization Participants were randomly assigned 1:1:1:1:1 when five groups were initially implemented, and were then assigned 1:1 to receive either standard of care or standard of care plus remdesivir, once the other three treatment groups had been stopped for futility. Randomisation was done in the electronic case report	Likely Participants allocated to standard of care alone or in combination with remdesivir were recruited contemporaneously. Allocated treatment was not masked to participants nor study investigator.	Likely Open-label trial	Likely Open-label trial	Likely Open-label trial	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely No lost to follow up.	Unlikely Participants included in the analysis are not significantly different from those who were randomized into the trial.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	form to ensure appropriate allocation concealment and used computer-generated blocks of various sizes; it was stratified on severity of disease at inclusion and on European administrative region.							
Barratt-Due et al., 2021	Computerized. Eligible patients were allocated in an equal ratio using computer randomization procedures. There were 2 separate allocation lists. The first was the global list, in which the allocation sequence was prepared by an independent statistician appointed by the international trial steering group. A secondary national list was additionally prepared as a backup if allocation according to the global list was not available. The randomization procedure ensured that a patient could be allocated only to an available treatment. The randomization lists were not stratified or blocked;	Unlikely The first was the global list, in which the allocation sequence was prepared by an <u>independent statistician appointed by the international trial steering group</u> . A secondary national list was additionally prepared as a backup if allocation according to the global list was not available.	Likely Open label	Likely Open label	Unclear Despite being a randomized controlled trial with blinded analyses of all relevant data, it did not include a placebo group.	Unlikely All outcomes were reported in main article of appendix ClinicalTrials.gov: NCT04321616	Likely 15 to 24% of participants in study groups were lost to follow-up. Missing data on outcomes due to discharge or participant withdrawal were imputed with best outcome.	Unlikely Each pairwise intention-to-treat analysis was between the remdesivir or HCQ group and its respective SoC. Some participants receiving SoC act as controls for both active treatment groups, whereas some act in one or the other, giving a partial overlap of the 2 control groups.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	thus, the randomization can be regarded as simple.							
Mahajan, 2021	Computerized (Excel) <i>“For administering intervention, random number was generated in Excel to follow simple random sampling technique.”</i>	Unclear Not described at what time the random number was generated and who had knowledge of it	Likely “We did not give placebo injection in the no-remdesivir group and did not do blinding.”	Likely “We did not give placebo injection in the no-remdesivir group and did not do blinding.”	Likely “We did not give placebo injection in the no-remdesivir group and did not do blinding.”	Unclear Trial not registered; some results described without data presented	Likely Relatively small sample size and multiple drop outs (I: 19.5%; C: 12.2%)	Likely Analysis not performed according to intention-to-treat protocol; drop outs and 1 cross over in relatively small study groups
Pan, 2020 (WHO Solidarity Trial Consortium)	Computerized Once a hospital has obtained approval, electronic entry of patients who have given informed consent takes only a few minutes. At the end of it, the randomly allocated treatment is displayed on the screen and confirmed by electronic messaging.	Unlikely Allocation displayed on screen after entry of patient in the system	Likely Unblinded trial (mortality: unlikely)	Likely Unblinded trial (mortality: unlikely)	Likely Unblinded trial (mortality: unlikely)	Unlikely Protocol published https://www.who.int/publications/m/item/a-n-international-randomised-trial-of-additional-treatments-for-covid-19-in-hospitalised-patients-who-are-all-receiving-the-local-standard-of-care	Unlikely Low rate of lost-to follow-up and reasons comparable between groups	Unlikely analyses performed according to intention-to-treat protocol
Beigel, 2020	Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir or placebo. Randomization was stratified by study site and disease severity at enrollment	Unlikely Adequate procedure	Unlikely No bias expected	Unlikely No bias expected	Unlikely At the time of the data and safety monitoring board report, which was based on data cutoff date of April 22, 2020, a total of 482 recoveries (exceeding the estimated number of recoveries needed for the trial) and 81 deaths had been	Unlikely Primary endpoints relevant and described. The protocol is available online.	Unlikely	Unlikely Intention-to-treat analysis performed

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
					entered in the database. At that time, the data and safety monitoring board recommended that the preliminary primary analysis report and mortality data from the closed safety report be provided to trial team members from the National Institute of Allergy and Infectious Diseases (NIAID).			
Spinner, 2020	The randomization list was created and validated by the interactive web response system (IWRS) vendor. A dummy randomization list was provided to the biostatistician employed by the study sponsor for review. A separate list of sequential patient numbers within each treatment group was generated by the IWRS vendor.	Unclear Patients were not stratified by site at enrolment, which may have led to imbalances in patientcare and discharge practices.	Unclear It was an open label study.	Likely It was an open label study, which might have led to differences in patient care.	Unclear It was an open label study, which might have led to differences in reporting the results.	Unlikely Outcome measures reported in the method section are also reported.	Unlikely One patient was lost to follow up (I2 group) and was therefore not included in the primary analysis.	Unlikely Not all randomized patients were included in analysis, but intention to treat analysis did not reveal different results.
Wang, 2020a	Eligible patients were randomly assigned (2:1) to either the remdesivir group or the placebo group. Randomisation was stratified according to the level of	Unlikely Eligible patients were allocated to receive medication in individually numbered packs, according to the	Unclear Double-blind, but method of blinding was not described.	Unclear Double-blind, but method of blinding was not described.	Unclear It was not described whether assessors were blinded.	Unlikely The protocol is available online. This trial is registered with ClinicalTrials.gov,	Unlikely Numbers lost to follow-up were not reported.	Unlikely All allocated patients were included in the intention-to-treat analysis.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	respiratory support as follows: (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation. The permuted block (30 patients per block) randomisation sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software, version 9.4.	sequential order of the randomisation centre. Envelopes were prepared for emergency unmasking.				before the start of recruitment		
2. Corticosteroids								
2.1. Dexamethasone								
Jamaati, 2021	Computerized The selected patients were allocated to either the dexamethasone group or the control group by block randomization. Ten blocks were generated by the Online Randomizer website. Each block included five patients; of these, two patients were assigned to the dexamethasone	Unclear It is unclear whether allocation of treatment was concealed to the patients and caretakers.	Unlikely The authors do not report whether the patients were blind to the randomization. However, it is not expected that patients influenced the reported outcome measures (need for invasive mechanical ventilation, death rate, length of hospital / ICU stay, and	Unclear The authors do not report whether any blinding occurred. This may have affected the more subjective outcome measures such as duration of hospital stay, and whether ventilation was started or maintained.	Unlikely The authors report that the radiologist who assessed the CT scans was blinded to the lab data and clinical findings.	Unlikely All outcome measures stated in the methods section were reported in the results.	Unlikely No patients seem to have been lost to follow up (except for those who died).	Unlikely No mention of ITT analysis, however the participants seem to be analyzed as allocated.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	group and three patients were assigned to the control group or vice versa.		radiological changes in the CT scan).					
Tomazini, 2020	The randomization list was generated by the trial statistician, not involved in patient care or enrolment, using the R software. The list comprised random blocks of two and four, unknown to researchers and stratified at center level and was uploaded and implemented in the on-line web-based system used for randomization data collection. The group treatment was disclosed to the investigator only after all information regarding patient enrolment was recorded in the online system. Patients were screened for enrolment by the principal investigator and the research team at each study center.	Unlikely The randomization list was generated by the trial statistician, not involved in patient care or enrolment, using the R software.	Likely Physicians, patients, and individuals who assessed the outcomes were not blinded for the assigned treatment	Likely Physicians, patients, and individuals who assessed the outcomes were not blinded for the assigned treatment	Likely Physicians, patients, and individuals who assessed the outcomes were not blinded for the assigned treatment	Unlikely All predefined outcome measures were reported	Unlikely All patients were included in the primary analysis. There was no loss to follow-up, and data on the primary outcome, mortality within 28 days, clinical status at day 15, ICU-free days at 28 days, and mechanical ventilation duration were available for all patients.	Unlikely ITT analysis performed.
Horby, 2020a	"using web based simple randomization with allocation concealment."	Unlikely Adequate concealment "webbased simple randomization with allocation concealment."	Likely Patients not blinded, primary outcome not susceptible for bias (death)	Likely Study staff not blinded to allocated treatment	Likely Study staff not blinded to allocated treatment	Unlikely Relevant outcomes reported; protocol and analysis plan available	Unlikely 28-day follow-up not available for 4.8% of patients; in absence of any information, they were assumed to have survived. No	Unlikely Analyses performed according to intention-to-treat protocol

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
							information on % loss to follow-up in intervention vs. control group	
2.2. Hydrocortisone								
Munch, 2021	Computerised Participants were randomised (1:1) using a centralised and web-based randomisation system at the Copenhagen Trial Unit (CTU). The randomisation was performed according to a computer-generated allocation sequence, stratification variables, and varying block sizes.	Unlikely The allocation sequence was only known by the data manager at the CTU.	Unlikely Participants were blinded to treatment allocation.	Unlikely Clinical staff members were blinded to the allocation.	Unlikely Management Committee, investigators, trial site staff registering outcome data and the trial statistician were blinded to the allocation.	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely No participants were lost to follow-up.	Unlikely All analyses were done in the intention-to-treat population, defined as all randomised participants for whom there were consent to use data.
Angus, 2020	Randomization will be conducted through a password-protected, secure website using a central, computer-based randomization program.	Unlikely Randomization will be at the patient level and occur after data necessary to implement the inclusion and exclusion criteria have been entered into the secure randomization website. The RAR will occur centrally as part of the computerized randomization process. Sites will receive the allocation status and will not be informed of the randomization proportions.	Unclear Not reported in the study	Unlikely The default position within the REMAP is that treatments determined by randomization will be provided on an open-label basis. However, the blinding of treatment status is not precluded within the REMAP. If required, details related to blinding of interventions will be specified in the DSAs.	Unlikely The primary outcome of all-cause mortality censored at 90 days is not subject to ascertainment bias. Wherever possible, trial management personnel, who are blinded to allocation status, will conduct any follow up after discharge.	Unlikely Wherever possible, trial management personnel, who are blinded to allocation status, will conduct any follow up after discharge.	Unlikely Missing data will be minimized through a clear and comprehensive data dictionary with online data entry including logical consistency rules. If values necessary for the Bayesian modelling of the primary endpoint and the RAR are missing they may be imputed, using available data.	Unlikely Analysis of the primary outcome was then repeated in a second model using only data from those patients enrolled in the corticosteroid domain with no adjustment for assignment to interventions in other domains. Although using less information, this analysis is more typical for an RCT. Further secondary analyses explored the

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
								effects of excluding patients who were ruled out for COVID-19 (defined as documented negative test results for SARS-CoV-2 infection and no positive test results), of excluding adjustment for site and time epoch, and of combining the fixed-dose and shock-dependent hydrocortisone groups.
Dequin, 2020	Computerized “Randomization was centralized and performed electronically. Allocation sequences were generated in a 1:1 ratio by a computer-generated random number using a blocking schema; the range of block sizes remains confidential until the completion of the parent trial. Randomization was stratified by center and by use of mechanical ventilation at the	Likely Randomization stratified by center	Unlikely	Unlikely “Both hydrocortisone and placebo were provided in industrially prepared packaging (Serb Specialty Pharmaceuticals).”	Unclear [short explanation]	Unlikely Trial registered; relevant outcomes reported	Unlikely 1 patient in the intervention group withdrew consent; this patient was considered to have experienced treatment failure on day 21 (primary outcome)	Unlikely Analyses performed according to intention-to-treat protocol

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	time of inclusion.”							
2.3. Inhaled corticosteroids (budesonide, ciclesonide)								
Clemency, 2022	Unclear The randomization schedule was generated by the contract manufacturing organization and incorporated into the labeling of kits. The metered-dose inhaler kits were sent to the study sites in blocks of 6, with 3 active and 3 placebo kits randomized within each block.	Unclear Not described.	Unlikely Patients were blinded to study treatment assignment.	Likely Investigators/study personnel were blinded to study treatment assignment.	Unclear Not described	Unlikely All outcome measures described in the trial protocol are reported in the results.	Likely The percentage of patients lost to follow-up is infrequent and similar between treatment groups.	Unlikely All randomized patients who received ciclesonide or placebo were included in the ITT analysis.
Song, 2021	<i>Eligible patients were randomly assigned in a 1:1:1 ratio.</i> <i>The randomization was performed by computer-generated variable blocks ranging from 4 to 8 patients per each center, and the code numbers for eligible patients were assigned in ascending sequential order.</i>	Unlikely <i>Computer-generated variable blocks ranging from 4 to 8 patients per each center, and the code numbers for eligible patients were assigned in ascending sequential order.</i>	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely All predefined outcome measures were reported.	Unlikely No lost to follow-up reported.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial
Yu et al., 2021	Computerized Eligible, consenting participants were randomly assigned	Unclear Not reported	Likely It was an open label study: participants were not blinded. (NB. Inhalers have been documented to have	Unclear It was an open label study in non-hospitalized patients. It is not clear whether care givers, others	Unlikely The trial team was blinded.	Unlikely Outcome measures mentioned in the protocol were also reported. Subgroup analysis on	Unclear It is only mentioned that 95% of the participants were included in analysis,	Unclear At the beginning of the trial participants with suspected COVID-19 were included in the primary analysis

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	using a secure, in-house, web-based randomisation system. Randomisation probabilities were established using response-adaptive randomisation via regular interim analyses, which allows allocation of more participants to interventions with better observed time-to-recovery outcomes. (...) when only the budesonide and usual care groups were open, there was 1:1 allocation between each, stratified by age (<65 years vs ≥65 years), and presence of comorbidity (yes vs no).		placebo effects, which might have had an effect on self-reported outcomes.)	than GPs, were involved.		vaccination status was not reported in the protocol.	since they provided follow-up data.	population, irrespective of confirmatory testing. When testing became more accessible, primary analysis was restricted to those with confirmed COVID-19. Furthermore, primary analysis includes data from participants who provided follow-up data (95%).
Ramakrishnan, 2021	Computerized "Participants were randomly allocated to usual care or budesonide, stratified by participant age (≤40 years or >40 years), sex, and number of comorbidities (≤1 or ≥2). The randomisation sequence was created using a random number generation function and allocation to each group	Unlikely Protocol: "Once a participant has been consented to the study (verbal or in person consent), a research nurse will contact the study team member responsible for randomisation [.....] The randomiser will then communicate the randomisation allocation and the participant ID	Likely Open-label trial	Likely Open-label trial	Likely Open-label trial	Unlikely Protocol available, trial registered (ClinicalTrials.gov, NCT04416399), publication consistent with registration	Unlikely Loss to FU 5.5% (I) and 4.1% (C) in per protocol analysis; in total 4 patients withdrew consent due to allocation. Analysis performed according to per protocol and intention-to-treat protocol show similar results.	Unlikely Analysis performed according to per protocol and intention-to-treat protocol show similar results. Unlikely that bias was induced.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	was done through block randomisation in a 1:1 ratio.”	number to the research nurse. The record of the randomisation allocation will be saved at a secure network location with a date and time stamp.”					Unlikely that bias was induced.	
2.4. Methylprednisolone								
Solanich, 2021	Computerized Patients were randomized using the RedCap, a secure web application for building and managing electronic case report forms (eCRF). Patients were randomly (1:1) assigned to one of the study arms with no baseline stratification.	Unclear No information on concealment	Likely Open-label RCT	Likely Open-label RCT	Unlikely The IDIBELL Biostatistical Unit performed the analysis and analysts were blinded to the treatment received by patients (intervention vs. usual care)	Unlikely All outcomes were reported in main article of appendix	Unlikely Similar loss to follow-up, no indications for bias	Unlikely Except for outcome on viral load, but no comparisons were done.
Tang, 2021	Computerized Randomization was stratified by the statistician of the leading site, who produced computer-generated block randomization lists with a block size of 4 patients.	Unlikely Allocation of treatment seems to have been concealed properly.	Unlikely Patients were blind to treatment allocation.	Likely Care providers were not blind to treatment allocation. Therefore, they could have biased the outcome measures that are prone to subjectivity, such as the duration of hospitalization and ICU admission.	Unlikely During the study, data collection and end point judgement were blinded, and the statisticians were also blinded during the statistical analysis.	Unlikely All outcome measures stated in the methods section were reported in the results.	Unlikely No patients were lost to follow up.	Unlikely Authors indicate that an ITT was not necessary and the included patients seem to be analyzed as allocated.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
				Unlikely It is unlikely that care providers biased objective outcome measures such as mortality, clinical deterioration or clinical cure, and virus shedding.				
Corral-Gudino, 2021	Partly randomized; i.e. some participants received treatment according to the clinician's preference, the other participants were randomized. If the clinical team decided that a strong preference for glucocorticoid therapy existed, the patient was allocated to the preference arm. Otherwise, the patient was randomized (1:1) and allocated to the MP or control arm accordingly. Patients were randomized based on a spreadsheet that transformed every	Unlikely Patients were randomized based on a spreadsheet that transformed every medical record number into a group allocation using a concealed mathematical formula	Likely Open-label trial	Likely Open-label trial	Likely Open-label trial	Unlikely Trial registered and all important outcomes reported	Likely Loss to follow-up was 14% in the intervention and 3% in the control group.	Unlikely An intention to treat analysis was done

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	medical record number into a group allocation.							
Edalatfard, 2020	Method not described <i>“the patients randomly allocated in control (n=34) and intervention group (n=34), in a 1:1 ratio by block randomization method.”</i>	Unclear not described	Unlikely Patients were blinded to treatment	Likely “ Physicians and clinicians team know about the medicine and intervention groups”	Likely “ Physicians and clinicians team know about the medicine and intervention groups”	Likely Follow up short compared to other studies; unclear definition of ‘improvement’ (clinical improvement, improvement, pulmonary improvement) while this is a main result Trial registered: Iranian Registry of Clinical Trials on 15 April 2020 (IRCT ID: IRCT20200404046947 N1	Likely 34/34 (100%) of patients of the intervention and 28/34 (82.4%) of patients of the control group included in analysis	Likely 6 patients (17.8%) discontinued treatment of control group and received intervention. They were excluded from the analysis.
Jeronimo, 2020	Stratified block randomisation with electronic system	Unclear No allocation concealment	Unclear No participant blinding	Unclear No blinding of care providers	Unlikely: Radiologists and other assessors were blinded	Unlikely Primary outcome was mortality	Unclear Not described	Likely A posteriori exclusion of patients resulted in only analysis of patients who completed follow up
3. Hydroxychloroquine								
Barratt-Due, 2021	See RoB assessment of Barrat-Due by remdesivir.							
Arabi, 2021	Online randomization system Using a concealed online randomization system, patients were randomized to receive lopinavir-ritonavir, hydroxychloroquine,	Unlikely Using a concealed online randomization system, patients were randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy of	Likely Unblinded cohort: Restricted to patients randomized to an intervention in domains that have been unblinded including the COVID-	Unlikely Although the interventions were given as open-label drugs, neither the clinical staff nor the ITSC were provided any information about	Unlikely Although the interventions were given as open-label drugs, neither the clinical staff nor the ITSC were provided any information about	Unlikely All predefined outcome measures were reported. NCT02735707	Unlikely Lost to follow-up differences between the groups were small.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	combination therapy of lopinavir-ritonavir and hydroxychloroquine or control (no antiviral agents against COVID-19). Based on local equipoise and drug availability, investigators at each participating site selected a priori two or more interventions, one of which had to be control, to which patients could be randomized. The REMAP-CAP platform uses response-adaptive randomization; however, the allocation in the COVID-19 Antiviral Therapy Domain did not deviate from the starting equal ratio before enrollment was halted. Although the interventions were given as open-label drugs, neither the clinical staff nor the ITSC were provided any information about aggregate patient outcomes.	lopinavir-ritonavir and hydroxychloroquine or control (no antiviral agents against COVID-19).	19 Antiviral Therapy Domain and domains that have ceased recruitment	aggregate patient outcomes.	aggregate patient outcomes.			
Schwartz, 2021	Computerized Randomization was conducted using a custom-developed	Unlikely Masking to allocation sequence was complete because randomization	Unlikely All participants were blinded.	Unlikely The research team was blinded, except for the research	Unlikely The research team was blinded, except for the research	Unlikely All outcome measures described in the	Unclear Based on the information presented in the flow chart (Fig.	Likely For most of the outcomes data was missing for ≥ 1

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	online tool to allow for dynamic randomization and allocation concealment. We used a minimal sufficient balance randomization tool to ensure balance on age, sex, risk status, days since symptom onset and provincial health zone. Participants were randomly assigned in a stochastically governed (not blocked) 2:1 ratio.	assignment was determined dynamically at randomization.		pharmacist and randomization website programmer.	pharmacist and randomization website programmer.	methods are reported in the results.	2), no participants were lost to follow-up in the ITT population. However, the table of results (Tab. 2) shows that for most of the outcomes data was missing for ≥ 1 participants, for which the reasons are not specified per treatment arm in the case of time to COVID-19 recovery.	participants. As a result, not all randomized participants were included in the ITT analyses, which is in contrary to information presented in the flow chart (Fig. 2).
Ader et al., 2021	Computerized randomisation Participants were randomly assigned to treatment arms in a 1:1:1:1 ratio, through computer ²²⁷ generated blocks of various sizes and stratification by administrative region and severity of disease at enrolment	Unlikely Randomization was implemented in the electronic Case Report Form to ensure appropriate allocation concealment	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely Outcomes mentioned in the Methods section were reported in the Results section.	Unlikely Loss to follow-up was limited : L/r: 1/145 (0.7%) L/r + IFN: 1/145 (0.7%) HCQ: 2/145 (1.4%) C: 0/148 (0%)	Unlikely The intention-to-treat population included all randomized participants for whom a valid consent form was obtained.
Réa-Neto, 2021	Web-bases in blocks of variable size (2, 4 and 6) Patients were randomized (1:1) within 48 h of admission to take Clq or HClq for 5 days plus standard treatment or control (standard treatment only).	Unlikely The allocated group was disclosed to the investigator only after all information regarding patient enrollment had been recorded in the web system.	Likely open-label trial	Likely open-label trial	Likely open-label trial	Likely Trial registered (NCT04333589); Retrospectively Registered protocol. "Although the outcomes presented in the latest version were updated late on ClinicalTrials.org, on	Unclear <u>Loss to follow-up:</u> I: 0/53 (0%) C: 1/52 (1.9%) The reason is not reported.	Likely 33 patients from ITT population (n=138) received the intervention (Clq/HClq) until the test result was returned.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	Randomization was performed in blocks of variable size (2, 4 and 6) in a centralized web-based automated system and stratified by site and whether the patient was on IMV.					October 23, 2020, these outcomes were already present in the trial protocol approved by the Brazilian National Commission for Ethics in Research on April 8, 2020 (approval number: 3960331) and amending the protocol, approved by the same National Commission on May 25, 2020 (approval number: 4044848)''		
Reis, 2021	Randomization schedule We randomized patients to the hydroxychloroquine, lopinavir-ritonavir, and placebo groups at 1:1:1. Randomization was stratified by site, age (aged 50 years or older vs less than 50 years), and time of onset of flulike symptoms (at least 5 days vs less than 5 days). Patients, investigators, health care practitioners, and sponsors were masked to the study drug assignment.	Unlikely The randomization schedule was prepared by a masked statistician and provided to site-level pharmacists.	Unlikely Patients, investigators, health care practitioners, and sponsors were masked to the study drug assignment.	Unlikely Patients, investigators, health care practitioners, and sponsors were masked to the study drug assignment.	Unlikely Patients, investigators, health care practitioners, and sponsors were masked to the study drug assignment.	Unlikely Outcomes mentioned in the Methods section were similar as the outcomes reported in the Results section.	Likely At the end of the trial, 79 participants (11.5%) did not complete all phases of the study. The lopinavir-ritonavir intervention group had 44 participants (18%) who did not complete the study, which was more than either of the other 2 groups. In addition, the independent DSMB, based on interim analysis results, made the decision to stop enrollment to the	Unlikely The Cox proportional hazards model was used for the analysis of time-to-event outcomes of COVID-19-associated and all-cause hospitalizations for both intention-to-treat (ITT) and per-protocol (PP) analyses.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
							hydroxychloroquine and lopinavir-ritonavir groups because of a low number of emerging events.	
Gupta, 2021a	Randomization was carried out by simple alternate allocation of patients in a1:1 fashion by the first author to either the control or HCQ arm.	Likely The allocation was not concealed either from the patient or the physicians and other medical staff.	Likely “This open-label randomized control trial with unblinded assessment...” “The chief limitation of our trial is that there was no blinding at randomization or at assessment...”	Likely “This open-label randomized control trial with unblinded assessment...” “The chief limitation of our trial is that there was no blinding at randomization or at assessment...”	Likely “This open-label randomized control trial with unblinded assessment...” “The chief limitation of our trial is that there was no blinding at randomization or at assessment...”	Unlikely All predefined outcome measures were reported.	Unlikely No loss to follow-up reported.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Dubée, 2021	Computerized “Patients were randomized immediately after their inclusion into the study using an online application on the study website”	Unclear Unclear at what point in time allocation concealment was available.	Unlikely “The allocation arm was concealed for the patient and for all medical and paramedical staff.”	Unlikely “The allocation arm was concealed for the patient and for all medical and paramedical staff.”	Unlikely “The allocation arm was concealed for the patient and for all medical and paramedical staff.”	Likely No trial register available or link to study protocol; Prematurely stopped after the inclusion of 19% of the planned number of patients; possible bias for over- of underestimating results and missing data	Unlikely Both intention-to-treat and per-protocol analyses conducted; only small percentage of lost to follow-up; no bias expected	Unlikely Both intention-to-treat and per-protocol analyses conducted; only small percentage of lost to follow-up; no bias expected
Purwati, 2021	Not described	Unclear Not described	Unclear Not described	Unclear Not described	Unclear Not described	Unclear	Unlikely Low number of lost to follow-up. All individuals included in analysis according to intention-to-treat protocol.	Unlikely All individuals included in analysis according to intention-to-treat protocol

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
Thakar, 2021	Computerized Patients were randomized in a 1:1 manner as per a computerized generated sequence.	Unlikely The microbiological team was blinded to the randomization allocation and also to clinical status.	Unclear Not reported.	Unclear Not reported.	Unlikely The microbiological team was blinded	Unclear Outcomes in the methods section were described very general: 'Primary outcomes were assessed for drug tolerance, clinical and virological metrics.'	Likely <u>Loss to follow-up:</u> I: 0/30 (0%) C: 1/30 (0.03%) Reasons: 1 discontinued intervention Eleven patients were excluded due to enrolment error (2 – recovered; 9 – false-positive referral)	Unlikely intention-to-treat analysis.
Chen, 2020a	"Randomization was performed through a computer-generated list stratified by site"	Unlikely	Unclear Blinding of participants was not described	Unclear Blinding of care providers was not described	Unclear Blinding of assessors was not described	Unclear The authors aimed to report the time to clinical recovery (TCCR), but was not clearly described in this version	Unlikely	Unlikely
Pan, 2020 (WHO Solidarity Trial Consortium)	See RoB assessment of Pan (2020) by remdesivir.							
Omrani, 2020	Unlikely <i>Randomization of the study's projected n of 456 was executed by computer in a location (Imperial College London) remote from the study site. Randomization was executed in a restricted (blocked) manner to</i>	Unlikely <i>Central allocation concealment was used. The randomization scheme was transmitted to the study institution's central pharmacy, where it was translated to identical-appearing sequentially numbered drug-bottle sets. Other</i>	Unlikely <i>Study participants were unaware of the specific contents of their medication bottles.</i>	Unlikely <i>Study staff (physicians and nurses who enrolled participants, executed virologic sampling, and assessed and recorded participant's clinical follow-up data) were unaware of study</i>	Unlikely <i>Study staff (physicians and nurses who enrolled participants, executed virologic sampling, and assessed and recorded participant's clinical follow-up data) were unaware of study</i>	Unlikely <i>All primary and secondary outcomes are reported</i>	Likely <i>The main internal validity problems included dropouts and other losses to follow-up.</i>	Unlikely <i>Study planning dictated intent-to-treat (ITT) analysis. Per-protocol analysis was also executed, but only for exploratory assessments.</i>

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	<i>equalize group sizes at the pre-planned interim analysis points (n = 100 and n = 200) as well as the final study n of 456. Randomization was communicated directly from the UK to the HMC pharmacy, and the randomization scheme was seen only by the pharmacist who prepared the study bottles. The author (SAT) executing randomization and communicating randomization to the pharmacy had no involvement in the analysis; her other investigation roles were researching and executing manuscript work relevant to cell biology, and executing Q-PROTECT's data-sharing plan after study completion.</i>	<i>routes of allocation concealment addressed three facets of appearances of bottles and study medications.</i>		<i>medication identity and did not see the contents of the study bottles.</i>	<i>medication identity and did not see the contents of the study bottles.</i>			
Self, 2020	Using a centralized electronic system, we randomly assigned enrolled patients to hydroxychloroquine or placebo in a 1:1 ratio stratified by enrolling hospital using randomization block sizes of 2 and 4.	Unlikely Allocation was concealed.	Unlikely Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.	Unlikely Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.	Unlikely Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.	Unlikely All outcome measures were reported	Unlikely No loss to follow-up	Unlikely None of the participants switched therapies

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Lyngbakken, 2020	Computer randomization procedures	Unclear No stratification was used for the computer randomization procedure.	Likely Our current investigation has several limitations. The study was nonblinded without placebo treatment and we recognize that the lack of blinding may have influenced the standard care treatment and decision making by the treating physician, ultimately affecting our results	Unlikely study personnel performing the RTqPCR and statistical analyses were blinded concerning group allocation	Unlikely study personnel performing the RTqPCR and statistical analyses were blinded concerning group allocation	Unlikely	Unlikely	Unlikely Intention-to-treat analysis were performed.
Horby, 2020b	Eligible and consenting patients were assigned in a ratio of 2:1 to treatment group using web-based simple (unstratified) randomization with allocation concealment	Unlikely A web-based randomization was performed.	Unclear Patients were not blinded to the allocated treatment. However, primary outcome (mortality) is a hard outcome measure. It might have had an impact on other outcomes.	Unclear Caregivers were not blinded to the allocated treatment. However, primary outcome (mortality) is a hard outcome measure. It might have had an impact on other outcomes.	Unclear Local study staff was not blinded to the allocated treatment. However, primary outcome (mortality) is a hard outcome measure. It might have had an impact on other outcomes.	Unclear Preliminary results are presented; not all data is reported yet.	Unlikely Follow-up information was complete for 98% of the patients.	Unlikely All analyses were done according to the intention-to-treat principle.
Ulrich, 2020	Enrolled subjects were randomized 1:1 to study drug or placebo and followed for 30 days. Randomization was stratified by age (>60 years old) and study site	Unlikely	Unlikely Subjects and investigators were blinded to the treatment assignment, but in cases of rapid COVID-19 progression meeting our primary	Unlikely	Unclear	Unlikely	Likely N = 21 lost to follow-up in the intervention group versus N = 15 lost to follow-up in the control group.	Unlikely Primary analyses used the intentionto-treat (ITT) paradigm in which participants are classified according to their randomized treatment assignment, regardless of

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
			end point, or at the request of the treating physician, we allowed for subject unblinding.					treatment receipt or compliance. Secondary analyses assessed the safety population (those who received any dose of study medication) and the per-protocol population (those who received at least 80% of their assigned dose).
Abd-Elsalam, 2020a	Patients were randomized into two groups using a computerized random number generator using simple randomization with an equal allocation ratio.	Unlikely During randomization, the proportional allocation of each clinical stratum was equalized in both groups.	Unlikely Blinding not necessary because of 'hard' outcome measure (mortality)	Unlikely Blinding not necessary because of 'hard' outcome measure (mortality)	Unlikely Blinding not necessary because of 'hard' outcome measure (mortality)	Unlikely All outcome measures in the method section are reported in the results.	Unlikely No lost to follow-up.	Unlikely All included patients in the analysis are exactly the patients who were randomized into the trial.
Brown, 2020	Permuted blocks with concealed allocation	Unlikely Eligible patients were randomly assigned (permuted blocks with concealed allocation) in a 1:1 ratio to hydroxychloroquine or azithromycin. Randomization was stratified by study site.	Likely Remdesivir was differentially prescribed to patients in the hydroxychloroquine arm. The differential use of remdesivir among hydroxychloroquine patients, which has expected efficacy in this patient population, likely biases our estimates in favor of hydroxychloroquine.	Unclear	Unlikely The statistical analysis plan was finalized by investigators/statisticians blinded to trial data	Unlikely	Unlikely	Unlikely Analyses were performed according to the intention to treat principle.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Cavalcanti, 2020	Electronic case-report form system Randomization was performed in blocks of six and was stratified according to the use or nonuse of supplemental oxygen at the time of randomization. Randomization was performed centrally by means of an electronic case-report form system (RedCap) as described in the Supplementary Appendix	Unclear Note: allocation concealment was not described	Likely Note: patients were not blinded	Likely Note: care providers were not blinded	Likely Note: All the trial outcomes were assessed by the site investigators, who were aware of the trial-group assignments (except for patients who had been discharged before day 15 and who were assessed for the primary outcome by means of a blinded telephone interview).	Unlikely Note: outcomes well defined	Unclear Note: loss to follow-up was not described	Unclear Note only patients with confirmed diagnosis were analysed.
Mitjà, 2020	Computer-generated random-number list Participants were randomized (1:1) using a computer-generated random-number list to either the control arm (no treatment aside from usual care) or the intervention arm (HCQ - Dolquine®, 800 mg on day 1, followed by 400 mg once daily for six days).	Unlikely Note: Random allocation was done remotely by a member of the study team not involved in participants' enrollment	Likely Note: Masking was not possible because a placebo could not be prepared due to the emergency nature of the trial.	Unclear Note: not clear whether care providers were blinded, and whether this have lead to potential bias.	Unlikely Note: Laboratory technicians were unaware of participants' treatment allocation, treatment response, and previous PCR results at all time points	Unlikely Note: outcomes well defined	Unlikely Note: loss to follow-up was small, and similar in both groups	Unlikely Note: All allocated patients were included in the intention-to-treat analysis.
Skipper, 2020	Permuted block randomization The trial statistician generated a permuted	Unlikely Note: Allocation assignment was concealed from investigators	Unlikely Note: Participants were blinded.	Unlikely Note: Care providers were blinded.	Unclear Note: not reported whether outcome assessors were blinded	Unclear Note: primary outcome was changed after interim analyses, but reasons were	Unlikely Note: only patients with complete data were analyses. Drop-out rated were similar in both groups.	Likely Note: it was reported that intention-to-treat analysis were performed, but only

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	block randomization sequence using differently sized blocks in a 1:1 allocation, stratified by country. A separate randomization stratum also existed for persons who were initially asymptomatic at the time of informed consent but became symptomatic before receiving the study medication on day 1.	and participants because the study medicine and placebo were similar in appearance.						participants with data were included.
Tang, 2020	Computerized, envelopes opened at enrolment According to disease severity, random 1:1 ratio. “ LL designed the randomisation rules together with the principal investigators, and an independent statistician who was not involved in data analysis implemented them. Equal numbers of cards with each group assignment number randomly generated by computer were placed in sequentially numbered	Unclear Unclear whether procedure is adequate as not all steps were computerized (envelopes)	Unlikely “Patients, investigators, and statisticians were not masked to treatment assignment.”	Unclear “The dose of hydroxychloroquine was adjusted when adverse events were related to hydroxychloroquine, as judged by investigators.” / “Patients, investigators, and statisticians were not masked to treatment assignment.”	Unlikely “Laboratory technicians who did virological, chemical, and other routine measurements were unaware of treatment information.”	Unlikely Authors adequately explain why changes in enrolment (also severe disease patients) and outcomes (viral clearance at day 28 instead of day 10) took place.	Unlikely No loss to follow-up	Unlikely Intention-to-treat analysis used for effectivity analysis. Safety analyses, were based on the patients’ actual exposure.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	envelopes that were opened as the patients were enrolled.”							
Borba, 2020	“An electronically generated randomization list was prepared by an independent statistician, with four blocks of 110 participants per block.”	Unlikely The randomization list associated each patient's study number with an opaque surface hiding the treatment group designation.	Unlikely Participants were blinded	Unlikely Care providers were blinded	Unclear Blinding of assessors was not described	Unclear Not all outcomes are reported in this preliminary study as registered at ClinicalTrials.gov, number NCT04323527.	Unlikely	Unlikely “An intention-to-treat analysis was conducted as part of the primary safety and efficacy Analysis”
4. Immunoglobulin								
4.1. Hyperimmunoglobulin								
Pollizzo (2022)	Participants were randomly assigned (1:1) to receive either hVIG or an equivalent volume of saline as placebo. Randomisation was stratified by site pharmacy; schedules were prepared using a mass-weighted urn design	Unclear No information.	Unlikely “Infusions were prepared by trial pharmacists and masked using opaque sleeves. All other investigators and research staff, and trial participants were masked to the treatment administered.”	Unlikely “Infusions were prepared by trial pharmacists and masked using opaque sleeves. All other investigators and research staff, and trial participants were masked to the treatment administered.”	Unlikely “Infusions were prepared by trial pharmacists and masked using opaque sleeves. All other investigators and research staff, and trial participants were masked to the treatment administered.”	Unlikely All predefined outcome measures were reported.	Unlikely No lost to follow-up reported.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Ali, 2021	Method not described “A randomization list was generated by a hospital personnel unrelated to this study while the study personnel were unaware of the sequence of assignment.”	Unlikely “At the time of randomization, the study personnel received a sealed opaque envelope with assignment to intervention or control group.”	Unlikely “All participants were blinded”	Likely (except for mortality and viral clearance) Not blinded	Likely (except for mortality and viral clearance) Not blinded	Unclear Primary and secondary outcomes differ from announcement in register	Unlikely No loss to follow-up	Unlikely No cross-overs and no loss to follow-up; patients analyzed according to allocation

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
						Registered at clinicaltrials.gov (NCT04521309)		
4.2. Intravenous immunoglobulin								
Mazeraud, 2021	Computerized Randomisation was done with a web-based system.	Unlikely Trial group designation was concealed and the randomisation group was electronically sent to the centre's pharmacy.	Unlikely Trial participants were masked to patient assignment. The double-blinding was provided by each hospital pharmacy, using opaque sleeves and tubing to conceal the product administered.	Unlikely Care providers were masked to patient assignment. The double-blinding was provided by each hospital pharmacy, using opaque sleeves and tubing to conceal the product administered.	Unlikely Outcome assessors were masked to patient assignment. The double-blinding was provided by each hospital pharmacy, using opaque sleeves and tubing to conceal the product administered. The statisticians who analysed the data were masked to group assignment.	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	Unlikely All prespecified primary and secondary outcomes were measured in the intention-to-treat population.
Raman, 2021	Computerized (SAS) "The biostatistician generated random numbers using block randomization with block sizes of 4 using SAS program and allocated eligible patients either to Test group or Control group"	Unclear No information	Likely Open-label study	Likely Open-label study	Likely Open-label study	Likely Not all predefined outcome measures were reported.	Unlikely Small differences in lost to follow-up per group and all data was used in the intention-to-treat analysis	Unlikely Participants included in the study were exactly those who were randomized into the trial.
Gharebaghi, 2020	Computer-generated randomization schedule.	Unlikely	Unlikely Neither patients nor physicians nor data analysts were aware	Unlikely Neither patients nor physicians nor data analysts were aware	Unlikely Neither patients nor physicians nor data analysts were aware	Unlikely	Unlikely Those patients who died before 72 h after the distribution of IVIg and placebos were excluded from our	Unclear

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
			of treatment versus placebo membership.	of treatment versus placebo membership.	of treatment versus placebo membership.		study due to an incomplete course of treatment.	
Tabarsi, 2020	Block randomization method was used for randomization. Eight blocks, including ten patients, were generated by the Online Randomizer website (www.sealesenvelop.com/simple/randomizer).	Unlikely In total, this study analyzed 84 patients who were randomly assigned into IVIg and control groups	Unclear Blinding of participants is not reported in the study	Unclear Blinding of care providers is not reported in the study	Unclear Blinding of outcome assessors is not reported in the study	Unlikely	Unlikely No loss to follow-up reported.	Unclear Not reported.
4.3. Normal immunoglobulin								
NA	NA	NA	NA	NA	NA	NA	NA	NA
5. Convalescent plasma								
Ray, 2022	A digitally derived random sequence divided into four blocks of twenty was used for randomizing the patients	Likely Open-label trial. The allocation of therapies was not concealed following randomization.	Likely Open-label trial. Patients were not masked to treatment allocation.	Likely Open-label trial	Unclear Not described	Unclear Some of the prespecified outcomes were not reported due to technical or operational limitations. This is reported in the article.	Unclear Loss to follow-up not described	Unclear Not reported
Baldéon, 2022	A simple randomization scheme was used to allocate participants in the two treatment groups.	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely No lost-to follow up	Unlikely
Bar, 2021	Unclear	Unclear Not described	Likely Open-label trial	Likely Open-label trial	Unclear Not described	Unlikely	Unlikely	Unclear Not described

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	Participants were assigned to treatment or control in a 1:1 ratio using randomization stratified on the use of remdesivir and mechanical ventilation at entry using block randomization with variable block size. Participants					All outcome measures described in the trial protocol are reported in the results.	The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	
Ortigoza, 2021	Computerized block randomization A centralized electronic system was used to randomly assign enrolled patients to receive CCP or placebo in a 1:1 ratio stratified by enrolment site and risk status using randomization block sizes of 4 and 6 to maintain balanced group sizes. Allocation was concealed.	Unclear <i>Allocation was concealed.</i>	Unlikely <i>Double blind RCT Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.</i>	Unlikely <i>Double blind RCT Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.</i>	Unlikely <i>Double blind RCT Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.</i>	Unlikely <i>All outcome measures described in the trial protocol are reported in the results</i>	Unlikely <i>The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.</i>	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Holm, 2021	Computerized Patients were randomly (1:1) assigned by REDCap to one of the study arms with no baseline stratification.	Unclear Not reported	Likely Open-label trial	Likely Open-label trial	Unclear Not described	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10%.	Unclear Not mentioned in the statistical analysis section.
Menichetti, 2021	Computerized A stratified permuted block randomization procedure with a 1:1	Unlikely Randomisation and subsequent data collection were done by	Likely Open-label trial	Likely Open-label trial	Unclear Not described	Unlikely All outcome measures described in the trial	Unlikely No patients were lost to follow-up	Unlikely The primary and supportive efficacy endpoints were

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	ratio, with blocks of variable sizes and stratification for clinical sites, was generated by using Stata version 16.1 (StataCorp).	means of the web based system REDCap.				protocol are reported in the results.		assessed in the intention-to-treat population.
Estcourt, 2021	Participants were randomized via a centralized computer program to each intervention (available locally) starting with balanced assignment	Unlikely	Likely "This was an open-label study because it was considered unethical to expose patients in the standard of care group, who may have severe lung injury and hypoxia, to receive a potentially harmful extra volume of fluid (with either nonconvalescent fresh frozen plasma or saline) as part of a usual care placebo intervention."	Unlikely "Although clinical staff were aware of their individual patient's intervention assignment, neither they nor the international trial steering committee were provided any information about aggregate patient outcomes. Data were collected prospectively at the bedside by local research teams."	Unlikely "Although clinical staff were aware of their individual patient's intervention assignment, neither they nor the international trial steering committee were provided any information about aggregate patient outcomes. Data were collected prospectively at the bedside by local research teams."	Unlikely All predefined outcome measures were reported.	Likely A lot of patients in the control group withdrew consent compared with the intervention group. Additionally, missing data was more frequent in the control group.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Bégin et al., 2021	Computerized Patients were randomized in a 2:1 ratio to receive convalescent plasma or standard of care using a secure, concealed, computer-generated, web-accessed randomization sequence. Randomization was	Unlikely Patients were randomized using a secure, concealed, computer-generated, web-accessed randomization sequence.	Likely Open-label trial	Likely Open-label trial	Likely An interim analysis by a biostatistician unblinded to the allocation of the intervention was planned for when the primary outcome was available for 50% of the target sample.	Unlikely All outcome measures described in the methods are reported in the results, except for the need for extracorporeal membrane oxygenation.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	Unlikely All randomized patients who received convalescent plasma or standard care were included in the ITT analysis.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	stratified by site and age with allocation made with permuted blocks of size 3 or 6.							
Avendaño-Solá, 2021	Computerized Patients were randomized using a centralized system embedded in the eCRF that ensures allocation concealment. Randomization list was 1:1 ratio, stratified by study site with variable block size multiple of 2 elements.	Unlikely Patients were randomized using a centralized system embedded in the eCRF that ensures allocation concealment.	Likely Open-label trial	Likely Open-label trial	Likely An interim analysis by a biostatistician unblinded to the allocation of the intervention was planned for when the primary outcome was available for 50% of the target sample.	Unlikely All outcome measures described in the methods are reported in the results, except for duration of hospital stay	Unlikely The percentage of patients lost to follow-up is less than 10%, but higher in the control group.	Unlikely All randomized patients who received convalescent plasma or standard care were included in the ITT analysis.
Körper, 2021	Web based permuted block randomization Patients (n=105) were randomized using a web-based system with a stratified 1:1 allocation ratio between each stratum (Figure 1). Patients were stratified prior to permuted block randomization by presence or absence of ventilation support, ECMO or ICU treatment.	Likely The allocation of CCP to a recipient was based on the following criteria – provided availability: ABO-identical units, all three CCP units for a patient from one donor. If availability of CCP did not allow transfusing ABO identical plasma, also minor compatible units were used, i.e. donor plasma did not contain isoagglutinins directed against ABO antigen(s) present on the recipient’s red blood cells, e.g. plasma from a type AB donor transfused to a type A	Likely Open label	Likely Open label	Likely Open label	Unlikely all predefined outcome measures were reported	Unlikely No lost to follow up.	Likely Cross over design

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
		recipient. When all criteria were met readily available products with the highest PRNT-50 titers were chosen.						
Devos, 2021	Patients were randomised through a computerised system according to a 2:1 allocation scheme stratified by study site using randomly selected block sizes of 6 or 9, to open-label convalescent plasma combined with standard of care (intervention group) or standard of care alone (control group).	Unlikely "stratified by study site using randomly selected block sizes of 6 or 9".	Likely "The study was designed as an open label study, where the intervention was not blinded. No placebo treatment was given".	Likely "The study was designed as an open label study, where the intervention was not blinded. No placebo treatment was given".	Likely "The study was designed as an open label study, where the intervention was not blinded. No placebo treatment was given".	Unlikely All predefined outcome measures were reported.	Likely Unequal exclusions between both groups. For the per protocol analysis, n=26 patients were excluded because they received less than 4 units of convalescent plasma. In the control group, n=2 patients were excluded because they received convalescent plasma within 30 days.	Unlikely Full analysis set and separate per protocol analysis.
Korley, 2021	Patients were randomized in a 1:1 ratio to receive an infusion of either one unit of ABO compatible Covid-19 convalescent plasma or 250 ml of normal saline (placebo) that was colored with a parenteral multivitamin concentrate to resemble plasma.	Unlikely Both convalescent plasma and placebo were covered with light-resistant bags to preserve the blinded group assignment.	Unlikely Both convalescent plasma and placebo were covered with light-resistant bags to preserve the blinded group assignment.	Likely Single blinded trial	Unlikely Single blinded trial; study has hard (objective) outcome measures	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% , but differs between treatment groups.	Unlikely All randomized patients who received study medication were included in the ITT analysis.
Karena, 2021	Permuted block randomisation	Unclear	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely	Unlikely Almost equal drop-outs in both groups.	Unlikely Participants included in the analysis are

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	<i>Permuted block randomisation with varying sizes of blocks was used to randomly assign eligible participants to receive either CCP plus standard of care (CCP +SOC) or standard of care only (SOC).</i>					All predefined outcome measures were reported.		exactly those who were randomized into the trial.
Bainbridge, 2021	Participants enrolled in June through October 2020 at 2 hospitals in San Francisco, California were randomized 1:1 to receive 1 unit of convalescent plasma or nonimmune FFP (200–250 mL).	Unlikely Randomization will be provided to an unblinded provider who is not part of the care team who will place the order for the plasma (CCP vs. control plasma) using a paper order that will not be part of the electronic medical record.	Unlikely Double-blind study.	Unlikely Double-blind study.	Unlikely Double-blind study.	Likely Primary and secondary outcomes in protocol not reported in the article.	Unlikely No loss to follow-up	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Sekine, 2021	Computerised Randomisation in a 1:1 ratio was performed using computer-generated randomization with random block sizes of 2 or 4 and stratified according to the unit of hospitalization on enrolment.	Unlikely random block sizes of 2 or 4 and stratification according to the unit of hospitalization on enrolment	Likely open-label trial; participants were unmasked	Likely open-label trial; investigators were unmasked	Likely researchers were aware of the trial-group assignments	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely no loss to follow-up	Unlikely Data were primarily analysed according to the intention to treat principle.
O'Donnell, 2021	Web-based randomization platform	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	Enrolled participants were randomized in a 2:1 ratio to receive either convalescent plasma or control plasma using a web-based randomization platform; treatment assignments were generated using randomly permuted blocks of different sizes. Randomization was stratified by site but not by severity of illness.	Treatment assignments were generated using randomly permuted blocks of different sizes. Randomization was stratified by site but not by severity of illness.	Use of control plasma was a strength since both study agents had the same appearance, enhancing the blinded nature of the trial.	The clinical teams directly managing patients and the trial clinicians who adjudicated clinical status and determined 28-day outcomes were blinded to treatment allocation.	The clinical teams directly managing patients and the trial clinicians who adjudicated clinical status and determined 28-day outcomes were blinded to treatment allocation.	All predefined outcome measures were reported.	Dropouts were almost equal in both groups.	Participants included in the analysis are exactly those who were randomized into the trial.
AlQahtani, 2021	“The patients were block randomised (in blocks of 4) by computer-generated random numbering to either the standard therapy or CP arms.”	Unclear Not reported	Likely Patients were not blinded	Likely Clinicians were not blinded	Unclear Not reported	Unlikely Primary outcomes and almost all secondary outcomes were reported	Unlikely Missing data was only reported for anti-body levels, being a secondary outcome measure	Unclear A primary analysis and per-protocol analysis was mentioned in the flow chart, but both analyses included 20 patients per group
Bennett-Guerrero, et al., 2021	Computerized Patients were randomized 4:1 to convalescent or standard plasma using permuted block randomization lists generated using SAS software, and implemented using an interactive web	Unclear The team members that randomized the patients were not blinded.	Unlikely Patients were blinded	Unlikely Care givers were blinded	Unlikely Outcome assessors were blinded	Unlikely Outcomes described in method section were also reported.	Unlikely None of the patients was lost to follow-up.	Unlikely Intention to treat analysis was performed.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	response randomization tool in REDCap.							
Pouladzadeh, 2021	A table of the 6-item randomized block by computer. randomly assigning patients to the intervention and control groups using a 6-item randomized block method and an equal allocation ratio (1:1). To maintain single blinding, we used a "Simple Central randomization" in which the individual recruiting the patient (senior physician responsible for therapeutic intervention) contacted the center by phone after the patient is enrolled.	Unlikely The respondent in the center was the second researcher, who had designed a table of the 6-item randomized block by computer and added concealment codes without knowing the patients' medical conditions.	Likely Patients were aware.	Likely Senior physician aware (senior physician responsible for therapeutic intervention).	Unclear Not reported.	Unlikely Outcomes mentioned in the Methods section were similar as the outcomes reported in the Results section.	Unlikely One patient was lost in the intervention group as well as the control group due to declining of participation.	Unclear Not reported.
Libster, 2020	Computerized A computergenerated randomization sequence with a balanced permuted block design (block size 2) was prepared at the data center.	Unclear No details provided	Unlikely Both the convalescent plasma and placebo were concealed with opaque bags and tape to cover the infusion catheter.	Unlikely Both the convalescent plasma and placebo were concealed with opaque bags and tape to cover the infusion catheter.	Unlikely Both the convalescent plasma and placebo were concealed with opaque bags and tape to cover the infusion catheter.	Unlikely Trial registered: NCT04479163. Primary and 4/5 secondary outcomes reported; 5 th secondary outcome not reported in publication (Duration of oxygen support; however, only 5% and	Unlikely No loss to follow up	Unlikely ITT analysis performed; in addition, analysis performed excluded n=6 patients that reached endpoint of study before administration of treatment

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
						8% of patients needed supplementation oxygen)		
Simonovich, 2020	Subsequently, patients were randomly assigned through the REDCap randomization program, in a 2:1 ratio to receive either Covid-19 convalescent plasma transfusion or placebo (normal saline solution).	Unlikely Randomization was performed in variable size blocks of 3, 6, 9 and 12 participants and stratified by clinical site.	Unlikely Both participants and the clinical research team remained blind to the treatment assignment	Unlikely Randomization process was carried out by the designated unblinded investigators, who were not blinded to treatment assignment. The same unblinded staff was responsible for preparing the infusion bag with the plasma/saline content and masking both the bag and the whole infusion line with an opaque sleeve.	Unlikely The study statistics team was also unblinded for the purpose of elaborating interim analysis and safety reports.	Unlikely All described outcomes were reported.	Unlikely No patients were lost to follow-up.	Unlikely All patients were analyzed except for just one patient who withdrew informed consent. This patient was the only patient that did not receive the assigned intervention (per protocol analysis). Therefore, bias to violation of intention to treat analysis looks unlikely.
Salman, 2020	Computerized “Using website software, enrolled patients were randomized in a 2:1 ratio to receive standard therapy alone, versus receiving standard therapy plus plasma of recovered COVID-19 individuals.”	Unlikely “Treatment allocation were assigned using randomized block design to provide symmetrically distributed base on key outcome-related characteristics. “	Unlikely “Patients were blinded to the intervention.”	Unlikely “ Plasma of recovered COVID-19 individuals was given and clinical data were monitored by the attending team, that was not aware of the research scheme.”	Unlikely “Radiological reports and laboratory parameter were registered by the administrative staff who was unaware of research protocol. The blood bank staff was blinded to group assignment.”	Unlikely The study was registered with ClinicalTrials.gov Identifier: NCT04530370	Unlikely Short follow-up, 5 days, no loss to follow-up	Unlikely Individuals analysed as randomized; no cross-over or drop-outs
Agarwal, 2020	A stratified block randomisation Strategy.	Unlikely	Likely Open label phase II	Likely Open label phase II	Likely Open label phase II	Unlikely	Unlikely	Unlikely

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		A stratified block randomisation strategy was used to allocate participants in a 1:1 ratio. Stratification was by sites; block randomisation was done with unequal block sizes.	multicentre randomised controlled trial	multicentre randomised controlled trial	multicentre randomised controlled trial		Vrijwel gelijk in beide groepen (N = 2 vs N = 1)	We performed an intention-to-treat analysis after imputing the missing composite outcomes for progression to severe disease or mortality.
Li, 2020b	Computer-generated random numbering Patients were randomly assigned via computer-generated random numbering (1:1) to treatment groups. The randomization was stratified based on the severity of COVID-19 and a randomization schedule was generated using block randomization with block size of 4 for each type of COVID-19 by SAS software.	Unlikely Patients were randomly assigned via computer-generated random numbering.	Unclear It was an open label trial, so participants were not masked. Furthermore, use of standard care was not protocolized.	Unclear It was an open label trial, so care providers were not masked. Furthermore, use of standard care was not protocolized.	Unclear It was an open label trial, but the evaluation of clinical outcomes was performed by an investigator who was blind to the study group allocation.	Unlikely Outcomes mentioned in methods section are also reported.	Unlikely None of the patients was lost to follow-up.	Unlikely Intention to treat analysis was performed. A per-protocol analysis was also performed for the primary end point as a sensitivity analysis.
6. Monoclonal antibodies								
6.1. Adalimumab								
Fakharian, 2021	Computerized The patients were randomized via permuted block randomization.	Unclear Not reported	Unclear It is not described whether participants were blinded.	Unclear It is not described whether care providers were blinded.	Unclear It is not described whether outcome assessors were blinded.	Unclear Outcomes like trend of symptom improvement and NIV/use of face/nasal mask were not	Unlikely None of the patients was lost to follow-up.	Unlikely Intention to treat analysis was performed.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
						mentioned in the methods section.		
6.2. Bamlanivimab (INN, codenamed LY-CoV555, neutralizing monoclonal antibody)								
Lundgren, 2021	Hospitalized patients with Covid-19 were randomly assigned in a 1:1 ratio to receive either bamlanivimab or matching placebo. Randomization was stratified according to the trial pharmacy, since each pharmacy could serve more than one trial site.	Unclear Not further explained in the study.	Unclear Not further explained in the study.	Likely The infusion was prepared by an unblinded pharmacist. All other site personnel and study participants were blinded to treatment assignment.	Unlikely All analyses of biological material were done in a blinded manner at laboratories affiliated with the funding source	Unlikely All outcome measures described in the trial protocol are reported in the results	Likely The percentage of patients lost to follow-up is more than 10% and is not similar between treatment groups.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Chen, 2021 Gottlieb, 2021 (same trial)	All participants will be centrally randomized to study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Participants will be stratified by duration since symptom onset to randomization (≤8 days versus >8 days).	Unlikely All eligible participants will be randomized, initially following an equal allocation to treatment arms. Given the staggered start of the treatment arms, periodic adjustments to the allocation ratio, informed by planned interim analyses, may be made in an effort to achieve an equal allocation across the treatment arms at the end of enrollment.	Unlikely This is a blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study. If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion	Unlikely This is a blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study. If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion	Unlikely This is a blinded study. Neither participants, nor investigators, nor the sponsor study team will be aware of treatment assignments prior to the final data base locks at the conclusion of the study. If an investigator, site personnel performing assessments, or participant is unblinded while the infusion is ongoing, the participant must be discontinued from the study intervention and the infusion	Unlikely All proposed outcomes were reported in the study.	Unlikely None of the patients were lost to follow-up	Chen, 2021 Gottlieb, 2021 (same trial)

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
			stopped. If any amount of study intervention was administered, follow procedures according to the SoA.	stopped. If any amount of study intervention was administered, follow procedures according to the SoA.	stopped. If any amount of study intervention was administered, follow procedures according to the SoA.			
Lundgren, 2020	Hospitalized patients with Covid-19 were randomly assigned in a 1:1 ratio to receive either LY-CoV555 or matching placebo. Randomization was stratified according to the trial pharmacy, since each pharmacy could serve more than one trial site.	Unclear Not further explained in the study.	Unlikely Double-blind study	Unlikely Double-blind study	Unlikely Double-blind study	Unlikely Predefined outcome measures are reported	Unlikely No lost to follow-up reported	Unlikely Participants included in the analysis are the participants who were randomized into the trial. ITT analysis performed.
6.3. Bamlanivimab and Etesevimab (LY-CoV016; recombinant fully human monoclonal neutralizing antibody; together is combination of two monoclonal antibodies)								
Dougan, 2021a	Computerized Participants were centrally randomized to either bamlanivimab and etesevimab together or placebo using an interactive web response system. Randomization was stratified by patients' symptom duration (≤ 8 days versus > 8 days), and age at the time of screening (< 18 years of age versus ≥ 18 years of age). All eligible patients were randomized in a	Unclear Allocation concealment was not reported.	Unclear Not stated.	Unclear Not stated.	Unclear Not stated.	Unclear Not all of the outcome measures mentioned in the method section were reported.	Unlikely Small difference in % of patients lost to follow-up, and reasons were not given.	Unclear No ITT-analysis was performed.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	1:2 (placebo: bamlanivimab and etesevimab) allocation ratio.							
Dougan, 2021b	No information on randomization process Text on randomization not available	Unclear No information on concealment	Unlikely It is stated that this is a double-blinded RCT, placebo was administered in the same way as the intervention.	Unclear No information on blinding of care providers.	Unclear No information of blinding of outcome assessors . One statement was found regarding the outcome mortality: "Of these 10 deaths, 9 were deemed to be Covid-19–related by trial staff who were unaware of the trial-group assignments."	Likely According to the methods, subgroup analysis for adolescents and adults were performed, but the outcomes were not reported. Some of the outcomes mentioned in the methods (e.g. the area under the response-time curve for the viral load through day 7) were not reported.	Unclear Loss to follow-up was comparable between the groups. However, the reasons with accompanying numbers were not clearly stated.	Unclear 14 patients were randomized but did not receive the infusion, it is unclear why.
Gottlieb, 2021	See risk of bias table of Gottlieb (2021) by bamlanivimab.							
6.4. Casirivimab and imdevimab (REGN-COV2; combination of two noncompeting, neutralizing human IgG1 antibodies)								
Weinreich, 2021	"Patients will be randomized according to a central randomization scheme using an interactive web response system (IWRS)."	Unclear No details provided	Unlikely "A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for IV administration. The drug infusion solution must be provided in identical form for active and placebo treatments, so that they remain	Unlikely See column 4	Unlikely See column 4	Unlikely Outcomes and timing according to study protocol "An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 in-clinic visit. Safety and efficacy analyses for phase 1 will be performed when all randomized	Likely Number of patients that did not complete the trial differ between treatment groups (I: 12/92 (13.0%); II: 6/90 (6.7%); C: 5/93 (5.4%))	Likely Percentage of patients not included in analyses of virological outcomes and safety outcomes not equal between groups; analyses not performed according to intention-to-treat protocol.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
			indistinguishable to both study personnel and patients. Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments". throughout the study."			patients have completed the day 29 visit." ClinicalTrials.gov number, NCT04425629.		
6.5. CERC-002								
Perlin, 2021	Computerized Randomization (1:1) was done via Prism eSource (PRA Health Sciences) using a permuted block randomization algorithm and a block size of 2. The Prism system assigned random numbers, which were used for treatment allocation.	Unlikely Randomization (1:1) was done via Prism eSource (PRA Health Sciences) using a permuted block randomization algorithm and a block size of 2. The Prism system assigned random numbers, which were used for treatment allocation.	Unlikely All patients, investigators, and study personnel were blinded to treatment assignment until after the database lock, with the exception of individuals (e.g., pharmacists, individuals from the contract research organization) who required access to the randomized treatment assignment in order to fulfil their role in the study conduct and data analysis.	Unlikely All patients, investigators, and study personnel were blinded to treatment assignment until after the database lock, with the exception of individuals (e.g., pharmacists, individuals from the contract research organization) who required access to the randomized treatment assignment in order to fulfil their role in the study conduct and data analysis.	Unlikely All patients, investigators, and study personnel were blinded to treatment assignment until after the database lock, with the exception of individuals (e.g., pharmacists, individuals from the contract research organization) who required access to the randomized treatment assignment in order to fulfil their role in the study conduct and data analysis.	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	Unlikely As specified a priori, the primary endpoint was evaluated among patients who did not receive high flow O ₂ or positive-pressure O ₂ prior to randomization, although patients receiving non-invasive O ₂ support was not excluded from the study or other secondary endpoints.
6.6. Granulocyte-macrophage colony-stimulating factor (GM-CSF)								
NA	NA	NA	NA	NA	NA	NA	NA	NA
6.7. Infliximab								

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Fisher, 2021	Computerized Randomisation was performed by an automated minimisation procedure that attempted to allocate participants in a balanced manner between treatment groups available at the site, allowing for the sole stratification variable and with a 20% random component.	Unlikely The in-house system for randomisation was managed by the programming team at the CRCTU. Site research staff would enter data via eCRFs. The system was designed with the capability of turning off arms or allowing for the addition of new arms given the platform nature of the trial. Programming were to be informed of any modifications to be made following the outcome of interim analyses and implemented them accordingly.	Likely Open-label trial. Patients were not masked to treatment allocation.	Likely Open-label trial. Although clinical staff were aware of treatment allocation, aggregate outcomes were not provided to them, the trial management committee, or the trial steering committee.	Unclear Not described	Unlikely All outcome measures described in the trial protocol are reported in the results, except for body temperature, respiratory rate and destination of discharge. The authors considered data on respiratory rate, body temperature and destination of discharge to be non-informative and, therefore, these data are not shown. Furthermore, data on lymphocyte and neutrophil counts, neutrophil-lymphocyte ratios, and ferritin, d-dimers, and lactate dehydrogenase will be presented alongside exploratory biological outcomes in a future publication.	Likely The percentage of patients lost to follow-up is more than 10% for 2 of 3 treatment groups and differs between treatment groups.	Unlikely The primary outcome was analysed on a modified intention-to-treat population, which included all participants who received trial treatment and had a baseline CRP measurement and at least one measurement after treatment. The modified intention-to-treat population for secondary outcomes included all patients who received any trial treatment and who had available data for the respective outcome.
6.8. Itolizumab (humanized monoclonal antibody (IgG1 kappa anti-CD6))								
Kumar et al., 2021	Computerized Randomization was centrally done using computer-generated sequences (SAS version 9.4)	Likely Concealment not described, but: "Initial dosing was done for the first five patients in a staggered manner wherein after	Likely Open-label (except for mortality)	Likely Open-label (except for mortality)	Likely Open-label (except for mortality)	Unclear Prospectively registered; Clinical Trials Registry of India (CTRI; number CTRI/2020/05/024959);	Unlikely No lost to follow-up	Likely "Patients who were randomized, but did not receive the full infusion, were considered unevaluable and the

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		a patient was dosed, safety was monitored for 24–48 hours prior to dosing the next patient”.				Participants that were discharged were excluded from analysis; could introduce bias in the results of the total group		same randomization code was allocated to the next patient enrolled by the study site”
6.9. Lenzilumab								
Temesgen et al., 2021	<p>Computerized block randomisation</p> <p>Enrolled patients were randomly assigned 1:1 to receive lenzilumab or matched placebo in addition to standard treatment per institutional guidelines at each site. Patients were stratified at randomisation by age (≤65 vs >65 years) and disease severity (severe, SpO2 ≤94% on room air or requiring low-flow supplemental oxygen; critical, requirement for high-flow oxygen delivery device or NPPV, or multi-organ dysfunction–failure or shock). A block randomisation method implemented with a central randomisation system (Rave Randomisation & Trial Supply Management;</p>	Unlikely Allocation of treatment was concealed to all investigators, study personnel, and patients. The investigational pharmacist was responsible for the preparation of study drug for each patient and was unmasked to the randomisation assignment.	Unlikely Allocation of treatment was concealed to all investigators, study personnel, and patients.	Unlikely Allocation of treatment was concealed to all investigators, study personnel, and patients.	Unlikely Allocation of treatment was concealed to all investigators, study personnel, and patients.	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	Unlikely The primary and secondary endpoints were assessed in the intention-to-treat population.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	Medidata, NY, USA) was used to assign patients to treatment groups.							
6.10. Mavrilimumab (human monoclonal antibody; anti-GM-CSF-Rα; human isoform IgG4)								
Cremer, 2021	Computerised Randomisation was centralised through REDCap Cloud with stratification by hospital site.	Unclear Concealment not described	Unlikely The participants and all clinical and research personnel were masked to treatment assignment, except for a research pharmacist who prepared the mavrilimumab infusion or equal volume infusion of diluent for placebo.	Unlikely The participants and all clinical and research personnel were masked to treatment assignment, except for a research pharmacist who prepared the mavrilimumab infusion or equal volume infusion of diluent for placebo.	Unlikely The participants and all clinical and research personnel were masked to treatment assignment, except for a research pharmacist who prepared the mavrilimumab infusion or equal volume infusion of diluent for placebo.	Likely Trial registered at ClinicalTrials.gov, NCT04399980, NCT04463004, and NCT04492514. Trial stopped due to slow enrolment after the first surge of COVID-19, the study was concluded after enrolment of 40 patients (in stead of 60). Study done during time of limited resources; results for PaO ₂ to FiO ₂ ratio after day 3, change in SOFA score, reduction in C-reactive protein concentration, and time to negative SARS-CoV-2 RNA concentrations are not reported due to missing data.	Unlikely 1 patient of control group lost to follow-up but included in almost all analyses; no bias expected	Unlikely 1 patient lost to follow-up but included in almost all analyses; no bias expected
6.11. Namilumab								
Fisher, 2021	See risk of bias table of Fisher (2021) by Infliximab.							
6.12. Sotrovimab								
Self, 2021	Web based	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	<p><i>Participants were randomly assigned to one of two active therapies (sotrovimab or BR11-196 plus BR11-198) or placebo using a web-based application that verified eligibility before randomisation</i></p>	<p>For sites consenting patients to both investigational agents (all but one site), randomisation allocation was 2:1:2:1 to sotrovimab, matching placebo for sotrovimab, BR11-196 plus BR11-198, or matching placebo for BR11-196 plus BR11-198. One site did not obtain regulatory approval for BR11-196 plus BR11-198, and so participants were randomly assigned 1:1 to sotrovimab or matching placebo. For the analysis, the concurrent placebo groups (placebo matching sotrovimab and placebo matching BR11-196 plus BR11-198) were pooled, resulting in approximately a 1:1:1 allocation of sotrovimab to BR11-196 plus BR11-198 to placebo. Randomisation was stratified by trial site pharmacy (geographically close clinical sites shared a single trial pharmacy in some cases).</p>	<p>Double-blind study.</p>	<p>Double-blind study.</p>	<p>Double-blind study.</p>	<p>All predefined outcome measures were reported.</p>	<p>No big differences in lost to follow-up. Moreover, all data was analyzed in the ITT analysis.</p>	<p>Participants included in the analysis are exactly those who were randomized into the trial.</p>

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
Gupta, 2021b	Computerized Eligible patients were randomly assigned in a 1:1 ratio with the use of an interactive Webbased response system. Patients were stratified according to age (≤ 70 years or >70 years), symptom duration (≤ 3 days or 4 or 5 days), and geographic region.	Unclear No information available	Unlikely The trial pharmacists reconstituted and dispensed sotrovimab and placebo within equal time frames in order to maintain blinding.	Unclear No information available	Unclear No information available	Unlikely Reported outcomes correspond with outcomes in protocol	Unclear No information for the safety analysis. The following was reported for the efficacy analysis: In this intention-to-treat population, both the numbers of patients who withdrew from or continued in the trial and the durations of follow-up were similar in the two trial groups. Overall, 4 patients each in the sotrovimab and placebo groups withdrew from the trial (3 patients in the sotrovimab group withdrew before they received sotrovimab).	Unlikely Only results from the intention-to-treat analysis were reported.
6.13. Tixagevimab and cilgavimab (AZD7442)								
NA	NA	NA	NA	NA	NA	NA	NA	NA
6.14. Vilobelimab (Anti-C5a antibody IFX-1; monoclonal anti-human complement factor C5a antibody)								
Vlaar, 2021	Unlikely "Randomisation was done by investigators centrally with an online tool within the electronic case report form and was stratified by study site."	Unlikely "The tool used a randomised variable block length of either 2 or 4. The randomisation list was only available to contract research organisation (Metronomia) staff involved in the production of the	Likely Open-label study (Outcome measure mortality unlikely)	Likely Open-label study (Outcome measure mortality unlikely)	Likely "The open-label design might have resulted in bias in outcome and safety assessments." (Outcome measure mortality unlikely)	Unlikely All predefined outcome measures were reported.	Unlikely No patients were lost to follow-up.	Unlikely "All 30 patients were included in the intention-to-treat analysis."

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
		randomisation list and set-up of the online randomisation tool.						
7. Polyclonal antibodies								
Lopardo, 2021	Patients were randomized in a 1:1 manner to receive either active treatment (INM005) or placebo. Permuted block randomization was performed with a block size of 6 in a mixed sequential fashion. Randomization was centrally performed through an allocation system based upon a R free software environment.	Unlikely Unblinded site personnel accessed the database with a non-delegable individual user and password in order to receive assignment information. As such, randomization results were concealed to the rest of the site research members. This procedure was maintained until the first twelve subjects were randomized in the study. From patient thirteen onwards randomization was stratified per participating site and directly performed by the unblinded pharmacist designated at each participating site through a close envelope method maintained in random order. Closed envelopes were only accessible to unblinded pharmacists	Unlikely Closed envelopes were only accessible to unblinded pharmacists and unblinded statisticians and concealed to all other personnel. Site pharmacist was responsible for properly masking the intervention, handing the corresponding optically indistinguishable infusion bag to the blinded clinical team.	Unlikely For the initial participants, random allocation was supervised by an unblinded statistician specifically designated by the Sponsor that did not participate in any patient-related activities and who was in either phone and email contact with a designated unblinded pharmacist from each participating site. Unblinded site personnel accessed the database with a non-delegable individual user and password in order to receive assignment information. As such, randomization results were concealed to the rest of the site research members.	Unlikely A blinded interim analysis was planned when about 60% of the enrollment was reached.	Unlikely All predefined outcome measures were reported.	Unlikely No patient was lost to follow-up	Unlikely The patients included in the analysis are the exact same patients who were randomized to the treatment groups.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		and unblinded statisticians and concealed to all other personnel. Site pharmacist was responsible for properly masking the intervention, handing the corresponding optically indistinguishable infusion bag to the blinded clinical team.						
8. Supplements								
8.1. Vitamin C								
Majidi, 2021	Web based This study was done as a double-blind, without placebo trial, such that the patients and researchers were not aware of the arms of the study. The allocation to the groups was done through web based randomization using https://www.randomizer.org .	Unlikely The allocation to the groups was done through web based randomization using https://www.randomizer.org . Sealed non-transparent envelopes with randomized sequences were used to hide the allocation.	Unlikely Patients and researchers were not aware of the arms of the study	Unlikely Patients and researchers were not aware of the arms of the study	Unlikely Patients and researchers were not aware of the arms of the study	Unlikely All predefined outcome measures were reported.	Unclear No information.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial
Zhang, 2021	Random number list, computerized, clinicians that included patients did not have insight in this list.	Unlikely "The generated random list was stored by the principal investigator who was not involved in the	Unlikely "The grouping and intervention were unknown to the participants and	Unlikely "The grouping and intervention were unknown to the participants and	Unlikely "The grouping and intervention were unknown to the participants and	Likely ClinicalTrials.gov (ID: NCT04264533; registered Feb 14 th , 2020	Unlikely All patients included in analysis	Unlikely No drop-out or cross-overs; all patients included in analysis

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	“Each ICU was assigned with an independent random numeric table generated by Microsoft Excel 2019 by the primary investigator alone. Each table had equal numbers of 1 and 2, which represented the placebo group (bacteriostatic water infusion) and treatment group (HDIVC), respectively.”	treatment of patients and hidden to the other investigators. When a patient was transferred to the ICU and met the enrollment criteria, the clinician on duty would inform the principal investigator and obtain a number from the list. Then, participants were enrolled in the corresponding group according to the chronological order of ICU recruitment.”	investigators who were responsible for data collection and statistical analysis.”	investigators who were responsible for data collection and statistical analysis. VC injection and sterile water for injection were both colorless and contained in the same brown syringes with different marks and without explanations on the syringe to make sure that patients could not distinguish the treatment they receive.”	investigators who were responsible for data collection and statistical analysis.”	Elaborate result section; APACHE score only described at baseline; protocol described time point for results at day 10 and 28, not consistent with publication.		
Thomas, 2021	The randomization grid was designed via the REDCap database and based on 25% of anticipated enrolled patients in each of the 4 groups.	Unlikely An automatically created link in REDCap randomized the patient to the supplement group based on the randomization grid.	Likely The current study was open label, and patients were not masked to which therapy they received.	Likely Open-label study	Likely Open-label study (mortality unlikely)	Unlikely All predefined outcomes were reported	Likely Numbers of lost to follow-up differ between the four groups.	Unlikely All allocated patients were analysed
JamaliMoghadam Siahkali, 2021	Block randomization	Unclear Concealment of allocation not described	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely All predefined outcome measures were reported	Unlikely No loss to follow-up reported in the study	Unlikely
Darban et al., 2021	Not reported	Unclear <i>Not reported</i>	Likely <i>It is an open-label study</i>	Likely <i>It is an open-label study</i>	Likely <i>It is an open-label study</i>	Unclear <i>Outcomes like ICU length of stay and deterioration of the disease were not</i>	Unlikely <i>None of the patients was lost to follow-up.</i>	Unclear <i>The study was stopped in 1 patient due to hypersensitivity to treatments. It is not</i>

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
						<i>mentioned in the methods section. However, it is a short communication paper.</i>		<i>clear whether data of this patient were included in the analysis.</i>
8.2. Vitamin D								
Elamir, 2021	Electronic randomization Eligible patients were allocated at a 1:1 calcitriol, no calcitriol ratio through electronic randomization on the day of admission.	Likely Enrolled subjects were assigned treatment with calcitriol 0.5 µg daily for 14 days or hospital discharge, whichever came first; or no treatment. The remainder of the patient's care was determined by the primary team. Medication was supplied by the inpatient pharmacy.	Likely Open-label trial	Likely Open-label trial	Likely Open-label trial	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely No lost to follow up.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Murai, 2020	Computerized Patients were assigned in a 1:1 ratio to the vitamin D3 group or the placebo group. The randomization list was created using a computer-generated code with block sizes of 20. A staff member who had no role in the study managed the randomization.	Unclear Unclear whether the randomization list is accessible before patient enrolment and whether allocation was concealed	Unlikely Patients and investigators remained blinded to randomization until the final analysis.	Unlikely The solutions were identical in color, taste, smell, consistency, and container. They were prepared by the pharmacy unit of the Clinical Hospital and labeled by a staff member who did not participate in the study. Patients and investigators remained blinded to randomization until the final analysis.	Unlikely Patients and investigators remained blinded to randomization until the final analysis.	Unlikely Relevant outcomes reported; described in publication why some outcomes are to follow and some were not possible.	Unlikely Resp. 1 and 2 patients dropped out; withdrew consent	Unlikely No ITT protocol, but low drop out rates, not expected to induce bias

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Rastogi, 2020	Method of randomisation not reported	Unclear No description of randomisation process.	Unclear Blinding of participants is not described	Unclear Blinding of care providers is not described	Unclear Blinding of outcome assessors is not described	Unlikely	Unlikely No loss to follow-up reported	Unlikely A modified intention-to-treat analysis was performed
Castillo, 2020	An electronically generated randomization 2:1 list was prepared by independent statisticians.	Unlikely	Unclear	Unlikely The list was accessible only to non-masked specialists in the study in an attempt to minimize observation bias.	Unlikely The patients' data were recorded in the hospital's electronic medical record, with blind access by the technical data collectors and the statistician who carried out the study.	Unlikely All outcome measures in the method section are reported in the results.	Unlikely No lost to follow-up	Unlikely All included patients in the analysis are exactly the patients who were randomized into the trial.
8.3. Zinc								
Patel, 2021	Computerized "Randomisation will be performed by the randomisation module in Research Electronic Data Capture (REDCap, Vanderbilt University, USA), which is a secure web application for managing online data collection"	Unclear Concealment of allocation not described	Unlikely "The investigators, study coordinators, treating physicians, bedside nurses, and patients/ family remained blinded to the allocated study solution."	Unlikely "The investigators, study coordinators, treating physicians, bedside nurses, and patients/ family remained blinded to the allocated study solution."	Unlikely "The investigators, study coordinators, treating physicians, bedside nurses, and patients/ family remained blinded to the allocated study solution."	Unlikely Registration: ACTRN12620000454976). Protocol: https://bmjopen.bmj.com/content/10/12/e040580.abstract	Unlikely No loss to FU reported	Unlikely No loss to FU reported and all participants analysed as allocated
Thomas, 2021	See RoB assessment of Thomas (2021) by Vitamin C / Ascorbic acid.							
Darban, 2020	See RoB assessment of Darban (2021) by Vitamin C / Ascorbic acid.							
Abd-Elsalam, 2020b	Method of randomisation is not described	Unclear It is not described if concealment of allocation takes place.	Unclear It is not described if participants were blinded to treatment allocation.	Unclear It is not described if care providers were blinded to treatment allocation.	Unclear It is not described if outcome assessors were blinded to treatment allocation.	Unlikely Outcomes written in the methods section were also described in the results.	Unclear Nothing described about (loss to) follow-up.	Unclear Not described if the results were analyzed according to the

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
								intention to treat analysis.
9. Antiviral treatment								
9.1. Darunavir (antiretroviral treatment; also in combination with cobicistat)								
Chen, 2020b	Participants were randomized to the DRV/c group or the control group depending on the parity of their medical record number.	Unclear Medical record number was used in the randomization process.	Unlikely Open-label trial. However, it is not likely that this results in risk of bias for the main outcome measure (viral clearance rate at day 7).	Unclear Open-label trial	Unclear The outcome assessors were not mentioned.	Unlikely The primary endpoint and secondary endpoints listed in the methods section are reported in the results section.	Unlikely All participants completed the study, except 1 patient in the DRV/c group who progressed to critical condition on day 4 and withdraw from the study	Unclear For the primary endpoint, both intention-to-treat (ITT) and per-protocol (PP) analysis were used. For the secondary endpoints, this was not mentioned in the article.
9.2. Favipiravir (be eventually used in combination with Baloxavir and/or marboxil)								
Ivashchenko, 2021	The patients were randomized at a 1:1:1 ratio to receive either AVIFAVIR 1600 mg BID on Day 1, followed by 600 mg BID on Days 2–14 (1600/600 mg), or AVIFAVIR 1800 mg BID on 532 • cid 2021:73 (1 August) • BRIEF REPORT Day 1, followed by 800 mg BID on Days 2–14 (1800/800 mg), or SOC according to the Russian guidelines for treatment of COVID-19	Unclear No information.	Likely “Open-label study”	Likely “Open-label study”	Likely “Open-label study”	Unlikely All predefined outcome measures were reported.	Unlikely No loss to follow-up reported.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Zhao et al., 2021	Computerized	Unlikely	Likely	Likely open-label trial	Likely open-label trial	Likely	Unlikely No loss to follow-up	Unclear Not reported

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	Patients were randomly assigned to either the favipiravir group or the control group, in the ratio of 2:1, by simple randomization with no stratification.	Patients were assigned to a serial number by the study coordinator. Each serial number was linked to a computer-generated randomization list assigning the antiviral treatment regimens.	open-label trial			Trial registered (NCT04333589); secondary outcomes differ from protocol and final inclusion number (36) differ from 210 in protocol.		
Udwadia, 2020	Patients were randomized in a 1:1 ratio to oral favipiravir plus standard supportive care for up to a maximum of 14 days or standard supportive care alone. The randomization was stratified based on baseline disease severity into mild and moderate COVID-19. Patients were assigned to stratified randomized treatments based on a central, computer-generated randomization scheme coordinated by an independent third party.	Unlikely Patients were assigned to stratified randomized treatments based on a central, computer-generated randomization scheme coordinated by an independent third party.	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely All predefined primary and secondary outcomes were reported.	Unclear Loss to follow-up was not reported. Therefore, risk of bias due to loss to follow-up is unclear.	Unlikely Intention to treat analysis performed.
Khamis, 2020	Patients within 10 days of COVID-19 symptoms onset were screened for eligibility and assigned the treatment (experimental arm or standard arm) by block randomization by a computer-generated	Unlikely Randomization prepared by an investigator with no clinical involvement in the trial.	Likely Open-label trial. Trial participants were not blinded to the group assignment	Likely Open-label trial. Care givers were not blinded to the group assignment	Likely Open-label trial. Outcome assessors were not blinded to the group assignment.	Unclear The findings represent an interim analysis. Time to viral clearance was not measured as repeating nasopharyngeal swabs was not done due to	Unlikely All participants completed the study.	Unlikely Not mentioned in the Methods section, but participants included in the analysis are exactly those who were randomized into the trial.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	random number list prepared by an investigator with no clinical involvement in the trial. The recruitment was within 24 hours following the screening process. Trial participants, investigators, care givers, outcome assessors, and data analysts were not blinded to the group assignment.					limited resources, nor the radiological imaging to assess improvement		
Lou, 2020	Patients were randomized assigned in a 1:1:1 ratio into baloxavir marboxil group, favipiravir group, and control group.	Unlikely “After the subjects passed screening, the researchers assigned the random number according to the order of enrolment, removed the random envelope according to the random number, and treated the subjects according to the random envelope group and treatment plan.”	Likely Open-label trial	Likely Open-label trial	Likely Open-label trial	Unlikely This trial is registered with Chinese Clinical Trial 12 Registry (ChiCTR 2000029544).	Unlikely One patient in the favipiravir group was subsequently excluded from the final analysis because of his personal refusal to continue to use favipiravir after Day 1. The remaining 29 patients were included in the analysis.	Unclear Intention-to-treat analysis analyses was not performed.
9.3. Lopinavir and ritonavir (brand name = Kaletra; fixed dose combination of antiretroviral treatment)								
Arabi, 2021	See RoB assessment of Arabi (2021) by hydroxychloroquine.							
Ader, 2021	See RoB assessment of Ader (2021) by hydroxychloroquine.							
Reis, 2021	See RoB assessment of Reis (2021) by hydroxychloroquine.							
Purwati, 2021	See RoB assessment of Purwati (2021) by hydroxychloroquine.							

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Pan, 2020 (WHO Solidarity Trial Consortium)	See RoB assessment of Pan (2020) by remdesivir.							
Horby, 2020c	Web-based simple (unstratified) randomisation with allocation concealed until after randomisation	Unlikely Randomisation to usual care was twice that of any of the active treatment groups the patient was eligible for (eg, 2:1 in favour of usual care if the patient was eligible for only one active group, 2:1:1 if the patient was eligible for two active groups). For some patients, lopinavir–ritonavir was unavailable at the hospital at the time of enrolment or was considered by the attending clinician to be either definitely indicated or definitely contraindicated. These patients were excluded from the randomised comparison between lopinavir–ritonavir and usual care and hence are not included in this report.	Likely Participants and local study staff were not masked to the allocated treatment.	Unclear	Unlikely The trial steering committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.	Unlikely	Unlikely Follow-up information was complete for 5018 (>99%) of 5040 patients (1606 [99%] of 1616 patients in the lopinavir-ritonavir group and 3412 [99%] of 3424 patients in the usual care group).	Unlikely An intention-to-treat comparison was made between patients randomly assigned to lopinavir–ritonavir and patients randomly assigned to usual care but for whom lopinavir–ritonavir was both available and suitable as a treatment.
Huang, 2020	Random sequencing random number sequence generated by a computer	Unclear Not reported	Unclear Not reported	Likely medical staff were not blinded.	Unlikely Laboratory staff Performing quantitative or	Unlikely Outcome measures were defined	Likely patients with continuous diarrhoea, vomiting were	Likely Intention to treat protocol was violated

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
					qualitative testing were blinded to treatment allocation		excluded from the analysis	in the RBV + LPV/r + IFN-a group
Li, 2020a	Computerized “All eligible participants were assigned a randomization number which them into one treatment group. The randomization numbers were computer-generated. Allocation concealment was achieved using a centralized web-based randomization system in which the participant identifier (hospitalization number) was entered before the allocation was revealed. The randomization number were used in case report form (CRF) pages. The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff.”	Unlikely “Allocation concealment was achieved using a centralized web-based randomization system in which the participant identifier (hospitalization number) was entered before the allocation was revealed.”	Unlikely “The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff.”	Likely “The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff.”	Unlikely “The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff.”	Unlikely Protocol is described	Unlikely No loss of follow up	Unlikely Intention to treat analysis is described
Cao, 2020a	“To balance the distribution of oxygen support between the two groups as an indicator of severity of	Unlikely “To minimize allocation bias, we performed allocation concealment	Unclear Blinding of participants was not described	Unclear Blinding of care providers was not described	Likely Blinding assessors not possible	Unlikely Protocol available &	Unlikely Intention-to-treat analysis &	Unlikely Intention-to-treat analysis +

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	respiratory failure, randomization was stratified on the basis of respiratory support methods at the time of enrolment: no oxygen support or oxygen support with nasal duct or mask, or high-flow oxygen, non-invasive ventilation, or invasive ventilation including ECMO. The permuted block (four patients per block) randomization sequence, including stratification, was prepared by a statistician not involved in the trial."	with an interactive Web-based response system until randomization was finished on the system through a computer or phone."	"The permuted block (four patients per block) randomization sequence, including stratification, was prepared by a statistician not involved in the trial."		"Our trial has several limitations. In particular, the trial was not blinded, so it is possible that knowledge of the treatment assignment might have influenced clinical decision-making that could have affected the ordinal scale measurements we used."	relevant clinical outcomes included in article	Reasons for lost-to-follow-up clearly described	Modified intention-to-treat analysis
9.4. Molnupiravir								
Fischer, 2021	Computerized Participants were randomized using the REDCap randomization application. Randomization was at a 3:1 ratio (molnupiravir:placebo)	Unlikely Randomization (1:1) was done via REDCap using a fixed block randomization.	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups and is clearly described.	Unlikely Intention to treat analysis was performed.
9.5. Nitazoxanide (brand name = Alinia; antiparasitic & broad-spectrum antiviral medication)								
Rocco, 2020	Patients were randomly assigned (1:1) using a computer-generated random number list to receive either placebo or nitazoxanide (500 mg	Unlikely Patients were randomly assigned (1:1) using a computer-generated random number list	Unlikely The study treatment (A or B) was revealed to the pharmacist only	Unlikely All outcomes were assessed by blinded investigators. We conducted source data	Unlikely Placebo and nitazoxanide were color-matched to ensure that assessors	Unlikely All predefined outcome measures were reported.	Likely High number of loss to follow-up in both groups.	Unclear No information provided.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	oral solution, 20 mg/mL [25 mL], three times daily for 5 days), dispensed by the pharmacy of each study site.		after patients were registered in the system, ensuring proper concealment of the allocation sequence.	verification of the D8 assessment from study sites and laboratory forms for all patients at sites.	were unaware of group allocation at all time points			
9.6. Novaferon (broad-spectrum antiviral drug)								
Zheng, 2020	Computer generated random-numbers SAS generated simple randomization schedule was prepared by a statistician not involved in the trial.	Unclear not reported	Unclear not reported	Unclear not reported	Unclear not reported	Unlikely outcome measures where pre-defined	Unlikely missing SARS-CoV-2 clearance status, Last Observation Carried Forward (LOCF) analysis was presented as the primary analysis	Unlikely intention to treat analysis was not violated
9.7. Oseltamivir (brand name = Tamiflu)								
NA	NA	NA	NA	NA	NA	NA	NA	NA
9.8. Paxlovid								
NA	NA	NA	NA	NA	NA	NA	NA	
9.9. Ribavirine (also known as tribavirin)								
Huang (2020)	See risk of bias table of Huang (2020) by lopinavir and ritonavir.							
Hung, 2020	Computerized “... Patients were assigned to a serial number by the study coordinator. Each serial number was linked to a computer-generated randomisation list assigning the antiviral treatment regimens.”	Unlikely Adequate procedure	Unlikely No bias expected	Unlikely No bias expected	Unclear Not described	Unlikely Primary endpoints relevant and described	Unlikely Intention-to-treat analysis performed, 1 patient in control group stopped treatment because of adverse event	Unlikely Intention-to-treat analysis performed

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
9.10. Sofosbuvir (brand name = Sovaldi; has role as a prodrug, an antiviral drug and a hepatitis C protease inhibitor; only recommended with some combination of ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir)								
9.10.1. Sofosbuvir i.c.m. Daclatasvir (brand name = Daklinza; used in combination with sofosbuvir, ribavirin, and interferon)								
Roозbeh, 2020	Computerized Patients were randomly assigned to either sofosbuvir/daclatasvir and hydroxychloroquine or hydroxychloroquine groups through unstratified block randomization with a block size of four. A block randomization list was created using a computer-generated randomization plan. Physician and analyser were blinded and randomization with coding was done by a third person.	Unlikely Allocation of treatment seems to have been concealed properly to the care provider and outcome assessor. Unclear It is unclear whether allocation of treatment was concealed properly to the patient. The article does not state specifically whether patients were blind to treatment allocation. The registration reads the following: "to hide the drugs, they are placed in the required number in the envelope. Then, according to the random codes created, one or two envelopes will be placed in a larger envelope." This may imply that the patient would receive one or two envelopes, from which the patient could infer the treatment allocation.	Unclear It is unclear whether allocation of treatment was concealed properly to the patient. If the patient was aware, this could have induced bias on the outcome measure symptom alleviation, as the patient's experience of severity of the symptoms can be influenced (subconsciously) by the patient.	Unlikely Care providers were blind to treatment allocation.	Unlikely Outcome assessors were blind to treatment allocation.	Unlikely All outcome measures stated in the methods section were reported in the results.	Unlikely Few patients were lost to follow up, reasons are clear.	Unclear Authors registered that they would study 60 patients. This target was met, however the study was registered while recruitment was ongoing and the authors conclude the target sample was too low to form solid conclusions. It is therefore a bit strange that the authors did not have a higher target to begin with.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
Sadeghi, 2020	Computerized “... they were randomly assigned to either the control arm or the treatment arm in a 1:1 ratio using a computer-generated randomization plan. Block randomization with a block size of 2 was used.”	Unlikely Adequate method	Likely Open label	Likely Open label	Unlikely “The investigator, outcome assessor and data analyser were masked.”	Unlikely Trial registered; IRCT.ir; IRCT20200128046294 N2.	Unlikely low rate of lost-to follow-up and reasons comparable between groups	Likely In both groups, 2 patients excluded after randomization. These patients are not included in the intention-to-treat analysis. It is unclear whether these patients might represent the most severely ill patients.
9.10.2. Sofosbuvir i.c.m. Ledipasvir (brand name = Harvoni; antiviral for hepatitis C-virus)								
Nourian, 2021	Randomization was performed by permuted blocked randomization.	Unlikely To maintain allocation concealment, we used sequentially numbered, opaque sealed envelopes (SNOSE) method. Ninety identical letter-sized envelopes were provided. Numbers 1 to 90 were written on the envelopes; “SOF/LDP” was written on one set of 45, and “control” was written on the second set. Papers were folded and put in the envelopes. Based on randomized numbers, patients were enrolled in the groups	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely All predefined outcome measures were reported.	Unlikely Five patients in the control group were excluded from analysis versus three patients in the intervention group.	Unclear Not described.
9.10.3. Sofosbuvir i.c.m. Velpatasvir (NS5A inhibitor (by Gilead); fixed-dose combination medication with sofosbuvir for the treatment of hepatitis C)								

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Sayad, 2021	The participants were randomly assigned in a 1:1 ratio	Unlikely In order to generate an allocation sequence, simple random allocation was applied using an Excel file; 80 eligible patients were enrolled in the study (40 individuals in each group). For allocation sequence concealment, the study arm for each patient was contained in a sealed envelope labelled with a number from 1 to 80.	Likely Open-label study	Likely Open-label study	Likely Except for hard outcome measure mortality.	Unlikely All predefined outcome measures were reported.	Unlikely Only one patient died within 24 hour after admission and did not receive sofosbuvir/velpatasvir.	Unlikely ITT analysis performed with same patients who were randomized into the trial.
9.11. Umifenovir (brand name = Arbidol)								
Darazam, 2021	Unclear Unstratified randomization was done in a 1:1 ratio utilizing a block balance randomization method.	Unlikely The investigator (IAD) enrolled the patients and only then opened envelopes to assign patients to the different treatment groups.	Likely This was an open-label RCT, there were no other statements on blinding	Likely This was an open-label RCT, there were no other statements on blinding	Likely This was an open-label RCT, there were no other statements on blinding	Unlikely All outcomes were reported.	Unclear The time to follow-up was not reported, as was the loss-to-follow-up	Unlikely All the participants who had undergone randomization were included in Intention-To-Treat (ITT) analysis.
Li, 2020a	See risk of bias table of Li (2020) by lopinavir and ritonavir.							
10. Antibiotic treatment								
10.1. Azithromycin								
Oldenburg, 2021	Participants will be randomized by the study biostatistician. The randomization will be implemented into REDCap. The randomization will be masked by treatment	Unclear The masked study coordinator will send the participant their corresponding study treatment. The coordinator will determine the	Unlikely Every attempt will be made to preserve masking and we will use a matching placebo to ensure masking of investigators and	Unlikely Every attempt will be made to preserve masking and we will use a matching placebo to ensure masking of investigators and	Unlikely Every attempt will be made to preserve masking and we will use a matching placebo to ensure masking of investigators and	Unlikely All predefined outcome measures were reported.	Likely High number of loss to follow-up in both groups.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	letters: AAA, BBB,CCC, HHH, TTT, or VVV.	participant's allocation by the patient's REDCap record ID.	participants. Laboratory staff will be masked for all laboratory outcomes.	participants. Laboratory staff will be masked for all laboratory outcomes.	participants. Laboratory staff will be masked for all laboratory outcomes.			
Hinks, 2021	Web-based automated service <i>Patients were randomly assigned (1:1) to either azithromycin plus standard care or standard care alone using a web-based automated service, with a minimization algorithm to ensure balanced allocation across treatment groups, stratified by center, sex, and presence of hypertension and diabetes.</i>	Unlikely <i>Allocation across treatment groups, stratified by center, sex, and presence of hypertension and diabetes. To ensure the unpredictability of treatment allocation, the first 30 participants were randomly assigned by simple randomization and the minimization algorithm included a probabilistic element (participants had an 80% chance of being allocated to the treatment, which minimised imbalance between the groups).</i>	Likely <i>Patients, investigators, and health-care providers were not masked to study drug assignment.</i>	Likely <i>Patients, investigators, and health-care providers were not masked to study drug assignment.</i>	Likely <i>Patients, investigators, and health-care providers were not masked to study drug assignment.</i>	Unlikely All predefined outcome measures were reported.	Unlikely 2 withdrawals in the intervention group and 1 withdrawal in the control group.	Unlikely Patients randomized in the study were the same patients who were analysed.
Butler, 2021	Computerized Participants were randomly assigned using an in-house, secure, fully validated and compliant web-based randomisation	Unlikely The trial team was masked to the randomisation ratios.	Likely This study is an open-label trial. The participant knew their allocation. This could have influenced the subjective outcome	Likely The recruiting clinician knew the participant's allocation. This could have influenced the clinician's (subjective) decisions to refer the	Unlikely Outcome assessors were blind to treatment allocation.	Unlikely All outcome measures stated in the methods and preregistration were reported in the results.	Unlikely Loss to follow-up was relatively low (<5%) and similar between groups.	Unlikely Trial was prospectively registered; assignment was stopped because the PRINCIPLE Trial Steering Committee advised the Trial

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	system called Sortition. Before July 24, 1:1 allocation with stratification by age (<65 years vs ≥65 years) and presence of comorbidities (yes vs no). From July 24, subsequent randomisation ratios were determined via response adaptive randomisation through regularly scheduled interim analyses.		measures such as self-reported symptom resolution.	patient to hospital or start respiratory support.				Management Group to stop random assignment of patients to the azithromycin group of the trial because the prespecified futility criterion was met.
Horby, 2021b (RECOVERY Collaborative Group)	Computerised web-based simple (unstratified) randomisation	Unlikely allocation concealed until after randomisation	Likely open-label trial; participants were not masked to the allocated treatment	Likely open-label trial; local study staff were not masked to the allocated treatment	Unlikely The steering committee, investigators, and all others involved in the trial were masked to the outcome data during the trial.	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely Loss to follow-up was small, and similar in both groups.	Unlikely Efficacy analyses were done according to the intention-to-treat principle.
Furtado, 2020	Computerized “Patients were randomly assigned (1:1) to either azithromycin plus standard of care or standard of care alone. Randomisation in blocks of variable size (4, 6, and 8) was performed in an electronic case report form system and stratified by site, age (...) Allocation was done by a	Likely Randomisation stratified per site	Unlikely No blinding; “Patients, investigators, and health-care providers were not masked to study drug assignment.”	<u>Clinical outcomes:</u> Unclear - unclear whether knowledge of treatment might influence assessment on six-point ordinal scale <u>Key secondary outcome (death):</u> Unlikely “Patients, investigators,	<u>Clinical outcomes:</u> Unclear - unclear whether knowledge of treatment might influence assessment on six-point ordinal scale <u>Key secondary outcome (death):</u> Unlikely “Patients, investigators,	Unlikely Trial registered (ClinicalTrials.gov, NCT04321278) and relevant outcomes reported	Unlikely 2 patients in intervention group lost to follow-up at 29 days; results available for 15-day follow-up.	Unclear 23 patients excluded from intervention group en 27 patients excluded from control group after randomization due to negative PCR results (all except 1), and 1 withdrawn consent. The patients left were included in the ‘modified ITT analysis’.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	centralised, web-based, automated randomisation system.”			and health-care providers were not masked to study drug assignment.”	and health-care providers were not masked to study drug assignment.”			2 patients of the intervention group were lost to follow up and were excluded from the analysis.
Sekhavati, 2020	Not described. Patients were randomly divided into two treatment groups,	Likely Note: open-label study	Likely Note: patients were not blinded to treatment allocation	Likely Note: care providers were not blinded to treatment allocation	Likely Note: outcome assessors were not blinded to treatment allocation	Unlikely Note: all outcomes mentioned in the method section were reported	Unlikely Note: no loss to follow-up	Unclear Note: not clear whether analyses were intention to treat.
Brown, 2020	See RoB assessment of Brown (2020) by hydroxychloroquine.							
Cavalcanti, 2020	See RoB assessment of Cavalcanti (2020) by hydroxychloroquine.							
10.2. Doxycycline								
Mahmud, 2021	Computerized, random number list “The allocation schedule was created with a list of random numbers generated using a random number generator program by the head of the Department of Medicine of Dhaka Medical College.”	Unlikely “The randomization code was maintained by the pharmaceutical company. Both the investigators and the patients were blinded to the treatment allocation. Decoding was performed at the end of the trial under the supervision of the principal of the institute.”	Unlikely placebo-controlled and decoded at end of trial	Unlikely placebo-controlled and decoded at end of trial	Unlikely placebo-controlled and decoded at end of trial	Likely The trial was registered retrospectively at ClinicalTrials.gov (identifier: NCT04523831). Unclear how many patients per treatment group were hospitalized at randomization and how many patients needed hospitalization or initiation of supplemental oxygen during study.	Likely Relatively high number of lost to follow up and patients excluded from analysis. Unclear whether these patients differ from the patients that were included in the analysis.	Likely Patients analysed as randomized, but high number of lost to follow-up.
10.3. Lincomycine								
NA	NA	NA	NA	NA	NA	NA	NA	NA
11. Antifungal treatment								

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
11.1. Intraconazole								
Liesenborghs, 2021	Computerized Randomization (1:1) with a computerized system was stratified according to disease severity.	Likely The study was open label without blinding for patients, healthcare workers or investigators. Throughout the study, the trial statisticians were blinded to the different treatments. They were not given direct access to the database and only received data from which any information regarding treatment allocation was removed. The randomization schedule was kept on a separate location, inaccessible to the statisticians, and was only sent at the time of database lock.	likely open-label trial	likely open-label trial	likely open-label trial	Unlikely Reported outcomes were the same as defined outcomes in the protocol and methods.	Unclear Not reported.	Unlikely intention-to-treat analysis were performed
12. Antiparasitic treatment								
12.1. Ivermectin (broad spectrum anti-parasitic agent)								
Buonfrate, 2022	Computerized Participants were randomly assigned by a centralized computer system to one of the three arms with an allocation ratio 1:1:1.	Unlikely Randomization (1:1:1) was prepared by a biostatistician according to a randomized permuted blocks procedure	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely The investigators, subjects, and sponsor were blinded to the treatments received	Unlikely All outcome measures described in the trial protocol are reported in the results.	Likely 40.6% of the participants in the high-ivermectine group were excluded in the per protocol analysis because they did not receive 5 days of treatment, compared to 6.2% in the control group and	Likely No intention to treat analysis was performed.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
							10.3% in the low ivermectine group	
Mohan, 2021	Computerized Eligible patients were randomized in a 1:1:1 ratio to receive a single dose of Ivermectin 12 mg or 24 mg elixir, or identical placebo. A variable block randomization stratified based on disease severity was done using a centralized telephone-based system.	Unlikely A variable block randomization stratified based on disease severity was done using a centralized telephone-based system.	Unlikely Patients, investigators, caregivers, and statisticians were blinded to the allocation.	Unlikely Patients, investigators, caregivers, and statisticians were blinded to the allocation.	Unlikely Patients, investigators, caregivers, and statisticians were blinded to the allocation.	Unlikely All outcome measures described in the methods are reported in the results.	Likely The percentage of patients lost to follow-up is greater than 10% and differs between treatment groups.	Unlikely All randomized patients who received study medication were included in the ITT analysis. Among these, patients with a positive RT-PCR on the day of enrolment were included in the mITT analysis. The primary outcomes were assessed in the mITT population.
Ravikirti, 2021	Online block randomisation list generating software. Block randomisation was done with variable random block sizes of 4, 6 and 8. A random allocation list of 120 patients was generated using the sealed envelope (an online block randomisation list generating software)..	Unlikely A random allocation list of 120 patients was generated using the sealed envelope (an online block randomisation list generating software) and kept with a third person (not a part of the investigation team) prior to the commencement of the trial.	Unlikely Double blind. After confirmation of the treatment group, the investigation team doctor used to indent 2 tablets designated for that particular group. Both these treatment groups received 2 tablets similar in size, shape, colour, odour, and packaging on subsequent days.	Unlikely Double blind. After confirmation of the treatment group, the investigation team doctor used to indent 2 tablets designated for that particular group. Both these treatment groups received 2 tablets similar in size, shape, colour, odour, and packaging on subsequent days.	Unlikely ... up until the analysis of the data, this information was confined to the pharmacist dispensing the tablets.	Unlikely All outcomes mentioned in Methods were reported.	Unlikely Loss to follow up was reported	Likely No intention to treat analyses were performed. Participants were excluded from the analyses after randomization.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Vallejos, 2021	Web-based system using randomly permuted blocks in a 1:1 ratio. The investigator who performed the randomization was not involved in the dispensing of the medication, inclusion, and follow-up of the patients.	Unlikely Patients were consecutively assigned to the treatment kit in ascending order at inclusion.	Unlikely Double-blinded study > “The rest of the investigators were blinded to the treatment received, as were the patients”	Unlikely Double-blinded study - > “The rest of the investigators were blinded to the treatment received, as were the patients”	Unlikely Double-blinded study > “The rest of the investigators were blinded to the treatment received, as were the patients”	Unlikely All predefined outcome measures were reported.	Unlikely Considering that an intention-to-treat analysis was performed, all 501 patients were included for the analysis of primary and secondary outcomes. There were no arm crossovers.	Unlikely The patients included in the analysis were exactly those who were randomized into the trial.
Abd-Elsalam, 2021b	Computerized randomization <i>The included patients were randomized using a computer random number generator to select random permuted blocks with a block size of eight and an equal allocation ratio.</i> <i>Three members of the study team (Soliman S, Mai Khalaf, and Eslam Saber Esmail) recruited, enrolled, and assigned participants to a computer-generated randomization sequence, held by an independent observer</i>	Unlikely <i>Sequentially numbered, opaque, sealed envelopes were used to ensure concealment.</i>	Likely <i>Open-label study Patients and physicians were aware of the assigned treatments.</i>	Likely <i>Open-label study Patients and physicians were aware of the assigned treatments.</i>	Unclear <i>Not reported.</i>	Unlikely <i>Outcomes mentioned in the Methods section were reported in the Results section as well.</i>	Unlikely <i>All the patients continued the study medications to the end of the duration of treatment and follow-up.</i>	Unlikely <i>The primary analysis was done based on an intention-to-treat basis including all randomly assigned individuals.</i>
Samaha et al., 2021	Computerized “..., the subjects were randomized (using	Unclear No information	Unclear No information	Unclear No information	Unclear No information	Unclear No protocol or trial registration available; sub groups analysis for	Unlikely No loss to follow-up reported	Unlikely No loss to follow-up reported and patients

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	stratified randomization) according to their characteristics of age, gender, marital status, and co-existing medical conditions and chronic diseases. After that, the subjects within each stratum were enlisted into separate digitally generated randomization schedules and assigned randomly to either the control or ivermectin group.”					gender; unclear whether clinical outcomes were comparable before treatment as they were not reported at baseline		analyzed in groups as randomized
Krolewiecki, 2021	2:1 allocation ratio, in patients with COVID-19.	Unlikely A blocked randomization with random block sizes (of 3 or 6 allocations) and stratified by center was used. The randomization list was developed prior to study initiation and by means of a centralized eCRF/IWRS web system (Jazz Clinical, Buenos Aires, Argentina). For reproducibility, a random seed of 1701214029 was used. Once the availability of the informed consent and the verification of all eligibility criteria had been confirmed, the assignment was	Likely The patients and center personnel were not blinded to the allocated group.	Likely The patients and center personnel were not blinded to the allocated group.	Unlikely The outcome assessors (personnel in charge of viral load determinations) were blinded to the allocated group upon receiving the samples labeled with the randomization number and the visit number.	Unlikely All predefined outcome measures were reported.	Unlikely Lost to follow-up almost equal in both groups.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		communicated to the investigators on the computer screen and by email.						
Mahmud, 2021	See risk of bias table of Mahmud (2021) by doxycycline.							
Shahbaznejad, 2021	Table of random numbers "The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of random numbers."	Unclear No information	Unlikely "Neither the participants nor the evaluators were aware of the randomization process or group allocation."	Likely Care providers not blinded; "Neither the participants nor the evaluators were aware of the randomization process or group allocation."	Unlikely "Neither the participants nor the evaluators were aware of the randomization process or group allocation."	Unclear Study registration not complete regarding planned outcomes; results inconsistent between text and tables	Likely 4 patients (10.5%) in control group withdrawn consent. Possible to induce bias in the results	Unlikely Patients analyzed according to randomization; 4 patients excluded from analysis as they had withdrawn consent
Okumuş, 2021	Quasi-randomized: based on odd-even patient number "Starting from the first patient included in the study, patients with odd numbers were grouped as the study group, and patients with even numbers as the control group."	Likely Quasi-randomized based on odd-even number	Unlikely Single-blind trial	Likely Single-blind trial; Except for mortality and laboratory outcomes	Unclear No protocol and roles of involved researchers described	Likely Main aim of study does not fit inclusion/exclusion criteria; Viral clearance reported for small subset of patients (57.1% of intervention group and 26.7% of control group)	Likely Short follow-up in severely ill group of patients; follow-up duration for mortality unclear ("were recorded until the study was completed (an average of 3 months)")	Likely No adherence to intention-to-treat protocol described; no report of handling missing or incomplete data; 6 patients of intervention group excluded after randomization and not included in analysis; this could induce a bias in the study results
López-Medina, 2020	Potential study participants were identified and selected by simple random sampling from the state's database. Eligible patients were randomly assigned in a	Unlikely Allocation assignment was concealed from investigators and patients.	Unlikely The placebo used in the first 65 patients differed in taste and smell from ivermectin. However, patients from	Unlikely Pharmacist provided masked ivermectin or placebo to a field nurse for home or hospital patient visits.	Unclear Not reported.	Unlikely The original primary outcome to detect the ability of ivermectin to prevent clinical deterioration was changed 6 weeks into	Unclear 38/238 (16.0%) patients of the intervention group were excluded from primary analysis due	Unclear Not mentioned in the statistical analysis section.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	<p>1:1 ratio to receive either oral ivermectin or placebo in solution for 5 days.</p> <p>Patients were randomized in permuted blocks of 4 in a randomization sequence prepared by the unblinded pharmacist in Microsoft Excel version 19.0 who provided masked ivermectin or placebo to a field nurse for home or hospital patient visits.</p>		<p>the same household were not included until the placebo with the same organoleptic properties was available.</p> <p>Bottles of ivermectin and placebo were identical throughout the study period to guarantee double-blinding.</p>			<p>the trial to time from randomization to complete resolution of symptoms within the 21-day follow-up period (i.e., the incidence of clinical deterioration was below 3%, making the original planned analysis futile).</p> <p>However, deterioration by ≥ 2 points in an ordinal 8-point scale was still reported as an secondary outcome.</p>	<p>to error in labeling from September 29 to October 15, 2020.</p> <p>40/238 (16.8%) patients of the control group were excluded due to error in labeling from September 29 to October 15, 2020.</p>	
Babalola, 2021	<p>Computerized</p> <p>Computers were used to generate random numbers which were employed for the allocation. Patients were allocated an envelope depending on the sequence, assigning them to one of three groups.</p>	<p>Unlikely</p> <p>The Blinding was assured by ensuring that the study medications were in labelled envelopes prepared by pharmacy, held by the nursing staff and administered by them without the knowledge of the clinical research team. Virological assays were done in a separate building on samples labelled only with the patients' trial number. Ivermectin came in 3mg tablets and all looked alike for the 12 and 6 mg arms.</p>	<p>Unlikely</p> <p>Patients were not aware of what was administered until the code was broken at the end of the study.</p> <p>A look alike placebo was dispensed in addition, to the patients in the control arm, in order to maintain concealment.</p>	<p>Unlikely</p> <p>The dispensing pharmacist, was the only one with knowledge of the group allocation.</p>	<p>Unlikely</p> <p>Virological assays were done in a separate building on samples labelled only with the patients' trial number.</p>	<p>Unlikely</p> <p>The primary and secondary outcomes listed in the methods section are reported in the results section.</p>	<p>Unclear</p> <p>One withdrawal, reason or arm of the study not reported. No baseline characteristics or results were reported of this patient.</p> <p>For the primary outcome measure Days-to-Negative of the PCR Test, tests were not completed in two cases.</p>	<p>Unclear</p> <p>Not mentioned in the statistical analysis section.</p>

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		The lopinavir / ritonavir tablets were not identical to the ivermectin tablets but neither the patients nor the investigators were aware of what was administered until the code was broken at the end of the study. The dispensing pharmacist, was the only one with knowledge of the group allocation.						
Chaccour, 2020	Computerized "The randomization sequence was computer-generated by the trial statistician using blocks of four to ensure balance."	Unclear "Allocation was made by the attending investigator using opaque envelopes." Not explicitly stated at which moment allocation was disclosed	Unlikely In protocol publication (Suppl.) stated that patients and clinical trial team will be blinded.	Unlikely "The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical trial team to remain blinded, treatment was administered under direct supervision by a non-participant nurse that picked up the opaque bottles directly from the pharmacy and administered the content behind closed doors"	Unlikely "The placebo tablets did not match ivermectin in appearance, therefore, in order for the clinical trial team to remain blinded, treatment was administered under direct supervision by a non-participant nurse that picked up the opaque bottles directly from the pharmacy and administered the content behind closed doors"	Unlikely Protocol publication (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04421-z) Announced outcomes are reported; Definition 'progression to severe disease' unclear	Unlikely All patients, 12 vs. 12, completed follow-up and were included in the analyses	Unlikely All patients, 12 vs. 12, completed follow-up and were included in the analyses
Ahmed, 2020	Not described	Unclear Not described	Unclear	Unclear	Unclear	Likely	Likely	Likely

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
			'Double-blind' and 'placebo' described, but methods not specified	'Double-blind' and 'placebo' described, but methods not specified	'Double-blind' and 'placebo' described, but methods not specified	Not all outcomes that were reported in the methods, also reported in the method section. Trial not registered. Unclear which results were used in case of missing values (e.g. sore throat reported in 3/4 (75%); unclear which 4 patients).	Loss to follow up indicated by total patients in each group at follow up; not clear which patients were lost to follow-up; reasons not described	Protocol for analysis not described; loss to follow up not described; handling of missing data not described;
13. Interferon								
13.1. Inhaled IFN-κ plus TFF2 (= Interferon kappa + Trefoil factor 2)								
Fu, 2020	Patients who met the inclusion criteria were enrolled in the study, assigned with randomized numbers, the random allocation sequence was generated through the website "https://www.randomizer.org/#randomize", and then sorted into either experimental group or control group.	Unlikely The random allocation sequence was generated through a website.	Unlikely Open-label, randomized, clinical trial. However, it is not likely that this results in risk of bias for the outcome measures (time of viral RNA negative conversion; time of CT imaging improvement)	Unclear It was possible that knowledge of the treatment assignment might have influenced clinical decision-making that could have affected the ordinal scale measurements that were used.	Unclear The outcome assessors were not mentioned.	Unlikely The primary endpoint and secondary clinical endpoint listed in the methods section are reported in the results section.	Unclear Not mentioned but all patients contributed to the outcome measure time of CT imaging improvement.	Unclear Not mentioned in the statistical analysis section.
13.2. Inhaled Interferon β-1b								
Khamis, 2020	See risk of bias table of Khamis (2020) by favipiravir.							
13.3. Interferon α-2b								
Pandit, 2021	Computerized Randomization was generated using SAS [®] software (Version 9.4)	Unclear Concealment of allocation was not reported	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely The primary endpoint and secondary endpoints listed in the methods section are reported in the results section.	Unlikely No loss to follow-up was reported (except for 1 participant who withdrew from the study).	Unlikely Analysis performed according to modified intention-to-treat protocol; as indicated by randomized participants minus

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
								participants that withdrew.
13.4. Interferon β-1a								
Kalil, 2021	Eligible patients were randomly assigned (1:1) to receive either interferon beta-1a plus remdesivir or placebo plus remdesivir. Randomisation was stratified by study site and disease severity at enrolment, and was done by use of the web-based data entry system Advantage eClinical.	Unclear	Unlikely Double-blind study. The study team (ie, those giving the interventions, assessing the outcomes, and analysing the data) was masked to treatment assignment until the end of the trial, after all data queries were resolved and the database was locked.	Unlikely Double-blind study. The study team (ie, those giving the interventions, assessing the outcomes, and analysing the data) was masked to treatment assignment until the end of the trial, after all data queries were resolved and the database was locked.	Unlikely The study team (ie, those giving the interventions, assessing the outcomes, and analysing the data) was masked to treatment assignment until the end of the trial, after all data queries were resolved and the database was locked.	Unlikely All predefined outcome measures were reported.	Unlikely No lost to follow-up.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Ader, 2021	See RoB assessment of Ader (2021) by hydroxychloroquine.							
Alavi Darazam, 2021	Computerized "Unstratified randomization was done in a 1:1:1 ratio utilizing a block balance randomization method. The permuted block (three or six patients per block) randomization sequence was generated using Package 'randomizeR'	Unlikely "The investigator (IAD) enrolled the patients and only then opened envelopes to assign patients to the different treatment groups."	Likely Open-label trial (except for mortality)	Likely Open-label trial (except for mortality)	Unlikely "It was not feasible to blind neither the patients nor the caregivers, but the outcomes assessor (MAP) was blinded to the study arms."	Unlikely Reported outcomes mainly consistent with protocol; Baseline scores for the primary outcome (ordinal clinical scale) would facilitate interpretation of difference score of this ordinal scale	Unlikely No participants lost to follow-up	Unlikely No participants lost to follow-up; all participants randomized in arm of allocation

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	in R software version 3.6.1 and placed in individual sealed and opaque envelopes for allocation concealment by an outside statistician.”					<i>ClinicalTrials.gov Identifier: NCT04343768</i>		
Pan, 2020 (WHO Solidarity Trial Consortium)	See RoB assessment of Pan (2020) by remdesivir.							
Monk, 2020	The unique patient identification number consisted of nine digits (two for the study number, three for the country [if applicable] and site number and four for patient number) and identified the patient throughout the study. The 4-digit patient number was assigned sequentially to each patient within each site starting with 1001 and was not re-assigned. Patients were randomised to one of two treatment groups (SNG001 or placebo) in a 1:1 ratio according to a prespecified randomisation schedule in addition to standard of care.	Unlikely Allocation to treatment for the pivotal phase will be decided after the pilot phase data review. It is anticipated that this will either be a 1:1 ratio as per the pilot phase or that all patients will receive SNG001. Should a patient withdraw after receiving any study medication then the randomisation number will not be re-assigned and the patient will not be replaced. If for any reason the patient has been randomised but does not receive any study drug, this randomisation number can be re-assigned and the patient can be replaced.	Unlikely The study will be patient- and investigator-blinded.	Unlikely The study will be patient- and investigator-blinded.	Unlikely The study will be patient- and investigator-blinded.	Unlikely The study will be patient- and investigator-blinded.	Unlikely All predefined outcome measures were reported.	Unlikely The intention-to-treat (ITT) population is defined as all randomised patients who receive at least one dose of study medication. Randomised patients who do not receive study medication will not be followed up as part of the study. Re-use of randomisation numbers for those randomised who do not receive study drug will be allowed to maximise use of the limited supply of study medication. The ITT population will also be split into ITT populations for

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
								patients in the hospital and home settings, determined by the assigned cohort.
Davoudi-Monfared, 2020	Numbered list The randomization was performed by permuted block randomization and block sizes of 2, 4, and 6, used randomly. The statistician prepared a list of numbers for randomization.	Unlikely Sequentially numbered opaque envelopes were prepared according to the list, and envelopes were delivered to the clinical investigators. The statistician that performed randomization and analysis was unaware of the treatment and follow-up of patients.	Unclear Open-label randomized clinical trial	Unclear Open-label randomized clinical trial	Unclear Open-label randomized clinical trial	Unlikely The primary and secondary outcomes listed in the methods section are reported in the results section.	Likely 4 patients (8.7%) were dropped out in the intervention group (2 patients died before the second dose of FN, 2 patients died before the third dose of IFN) 7 patients (15.2%) were dropped out in the control group (they entered other trial)	Likely The analysis was performed on a per-protocol basis, and patients who did not receive at least four doses of IFN were not included.
Huang, 2020	See evidence table of Huang (2020) by lopinavir and ritonavir.							
13.5. Interferon β-1b								
Alavi Darazam, 2021	See RoB assessment of Alavi Darazam (2021) by interferon β -1a.							
Rahmani, 2020	Permuted block randomization.	Unlikely Despite some differences at baseline, inadequate concealment of allocation was unlikely.	Unclear It was an open-label trial.	Unclear It was an open-label trial.	Unclear It was an open-label trial.	Unlikely Outcomes mentioned in the method section were also reported.	Unclear It was not reported whether patients were lost to follow-up.	Unclear No intention to treat analysis was performed. 4 patients dropped out in the interferon group versus 3 patients in the control group.
Hung, 2020	See RoB assessment of Hung (2020) by ribavirin.							
13.6. Peginterferon Lambda								
Feld, 2021	A computer generated randomisation list was created by the study statistician (BEH) with a	Unlikely At the time of randomisation, the	Unlikely All participants were instructed to look	Likely Because we did not have an identical	Unlikely After administering the medication, all	Unlikely	Unlikely Only one patient in the intervention group	Unlikely The main efficacy outcome was analysed

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	randomisation schedule in blocks of four.	study personnel received a sealed opaque envelope with the treatment allocation number that indicated which vial to administer to the participant.	away during the administration and the syringe had no identifiable features on to unmask allocation to the participant. A	matching placebo, one of two study personnel administering the medication was aware of the treatment allocation.	further follow-up (phone calls and study visits) was completed by study personnel unaware of treatment allocation.	All predefined outcome measures were reported.	was lost to follow-up after day 3.	following an intention-to-treat principle.
13.7. Peginterferon Lambda-1a								
Jagannathan, 2021	Computerized <i>“A password-protected electronic spreadsheet containing the randomization allocation, along with the code used to generate the allocation and seed used in the random number generation, was stored on secure servers at Stanford.”</i>	Unlikely <i>“A password-protected electronic spreadsheet containing the randomization allocation, along with the code used to generate the allocation and seed used in the random number generation, was stored on secure servers at Stanford.”</i>	Unlikely placebo-controlled	Unlikely placebo-controlled; “Lambda and placebo syringes were identically labelled but differed in the appearance of the needle hub. Since the nurse administering the medication might see syringe differences, the study was not strictly “double-blind” even though all participants and investigators were blinded to treatment arm.”	Unlikely placebo-controlled	Unlikely Consistent with registration; NCT04331899	Unlikely 3 participants in each group did not complete the 28-day visit; comparable reasons. “The proportion of missing follow-up visits was 44/960 (4.6%). Only 16/960 visits were missed among patients not hospitalized or prematurely withdrawn.”	Unlikely
13.8. Pegylated Interferon-2b								
Bhushan, 2021	Computerized* Eligible subjects were randomized in a 1:1 ratio. Randomization was generated using	Unclear Not reported	Likely It was an open-label study.	Likely It was an open-label study.	Likely It was an open-label study.	Unclear Subgroup analyses (remdesivir/steroids) were not defined in the study protocol.	Unlikely Lost to follow-up was not different between the groups.	Unlikely ITT analysis was performed (PP analysis also available).

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	SAS® software (Version 9.4). *Interactive voice/web response system was not used for randomization leading to an imbalance in the numbers randomized because of competitive recruitment at the study sites.							
14. JAK-inhibitors								
14.1. Baricitinib (selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)								
Marconi, 2021	Computerized Randomisation was facilitated by a computer-generated random sequence using an interactive web-response system, and was permitted by a study investigator or designee to allocate participants 1:1 to the baricitinib or the placebo group. Participants were stratified according to the following baseline factors: disease severity, age, region, and use of corticosteroids for primary study condition.	Unlikely Randomisation was facilitated by a computer-generated random sequence using an interactive web-response system.	Unlikely Participants, study staff, and investigators were masked to the study assignment.	Unlikely Participants, study staff, and investigators were masked to the study assignment.	Unlikely Participants, study staff, and investigators were masked to the study assignment.	Unlikely All outcome measures described in the methods are reported in the results.	Likely The percentage of patients lost to follow-up is greater than 10% and differs between treatment groups.	Unlikely All randomized participants were included in the ITT analyses.
Kalil, 2020	Randomization was stratified by study site and disease severity at enrollment and was	Unlikely Eligible patients were randomly assigned in a	Unlikely	Unlikely The trial team was unaware of the trial-	Unlikely The trial team was unaware of the trial-	Unlikely	Unclear	Unlikely

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	performed using a web-based Internet Data Entry System, Advantage eClinical.	1:1 ratio to receive either remdesivir and baricitinib or remdesivir and placebo.	Patients were blind to treatment assignments.	group assignments until after all data queries were resolved and the database was locked.	group assignments until after all data queries were resolved and the database was locked.	All predefined outcomes were reported	Reasons for lost to follow-up not mentioned.	Intention-to-treat analysis was performed.
14.2. Fedratinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
14.3. Filgotinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
14.4. Nezulcitinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
14.5. Oclacitinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
14.6. Peficitinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
14.7. Ruxolitinib (Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)								
Cao, 2020b	"The enrolled patients were randomly allocated into two groups (1:1 allocation ratio) by an independent statistician using permuted blocks of 4 for all sites. The whole process of randomization was masked to all treating physicians."	Unlikely "Patient unique identification number and treatment allocation codes were provided by a clinical research associate in sequentially numbered opaque envelopes."	Unlikely "Treating physicians were aware of group allocations for safety concern while the enrolled participants, the staff at trial sites, CT radiologists, and laboratory personnel were masked to the trial group assignment."	Likely "Treating physicians were aware of group allocations for safety concern while the enrolled participants, the staff at trial sites, CT radiologists, and laboratory personnel were masked to the trial group assignment."	Unlikely "Treating physicians were aware of group allocations for safety concern while the enrolled participants, the staff at trial sites, CT radiologists, and laboratory personnel were masked to the trial group assignment."	Unclear Authors aimed to describe time from randomization to invasive mechanical ventilation, but was not clearly described in this version, length of invasive mechanical ventilation is described	Unlikely Reasons for lost-to follow up are described	Unlikely Intention-to-treat analysis and Modified intention-to-treat analysis are made
14.8. Tofacitinib								
Murugesan, 2021	Not described	Unlikely Not described	Likely Open-label trial. Patients were not masked to treatment allocation.	Likely Open-label trial	Unclear Not described	Unclear Authors reported in the abstract that there was no difference in duration of	Unclear Loss to follow-up not described	Unlikely No cross-over of participants between groups described and no drop-outs reported

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
						hospitalization. This result is not reported in the article itself.		
Guimarães, 2021	Patients were randomly assigned in a 1:1 ratio to receive either tofacitinib or placebo.	Unlikely Stratification according to site, was performed with the use of a central concealed, Web-based, automated randomization system	Unlikely Double-blinded trial	Unlikely Double-blinded trial	Unlikely An independent data and safety monitoring board reviewed unblinded patient-level data for safety on an ongoing basis during the trial.	Unlikely All predefined outcome measures were reported.	Unlikely All the patients in both groups completed the 28-day follow-up or died. No patient was lost to follow-up or withdrew consent.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
14.9. Upadacitinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
15. IL1-remmers								
15.1. Anakinra								
Declercq, 2021	Computerised Included patients were randomly assigned by means of permuted block randomization with varying block size and stratification by center. Patients were allocated in a 1:2 ratio to anakinra or no IL-1 blockade. Simultaneously, patients were randomly assigned in a 1:1:1 ratio to siltuximab, tocilizumab, or no IL-6 blockade. Randomization and subsequent data collection were done by	Unlikely Randomization and subsequent data collection were done by means of the web based system REDCap.	Likely open-label trial	Likely open-label trial	Unclear not described	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	Unlikely The primary and supportive efficacy endpoints were assessed in the intention-to-treat population. Safety was assessed in the safety population.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	means of the web based system REDCap.							
Kharazmi, 2021	The sample size of 30 patients was divided into parallel groups of intervention and control considered.	Unlikely Permuted block randomization with the sample size of four patients in each block which was stratified based on receiving invasive mechanical ventilation at baseline was performed.	Likely Open-label study	Likely Open-label study	Likely Open-label study	Unlikely All predefined outcome measures were reported.	Unlikely No loss to follow-up reported.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Kyriazopoulou, 2021	<i>"Patients were electronically 1:2 randomized into treatment with placebo or anakinra using four randomization strata: classification into moderate or severe disease using the WHO definition based on the need for oxygen support (https://www.who.int/publications/i/item/clinical-management-of-covid-19); need for dexamethasone intake; body mass index (BMI) higher than 30kg m⁻²; and country."</i>	Unlikely Patients were randomized using for randomization strata: <ul style="list-style-type: none"> • classification into moderate or severe disease using the WHO definition based on the need for oxygen support (https://www.who.int/publications/i/item/clinical-management-of-covid-19); • need for dexamethasone intake; • body mass index (BMI) higher than 30kg m⁻²; • country. 	Unlikely Double-blind study.	Unlikely The study drug was prepared by an unblinded pharmacist with access to the electronic study system using a separate username and password. Administration was done by a blinded study nurse	Unlikely Data were captured after review of all medical and nursing charts by a physician team blinded to the allocation group	Unlikely All predefined outcome measures were reported.	Unlikely Only one patient was lost to follow-up in the study. The patient was initially allocated to the intervention group.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial
Mariette, 2020	Computerized	Unclear	Likely	Likely	Likely	Unlikely	Unlikely	Mariette, 2020

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	<i>Participants were randomly assigned (1:1) using a web-based secure centralised system to either usual care plus anakinra or usual care alone. An independent statistician provided a computer-generated assignment randomisation list stratified by centre and blocked with varying block sizes (randomly of sizes two or four) unknown to the investigators.</i>	Concealment of allocation was not described.	(mortality: unlikely) 'Patients and investigators were not masked to treatment assignment due to the nature of the intervention.'	(mortality: unlikely) 'Patients and investigators were not masked to treatment assignment due to the nature of the intervention.'	(mortality: unlikely) 'Patients and investigators were not masked to treatment assignment due to the nature of the intervention.'	Not all outcomes that are reported in trial registration are reported in publication. Registered ClinicalTrials.gov: NCT04341584.	4 patients (6.8%) in the intervention group and 2 patients (3.5%) in the control group were lost to FU or withdrew consent. This is not expected to induce a bias in the results.	
15.2. Canakinumab								
Caricchio, 2021	Block randomisation The randomization was stratified by country, with a block size of 4 within each stratum. It was implemented using an interactive response technology system in which a new patient meeting the inclusion and exclusion criteria was randomly assigned to a treatment group based on a random allocation sequence. This sequence was created by a separate randomization office of	Unlikely It was implemented using an interactive response technology system in which a new patient meeting the inclusion and exclusion criteria was randomly assigned to a treatment group based on a random allocation sequence.	Unlikely Double blinded The study therapy was prepared by an unblinded pharmacist independent of the study team to maintain the blind. After dilution, canakinumab and placebo preparations were indistinguishable.	Unlikely Double blinded	Unlikely Double blinded	Unlikely All outcomes mentioned in Methods were reported. ClinicalTrials.gov Identifier: NCT04362813	Unclear Reason for loss to follow up was not reported	Unlikely Patients randomized in the study were the same patients who were analysed.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
	the sponsor and kept blinded to the study team until the scheduled unblinding for data analysis.							
16. IL6-remmers								
16.1. Clazakisumab								
NA	NA	NA	NA	NA	NA	NA	NA	NA
16.2. Levilimab (Monoclonal antibody- IL-6 inhibitor-BCD-089; Ilsira)								
Lomakin, 2021	Computerized Randomization was performed centrally. After the investigator entered the eligibility screening data, the central electronic system generated a unique subject identifier and a unique investigational product lot number.	Unlikely Randomization was performed centrally	Unlikely Patients were blinded to the treatment allocation.	Unclear Not reported. However, levilimab and placebo were provided in identical primary and secondary packages with identical labels.	Unlikely The investigator was blinded to the treatment allocation.	Unlikely All outcome measures described in the methods are reported in the results, except for duration of hospital stay. Noteworthy, the initial primary endpoint was overall mortality, but because the mortality was significantly lower than assumed, the study did not have enough power to detect a meaningful difference.	Unlikely The percentage of patients lost to follow-up is less than 10%, but higher in the control group.	Unlikely All randomized patients who received levilimab or placebo were included in the ITT ('as randomized') analysis.
16.3. Olokizumab								
NA	NA	NA	NA	NA	NA	NA	NA	NA
16.4. Sarilumab (human monoclonal antibody; against the interleukin-6 receptor; sold under the brand name Kevzara)								
Merchante, 2021	Unclear Patients were randomized in a 1:1:1	Unclear Not reported	Likely Open-label trial	Likely Open-label trial	Unclear Not described	Likely Not all outcome measures described in	Unlikely No participants were lost to follow-up.	Unlikely Efficacy analyses of the primary outcome

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	ratio, further details are not reported.					the trial protocol are reported in the results		were performed both in the intention-to-treat population and per protocol population.
CORIMUNO-19 Collaborative Group, 2021	Computerized Participants were randomly assigned in a 1:1 ratio via a web-based secure centralised system. An independent statistician provided a computer-generated randomisation list stratified by centre and blocked with random block size (randomly selected among 2 and 4); the block size was unknown to the investigators and statisticians analysing the data.	Unlikely Participants were randomly assigned via a web-based secure centralised system. An independent statistician provided a computer-generated randomisation list.	Likely Open-label trial	Likely Open-label trial	Unlikely Analyses were done by the study statisticians who were blinded to the actual randomisation groups.	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely No patients were lost to follow-up	Unlikely Analyses were done on an intention-to-treat basis with no correction for multiplicity for prespecified secondary outcomes
Sancho-López, 2021	Computerized Participants were randomly assigned in a 1:1 ratio to receive either sarilumab plus SOC or SOC alone. Randomization codes were produced by means of the RERAND system integrated within the eCRF system based on Oracle, stratified by center and using blocks multiple of 2 elements.	Unlikely The randomization schedule was managed through the eCRF in a concealed manner.	Likely <i>It is an open label study, which mainly will have an impact on the subjective outcomes.</i>	Likely <i>It is an open label study. However, medical decisions to increase oxygen support were taken by different physicians, many of them not investigators of the trial.</i>	Likely <i>It is an open label study, which mainly will have an impact on the subjective outcomes.</i>	Unclear <i>Some of the outcome measures mentioned in the study protocol were not reported in the study (e.g. duration of hospitalization, non-invasive ventilation)</i>	Unlikely <i>Number of lost to follow-up and reasons were not different between the treatment groups.</i>	Unlikely <i>ITT-analysis was performed.</i>

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Lescure, 2020	Computerized <i>Eligible patients were randomly assigned (2:2:1) to one dose of intravenous sarilumab 400 mg, sarilumab 200 mg, or placebo according to a central randomisation scheme using permuted blocks of five and implemented through an interactive response technology.</i>	Unclear Concealment was not described	Unlikely “Patients, care providers, outcome assessors, and investigators remained masked to assigned intervention throughout the course of the study. An unmasked pharmacist was responsible for the preparation and dispensation of all study interventions.”	Unlikely “Patients, care providers, outcome assessors, and investigators remained masked to assigned intervention throughout the course of the study. An unmasked pharmacist was responsible for the preparation and dispensation of all study interventions.”	Unlikely “Patients, care providers, outcome assessors, and investigators remained masked to assigned intervention throughout the course of the study. An unmasked pharmacist was responsible for the preparation and dispensation of all study interventions.”	Unlikely Elaborate description of outcomes in register; not all FU’s included in the publication Register: ClinicalTrials.gov, NCT04327388; EudraCT, 2020-001162-12; and WHO, U1111-1249-6021.	Unlikely	Unlikely
The REMAP-CAP Investigators, 2020	Computerized randomization Participants were assigned by means of a centralized computer program to each intervention, starting with balanced assignment for tocilizumab, sarilumab, or control, with actual proportions dependent on the number of interventions available at each site.	Unlikely Centralized randomization was used that was remote from study sites.	Likely Open-label trial.	Likely Open-label trial. Clinical staff were aware of the intervention assignment of individual patients.	Unclear Not reported.	Unlikely Secondary outcomes were all prespecified, and details are provided in the Supplementary Appendix.	Unclear Because this is an early, preliminary report, some data are missing, including 11 outcomes.	Unclear Not reported.
16.5. Siltuximab								
Declercq (2021)	See RoB assessment of the Declercq (2021) by Anakinra.							
16.6. Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor)								
Declercq (2021)	See RoB assessment of the Declercq (2021) by Anakinra.							

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Rosas, 2021b	Eligible patients were randomly assigned in a 2:1 ratio using an interactive web-based response system and a permuted block method to receive blinded treatment with tocilizumab plus remdesivir or placebo plus remdesivir. Randomization was stratified by geographic region (North America, Europe, other) and by a 2-level factor based on clinical status at screening (ordinal scale categories 4–5, category 6) on a 7-category ordinal scale (additional details are in the Online Resource).	Unlikely	Unlikely Double-blind study.	Unlikely Double-blind study	Unlikely Double-blind study	Unlikely All predefined outcome measures were reported.	Unlikely A slightly higher proportion of patients in the placebo plus remdesivir arm than the tocilizumab plus remdesivir arm discontinued remdesivir before completing 10 days of treatment (44.2% vs 39.4%); however, most of these early discontinuations were the result of hospital discharge, consistent with remdesivir use in other trials [17] and in clinical practice	Unlikely Participants included in the analysis are exactly those who were randomized into the trial
Horby, 2021a Recovery Collaborative group, 2021	Computerized Patients were assigned to either usual standard of care or usual standard of care plus tocilizumab in a 1:1 ratio by means of web-based simple (unstratified) randomisation.	Unlikely Allocation was concealed until after randomisation.	Likely It was an open-label trial; participants were not masked to the allocated treatment	Likely Local study staff was not masked to the allocated treatment. (except for mortality)	Unclear Local study staff was not masked to the allocated treatment. However, the steering committee, investigators, and all others involved in the trial were masked to the outcome data during the trial.	Unlikely Outcome measures described in the protocol were also reported.	Unlikely 97% versus 98% completed the trial.	Unlikely Intention to treat analysis was performed.
Wang, 2021	Computerized	Unclear	Likely	Likely	Unclear	Unlikely	Unlikely	Unlikely

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	Randomization numbers were generated using SAS statistical software package. Each consecutively coded patient was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached. The patients were randomly assigned in a 1:1 ratio.	Not described.	open-label RCT	open-label RCT	Not described.	However, the worsening rate of hypoxia during hospitalization was only reported for subgroups of patients with moderate or severe COVID-19.	No participants were lost to follow-up.	However, one patient in the control group, who worsened severely 3 days after randomization, was crossed over to the tocilizumab group in accordance with the study protocol. However, this patient was erroneously included in the intervention group for the ITT analyses.
Soin, 2021	Computerized “Eligible patients were randomly assigned using block randomisation in a 1:1 ratio to receive open-label tocilizumab plus current standard care (tocilizumab group) or current standard care alone (standard care group). The randomisation sequence was generated using SAS, version 9.4 and an interactive web response system.”	Unclear Concealment not described “Randomisation numbers were assigned in sequential order to the study sites according to the pregenerated sequence provided by the investigational medicinal product team at the Medanta Institute of Education and Research.”	Likely “After randomisation, none of the study personnel or patients were masked to treatment assignment in this open-label trial.”	Likely “After randomisation, none of the study personnel or patients were masked to treatment assignment in this open-label trial.”	Likely “After randomisation, none of the study personnel or patients were masked to treatment assignment in this open-label trial.”	Unlikely Relevant and announced outcomes reported; registered with the Clinical Trials Registry India (CTRI/2020/05/025369)	Unlikely 1 cross-over from control to intervention group, 1 withdrawn consent in standard care group; not expected to induce bias in results	Unlikely Analysis not performed according to ITT-protocol; small number of patients not included in the analysis, 1 cross-over; not expected to induce bias in results
Rosas, 2021a	Web-based response system and permuted block randomization / Stratification according	Likely Patients were stratified according to geographic region and use of	Unlikely The study was a double-blinded,	Unlikely The study was a double-blinded,	Unlikely The study was a double-blinded,	Unlikely All predefined outcomes were reported.	Unlikely Lost to follow-up did not significantly differ	Unlikely Participants included in the analysis are exactly those who

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	to use of mechanical ventilation (yes or no). <i>Eligible patients were randomly assigned in a 2:1 ratio to receive a single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight, with a maximum dose of 800 mg) or placebo plus standard care by means of an interactive voice or Web-based response system and permuted-block randomization. Randomization was stratified according to geographic region (North America or Europe) and the use of mechanical ventilation (yes or no).</i>	mechanical ventilation (yes or no).	placebo-controlled study.	placebo-controlled study.	placebo-controlled study.		between the two groups.	were randomized into the trial and analysed by intention-to-treat analysis.
The REMAP-CAP Investigators, 2020	See RoB assessment of the REMAP-CAP Investigators (2020) by sarilumab.							
Veiga, 2021	Patients were randomised in a 1:1 ratio to receive either standard care or tocilizumab plus standard care, with random blocks of sizes 2, 4, 6, and 8, and stratified by age (<60 and ≥60 years) and sex, according to a	Unlikely Allocation concealment was ensured by a central automated web accessed system (REDCap), developed by CZO.	Likely Open label trial	Likely Open label trial	Likely Open label trial + “Hospital researchers, unblinded to treatment assignment, collected outcome data during the patients’ hospital stay”.	Unlikely Results of all predefined outcome measures were reported.	Unclear “The 15 day follow-up was completed for all patients.” However, it is unclear if the 28/29 days follow-up also was completed for all patients.	Unlikely “The primary analysis followed the intention-to-treat principle, except for adverse events, which were analysed in a safety population that included patients according to the drug

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	computer-generated schedule using the sample function of software R 3.6.3 (R Foundation).							received, regardless of assigned group.” Two patients in the placebo group received tocilizumab at discretion of the doctor
Salama, 2020	Computerized “Using permuted-block randomization and an interactive voice- or Web-response system, we randomly assigned the patients, in a 2:1 ratio, to receive standard care plus one or two doses of either intravenous tocilizumab (8 mg per kilogram of body weight, to a maximum of 800 mg per dose) or placebo. The randomization was stratified according to country (the United States, Mexico, Kenya, South Africa, Peru, or Brazil) and age (≤60 or >60 years).”	Unlikely “After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).”	Unlikely “Study site personnel and patients will be blinded to treatment assignment during the study, with the exception of the study pharmacist.”	Unlikely “Study site personnel and patients will be blinded to treatment assignment during the study, with the exception of the study pharmacist.”	Unlikely “Study site personnel and patients will be blinded to treatment assignment during the study, with the exception of the study pharmacist.”	Unlikely ClinicalTrials.gov number, NCT04372186. Primary outcome slightly different (protocol: proportion of patients requiring mechanical ventilation at day 28; publication: proportion of patients who had received mechanical ventilation or who had died by day 28.	Likely Percentage of loss to follow-up differs between groups (intervention group 3.9%, control group 0.8%). Unclear why more participants of the intervention group withdrew from study participation.	Unlikely Analysis performed according to (modified) intention-to-treat protocol; as indicated by randomized participants minus participants that withdrew or were withdrawn.
Stone, 2020	Block randomization	Unlikely Randomization was performed with randomly permuted blocks of sizes 3 and 6. Randomization was	Unlikely It was a randomized, double-blind, placebo-controlled trial.	Unlikely It was a randomized, double-blind, placebo-controlled trial.	Unlikely A blinded interim analysis for safety was performed.]	Unlikely	Unlikely	Unlikely Intention-to-treat analysis was performed.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		stratified according to site.						
Salvarani, 2020	Computerized "Patients were randomized using a web-based system with a 1:1 allocation ratio. Randomization was stratified by center"	Unlikely "allocation concealment was based on a centralized randomization list that was not available to clinicians"	Unclear It was an open label study.	Likely It was an open label study, which might have led to differences in patient care.	Unclear It was an open label study, which might have led to differences in reporting the results.	Unlikely Outcomes reported in accordance with study protocol / trial register Trial Registration: ClinicalTrials.gov Identifier NCT04346355; EudraCT Identifier: 2020-001386-37	Unclear 3 patients withdrew consent in control group.	Unlikely 3 patients withdrew consent in control group. Other patients were included in the analysis according to randomization; adherence to ITT analysis protocol.
Hermine, 2020	Participants were randomly assigned in a 1:1 ratio to receive TCZ plus usual care (TCZ group) or usual care alone (UCgroup) via a web-based secure centralized system.	Unlikely An independent statistician provided a computer-generated assignment randomization list stratified by center and blocked with varying block sizes unknown to the investigators	Likely The trial was not blinded because it was logistically impossible at the time of the pandemic to set up a double-blind study quickly	Likely	Likely	Unlikely	Likely 8 patients were lost to follow-up at day 28 in the TCZ group versus 3 in the UC group	Unlikely Analyses were performed on an intention-to-treat basis with no correction for multiplicity for secondary outcomes. Thus, these results are exploratory and reported as point estimates and 95% confidence intervals (CIs)
17. Other immunomodulators								
17.1. Auxora (potent and selective small molecule inhibitor of calcium release-activated calcium (CRAC) channels)								
Miller, 2020	Not reported	Unclear Not reported	Unclear Not reported	Unclear Not reported	Unclear Not reported	Unclear Trial registration available (NCT04345614); not all outcomes reported in register were	Unlikely Information on endpoint available for all participants	Unlikely No cross-over of participants between groups described and no drop-outs reported

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
						provided and absolute values often not reported		
17.2. Colchicine (anti-inflammatory and analgesic medication)								
Pourdowlat, 2022	Patients were randomly assigned in a 1:1 ratio	Likely Open-label trial. The allocation of therapies was not concealed following randomization.	Likely Open-label trial. Patients were not masked to treatment allocation.	Likely Open-label trial	Unclear Not described	Unlikely All predefined outcome measures were reported.	Likely Percentage of loss to follow-up differs between groups (intervention group 12.7%, control group 37%)	Unclear Not mentioned in the statistical analysis section.
Diaz, 2021	Computerized Research electronic data capture (REDCap; Vanderbilt University) online web-based forms hosted at the Population Health Research Institute in Hamilton, Canada, were used for the concealed sequential randomization process. Patients were assigned in a 1:1 ratio.	Unlikely Randomization (1:1) was done via REDCap using a permuted block randomization. Randomization was restricted with blocks of random sizes and stratified by mechanical ventilation status at baseline.	Likely Open-label trial	Likely Open-label trial	Unclear Not described	Unlikely All outcome measures described in the trial protocol are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and is similar between treatment groups.	Unlikely Efficacy analysis was conducted on an intention-to-treat basis.
Absalón-Aguilar, 2021	Sequentially numbered containers Patients were randomized with a non-stratified 1:1 allocation rate. A third-party person not involved in the conduction of the protocol was responsible for the randomization of	Unlikely A third-party person not involved in the conduction of the protocol was responsible for the randomization of patients using sequentially numbered containers.	Unlikely Participants were blinded to treatment allocation.	Unlikely Treating physicians were blinded to the allocation.	Unlikely The researchers in charge of recruitment and the statistician in charge of the statistical analysis were blinded to the allocation f..	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely No participants were lost to follow-up.	Unlikely All analyses were done in the intention-to-treat population.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss of follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	patients using sequentially numbered containers.							
RECOVERY Collaborative Group, 2021	Computerized Eligible patients were allocated using a central web-based randomisation service (without stratification or minimisation).	Unlikely Randomization was performed centrally.	Likely This is an open-label study; participants and local study staff were not masked to the allocated treatment.	Likely This is an open-label study; participants and local study staff were not masked to the allocated treatment.	Unlikely The trial steering committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely The percentage of patients lost to follow-up is less than 10% and similar between treatment groups.	Unlikely All randomized patients were included in the ITT analysis.
Pascual-Figal, 2021	Web based randomization centrally randomized to “colchicine” or “control” group using an automated interactive web-based system.	Likely Patients in both groups received the standard therapy for COVID-19 according to the established contemporary hospital protocols. Participants were allocated to colchicine group or control group (1:1) using the minimization method, in order to minimize the imbalance between groups for the following patient risk factors: age (≤ 60 , 60–80 or ≥ 80), sex (male or female), time from initiation of symptoms (< 5 or ≥ 5 días), cardiovascular disease (yes or no), 7-point World Health Organization (WHO)	Likely Open-label trial	Likely Open-label trial	Likely Open-label trial	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely No lost to follow up.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
		class (3 or 4) and levels of C-reactive protein (<5, 5–10 or >10 mg/dl), ferritin (<1000 or ≥1000 ng/mL), D-dimer (<500 or ≥500 ng/mL), IL-6 (<70 or ≥70 pg/mL) and lymphocyte count (<1000 or ≥1000/mm ³) at randomization.						
Tardif et al., 2021	Computerised Participants were randomised (1:1) using an allocation sequence that was computer-generated using a blocking schema with block sizes of six. Allocation sequence was not stratified.	Unlikely Eligible patients were randomly assigned by research nurses through the IWRS system that provided the bottle number to send to patients. The randomisation list was computer-generated by an unmasked biostatistician and uploaded to an interactive web response system.	Unlikely Patients were blinded to treatment allocation.	Unlikely During the entire duration of the trial, the study team, including the biostatisticians who wrote the statistical analysis plan and generated the final results, remained masked to treatment allocation.	Unlikely During the entire duration of the trial, the study team, including the biostatisticians who wrote the statistical analysis plan and generated the final results, remained masked to treatment allocation.	Unlikely All outcome measures described in the methods are reported in the results.	Unlikely Loss to follow-up was small, and similar in both groups.	Unlikely Efficacy analyses were done according to the intention-to-treat principle.
Lopes, 2021	“The randomization was performed 1:1 for placebo or colchicine by using the online tool at https://www.randomizer.org/ .”	Unlikely They used an online tool to randomize patients into treatment groups.	Unclear Trial reported as double blinded, but no details provided	Unclear Trial reported as double blinded, but no details provided	Unclear Trial reported as double blinded, but no details provided	Unclear Outcomes mentioned in trial register are also reported; trial registered (July 2020) after start of study and enrolment of patients (April 2020)	Unlikely 1 patient in each group discontinued due to ICU admission	Unlikely No intention to treat analysis was performed, but only 1 patient in each group dropped out, no crossovers.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
Deftereos, 2020	“The randomization sequence was prepared by a statistician not involved in the trial using R software version 3.6.2 (R Project for Statistical Computing), and the corresponding assignment was provided to site coordinators electronically on each patient enrolment.”	Unlikely Statistician and coordinators not involved in the trial were responsible for allocation	Likely Due to open-label design of the trial	Likely Due to open-label design of the trial	Likely Due to open-label design of the trial	Unlikely It is mentioned if outcomes were not possible to report	Unclear Follow up period not clearly described	Unlikely Intention to treat analysis is provided
17.3. Fostamatinib								
NA	NA	NA	NA	NA	NA	NA	NA	NA
17.4. Imatinib								
Aman, 2021	Computerized based on study site. Randomisation was done with the Castor Electronic Data Capturing System (Castor EDC; Amsterdam, Netherlands) using variable block sizes (two, four, or six patients), stratified by study site.	Unlikely Allocation to study groups was done by Castor, and was not accessible to study investigators	Unlikely Patients, medical staff, and investigators were masked to group assignment.	Unlikely Patients, medical staff, and investigators were masked to group assignment.	Unlikely Patients, medical staff, and investigators were masked to group assignment.	Unlikely All predefined outcome measures were reported.	Likely 14 (7%) of 188 patients in the placebo group and nine (5%) of 197 patients in the imatinib group were lost to follow-up or withdrew consent between randomisation and the first dose of study medication. This attrition was partly explained by the fact that, during the pandemic, high numbers of	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.

	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)
							admissions in particular regions in the Netherlands forced hospitals to relocate their patients to hospitals in other regions.	
17.5. Leflunomide (immunosuppressive disease-modifying antirheumatic drug, DMARD)								
Wang, 2021	Non-randomized controlled trial	Likely The study was a non-randomized controlled trial.	Likely Cross-over study without placebo.	Unclear No information provided.	Unclear No information provided.	Unlikely All predefined outcome measures were reported.	Unlikely No loss to follow-up reported.	Unlikely Participants included in the analysis are exactly those who were randomized into the trial.
Wang, 2020b	Not described	Unclear [Method of randomization was not described in the study.]	Likely [Trial was unblinded.]	Likely [Trial was unblinded.]	Likely [Trial was unblinded.]	Unlikely [Outcomes described in the methods were also described in the results.]	Unclear [Loss to follow-up not described.]	Likely [Not all randomized people were included in the analysis.]
17.6. Mycobacterium W								
Sehgal, 2021	<i>A central team not directly involved in patient care or patient data analysis provided a computer-generated randomisation sequence. The randomisation was stratified according to the centres. The subjects at each centre received either the investigational drug or a matched placebo in individually numbered packs</i>	Unlikely <i>The investigators at each participating centre and the subjects were blinded to the treatment allocation. Envelopes were provided to each participating centre for emergency unmasking.</i>	Unlikely <i>the subjects were blinded to the treatment allocation.</i>	Unlikely <i>The investigators at each participating centre were blinded to the treatment allocation</i>	Unclear	Unlikely All predefined outcome measures were reported.	Unlikely Two patients withdrew consent, but were included in the primary and safety analysis.	Unlikely The patients included in the analysis were the exact same patients as randomized in the study.

	Describe method of randomisation¹	Bias due to inadequate concealment of allocation?² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up?⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?⁶ (unlikely/likely/unclear)
	<i>according to the sequential order. The investigators at each participating centre and the subjects were blinded to the treatment allocation. Envelopes were provided to each participating centre for emergency unmasking.</i>							
17.7. Tractolimus								
Solanich, 2021	See RoB assessment of Solanich (2021) by 'Methylprednisolone'.							

Selectiecriteria

Tot 2 september werden alle RCTs die voldoen aan de volgende vergelijking geïnccludeerd in bovenstaande tabellen:

- P: Patiënten met (bewezen) COVID-19 infectie
I: Middel X (of meerdere middelen)
C: Geen middel
O: Clinical outcomes
- Mortality (28-30 day) / Mortality (other?)
 - Duration of hospitalization (time to discharge from hospital/ICU, days at ICU/hospital during X days)
 - Time to symptom resolution
 - Respiratory support (% of population requiring oxygen / NIV / mech. vent etc. at day X, OR, ordinal scale indicating need for respiratory support at day X)
 - Adverse events
 - Viral clearance (% negative RT-PCR at day X, viral load at day X, etc.)

Studies over de volgende middelen (X) werden geïnccludeerd:

1. Remdesivir
2. Corticosteroïden
 - Dexamethasone
 - Hydrocortisone
 - Inhaled corticosteroids: budesonide, ciclesonide
 - Methylprednisolone
3. Hydroxychloroquine & Chloroquine
4. Immunoglobulines
 - Hyperimmunoglobulin
 - Intravenous immunoglobulin
 - Normal immunoglobulin
5. Convalescent plasma
6. Artificieel gemaakte monoklonale antistoffen
 - Interleukineremmers
 - Anakinra (humane interleukine-1-receptorantagonist)
 - Canakinumab

- Sarilumab (human monoclonal antibody; against the interleukin-6 receptor; sold under the brand name Kevzara)
- Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor)
- Other
 - Adalimumab
 - Bamlanivimab (INN, codenamed LY-CoV555) neutralizing monoclonal antibody
 - Bamlanivimab & Etesevimab (LY-CoV016; recombinant fully human monoclonal neutralizing antibody; together is combination of two monoclonal antibodies)
 - Casirivimab/imdevimab (REGN-COV2; combination of two noncompeting, neutralizing human IgG1 antibodies)
 - Granulocyte-Macrophage colony-stimulating factor (GM-CSF)
 - Itolizumab (humanized monoclonal antibody (IgG1 kappa anti-CD6)
 - Mavrilimumab (human monoclonal antibody; anti-GM-CSF-R α ; human isoform IgG4)
 - Vilobelimumab (Anti-C5a antibody IFX-1; monoclonal anti-human complement factor C5a antibody)

7. Polyklonale antistoffen

8. Supplementen

- Vitamine C
- Vitamine D
- Zink

9. Antiviral treatment

- Darunavir (antiretroviral treatment; evt. in combinatie met cobicistat)
- Favipiravir (evt. in combinatie met Baloxavir en/of marboxil)
- Lopinavir/ ritonavir (brand name = Kaletra; fixed dose combination of antiretroviral treatment)
- Molnupiravir
- Nitazoxanide (brand name = Alinia; antiparasitic & broad-spectrum antiviral medication)
- Novaferon (broad-spectrum antiviral drug)
- Oseltamivir (brand name = Tamiflu)
- Ribavirine (also known as tribavirin)
- Sofosbuvir (brand name = Sovaldi; has role as a prodrug, an antiviral drug and a hepatitis C protease inhibitor; only recommended with some combination of ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir)
 - i.c.m. Daclatasvir (brand name = Daklinza; used in combination with sofosbuvir, ribavirin, and interferon)
 - i.c.m. Ledipasvir (combinatie brand name = Harvoni; antiviral for hepatitis C-virus)
 - i.c.m. Velpatasvir (NS5A inhibitor (by Gilead); fixed-dose combination medication with sofosbuvir for the treatment of hepatitis C)
- Umifenovir (brand name = Arbidol)

10. Antibiotic treatment

- Azithromycin
 - Doxycycline
 - Lincomycine
11. Antifungal treatment
- Intraconazole
12. Antiparasitic treatment
- Ivermectine (broad spectrum anti-parasitic agent)
13. Interferon
- Inhaled IFN- κ plus TFF2 (= Interferon kappa + Trefoil factor 2)
 - inhaled Interferon beta-1b
 - Interferon alfa-2b
 - Interferon β -1a
 - Interferon β -1b
 - Peginterferon Lambda
 - Peginterferon Lambda-1a
 - Pegylated Interferon-2b
14. Other immunomodulators
- Auxora (potent and selective small molecule inhibitor of calcium release-activated calcium (CRAC) channels)
 - Baricitinib (selective and reversible Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)
 - Colchicine (anti-inflammatory and analgesic medication)
 - Imatinib
 - Leflunomide (immunosuppressive disease-modifying antirheumatic drug, DMARD)
 - Mycobacterium W
 - Nezulcitinib
 - Ruxolitinib (Janus kinase 1 (JAK1) and 2 (JAK2) inhibitor)
 - Tofacitinib
 - Tractolimus

Vanaf 2 september zijn de selectiecriteria aangescherpt, minder middelen werden meegenomen. In de volgende tabel staat welke middelen al dan niet werden meegenomen: <https://kennisinstituut.viadesk.com/do/document?id=1424556-646f63756d656e74>. Mocht u niet bij deze tabel kunnen, dan kunt u deze opvragen via Andrea Kortlever (a.kortlever@kennisinstituut.nl).

Per 14-10-2021 werd bij het toevoegen van nieuwe middelen ook gekeken of er eerdere studies over het betreffende middel zijn geëxcludeerd.