ONGOING LIVING UPDATE OF COVID-19 THERAPEUTIC OPTIONS

Summary of Evidence • Rapid Review, 30 January 2023

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Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence, Rapid Review. 30 January 2023
PAHO/IMS/EIH/COVID-10/23-0002

Disclaimer

This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. In recognition of the fact that there are numerous ongoing clinical studies, PAHO will periodically update this review and corresponding recommendations as new evidence becomes available.

Contents

Executive summary

Background

The urgent need for evidence on measures to respond to the COVID-19 pandemic had led to a rapid escalation in numbers of studies testing potential therapeutic options. The vast amount of data generated by these studies must be interpreted quickly so that physicians have the information to make optimal treatment decisions and manufacturers can scale-up production and bolster supply chains. Moreover, obtaining a quick answer to the question of whether or not a particular intervention is effective can help investigators involved in the many ongoing clinical trials to change focus and pivot to more promising alternatives. It is crucial for healthcare workers to have access to the most up-to-date research evidence to inform their treatment decisions.

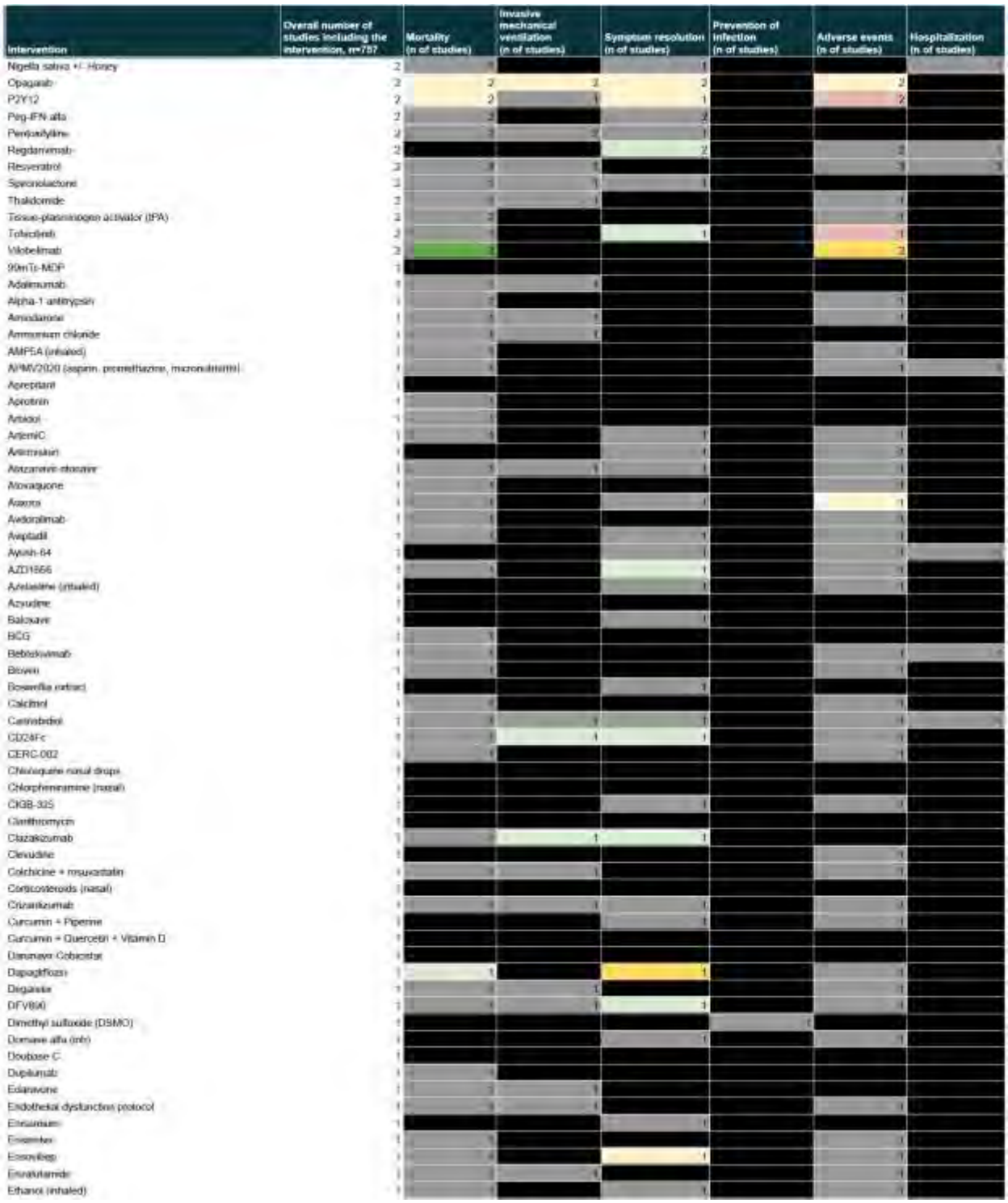
To address this evidence gap, we compiled the following database of evidence on potential therapeutic options for COVID-19. We hope this information will help investigators, policy makers, and prescribers navigate the flood of relevant data to ensure that management of COVID-19, at both individual and population levels, is based on the best available knowledge. We will endeavor to continually update this resource as more research is released into the public space.

Summary of evidence

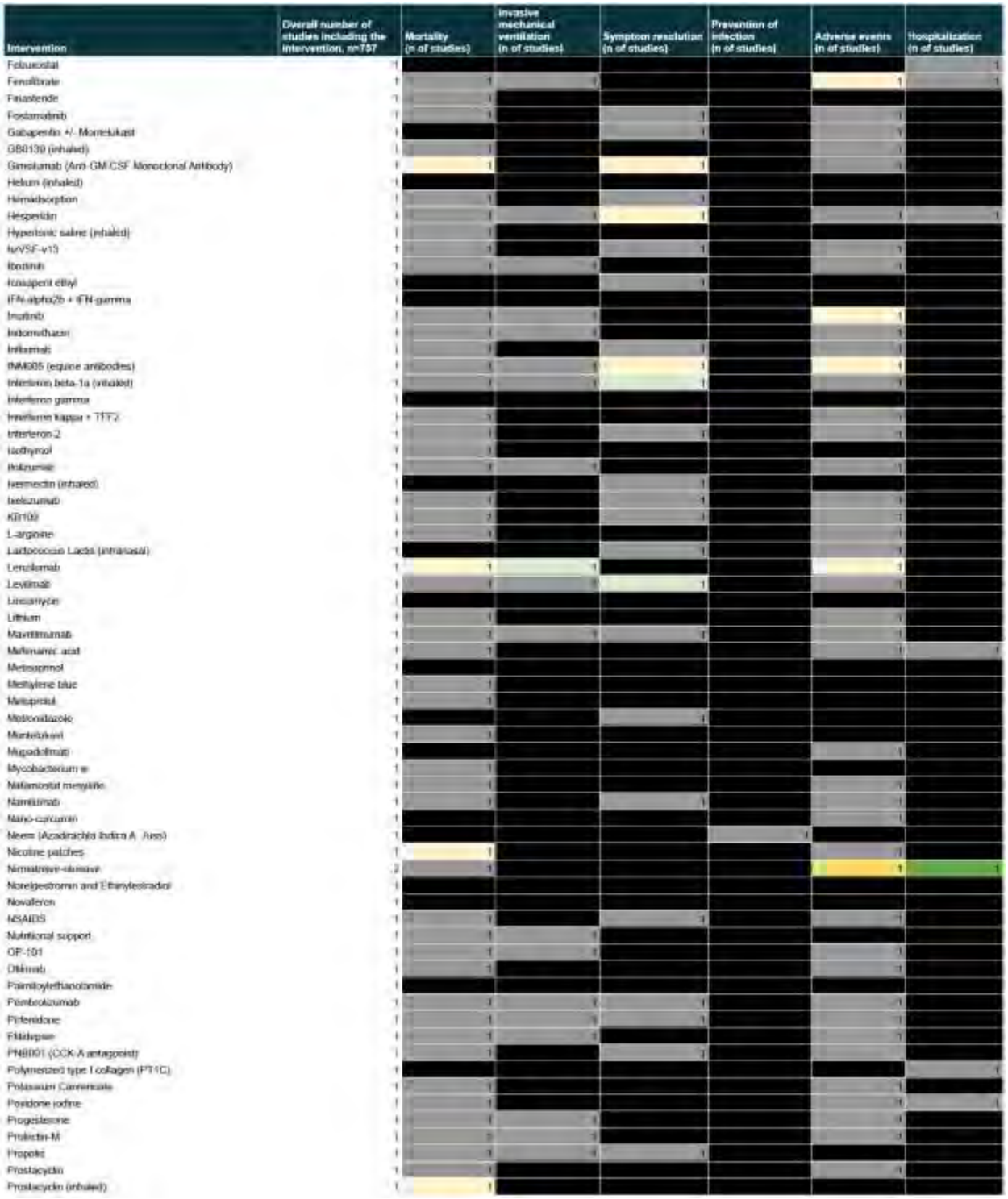
Tables 1 and 2, which divide the total group of identified studies into randomized (Table 1) and non-randomized (Table 2) designs, indicate the primary outcome measures used for each investigation and the level of certainty. A living interactive version of tables 1 and 2 is available here. Table 3 summarizes the status of evidence for the 243 potential therapeutic options for COVID-19 for which studies were identified through our systematic review.

Table 1. List of RCTs of interventions for COVID-19 with primary outcome measures and certainty (n=757) (interactive online version)

Intervention		Overall number of studies including the intervention, n=757	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Hydroxychloroquine or Chloroquine	NEW	63	9	10	10	14	20	13
Convalescent plasma		58	20	22	13	3	17	4 (§)
Ivermectin		49	12(*)	8(*)	7(*)	1(*)	8	11
Favipiravir		29	12	6	4(*)		8	6
Tocilizumab		29	21	21	12		17	
Corticosteroids	NEW	27	10(§§)	7	6		6	
Anticoagulants	NEW	22	17		1		11 (†)	4
Lopinavir-Ritonavir		21	4	4	2	3	3	2
Vitamin D		20	6	3		2(§§§)	2	3
Colchicine		16	14(**)	6(**)	5(**)		4	3
Sofosbuvir +/- Daclatasvir or others		16	2(*)	2(*)	2(*)			2
Mouthwash		14	1	1	2			
ACEIs or ARBs		14	6(*)	10	1		1	2
REGEN-COV (casirivimab and imdevimab)		12	2(§§)	2(§§)	2(§§)	2	5	4
Azithromycin		11	5	5	6		1	2
Molnupiravir		11	5		4		5	7
Siltuximab		11	11	8	8		8	
Mesenchymal cell transplantation	NEW	10	6	2	2		1	
Remdesivir		10	6	7	4		4	1
Vitamin C		10	7	8	4		1	
Bamlanivimab +/- etesevimab		9	3		3	1	6	1
Corticosteroids (inhaled)		9	4	1	5		4	5
Melatonin		9	4	1	3	1		
Zinc		9	3	1	2	2	1	1
Baricitinib		7	5	3	3		3	
Interferon beta-1a		7	6	4	3		2	
Nitazoxanide		7	2	1	1		3	2
Umifenovir		7	1	2			1	
Anakinra		6	5	2	3		5	
Bromhexine Hydrochloride	NEW	6	3	1		2	1	1
IVIG		6	13	10			1	
Aspirin	NEW	5	4	4	1		2	
Camostat mesilate		5	2	1	3		2	2
Fluvoxamine	NEW	5	1	1	1		2	4 (§)
Probiotics		5	2	1	1	1		
Tenofovir + emtricitabine		5	2	2	1	1	3	2
Doxycycline		4	3	1	2	1		1
Hyperbaric oxygen	NEW	4	4	3	1		3	
Hyperimmune anti-COVID-19 IVIG		4	4		1		2	
Nasal hypertonic saline		4			1			
Nitric oxide		4	2	2	1			
Procalcitonin		4	3	3	2			2
Peg-IFN lambda		4			1		1	1
Quercetin		4	3		2		1	1
Statins		4	4	1	1			1
Cofactors		3	1		1		1	
Famotidine		3	2	2	1			
Interferon beta-1b		3	2	3	1			
Low-dose radiation therapy		3	2	1				
Metformin		3	1				1	2
N-acetylcysteine		3	3	2			1	
Omega-3 fatty acids		3	2					
Ruxolitinib		3	3	2	3		3	
Sotrovimab		3	1	1	1		1	1
Tixagevimab–Cilgavimab		3	2		1	1	3	1
Beta glucans		2					1	
Bicarbonate (inhaled)		2	2					1
Canakinumab		2	2	1	1		1	
Dutasteride		2			1			
Electrolyzed saline		2	2		1		1	
Icatibant	NEW	2	2	1	1		1	
Iota-Carrageenan		2	1				2	1
Ladarixin		2			1	1		
Leflunomide		2						
Levamisole		2	1		1			2
Linagliptin		2	2	2				
N-acetylcysteine (inhaled)	NEW	2	2					
Niclosamide		2	1	1			1	1



Intervention	Overall number of studies including the intervention, n=757	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Nigella sativa +/- Honey	2	1		1			1
Opaganib	2	2	2	2		2	
P2Y12	2	2	1	1		2	
Peg-IFN alfa	2	2		2			
Pentoxifylline	2	2	2	1			
Regdanvimab	2			2		2	1
Resveratrol	2	1	1			1	1
Spironolactone	2	1	1	1			
Thalidomide	2	1	1			1	
Tissue-plasminogen activator (tPA)	2	2				1	
Tofacitinib	2	1		1		1	
Vilobelimab	2	1				2	
99mTc-MDP	1						
Adalimumab	1	1	1				
Alpha-1 antitrypsin	1	1				1	
Amiodarone	1	1	1			1	
Ammonium chloride	1	1	1				
AMPSA (inhaled)	1	1				1	
APMV2020 (aspirin, promethazine, micronutrients)	1	1				1	1
Aprepitant	1						
Aprotinin	1	1					
Artelol	1	1					
ArtemiC	1	1		1		1	
Artemisinin	1			1		1	
Atorvastatin +Ezetimibe	1	1	1	1		1	
Atovaquone	1	1				1	
Azacitidine	1	1		1		1	
Azvudine	1	1					
Baloxavir	1			1			
BCG	1	1					
Bebtelovimab	1	1				1	1
Bevasizumab	1	1				1	
Boswellia extract	1			1			
Calcitriol	1	1				1	
Camrelizumab	1	1	1	1		1	1
CD24Fc	1	1	1	1		1	
CERC-002	1	1				1	
Chloroquine nasal drops	1						
Chlorpheniramine (nasal)	1						
CIGB-325	1			1		1	
Clarithromycin	1						
Clazakizumab	1	1	1	1			
Clevudine	1					1	
Colchicine + rosuvastatin	1	1	1			1	
Corticosteroids (nasal)	1						
Crizanlizumab	1	1	1	1		1	
Curcumin + Piperine	1			1		1	
Curcumin + Quercetin + Vitamin D	1						
Danunavir Cobicistat	1						
Dapagliflozin	1	1		1		1	
Deganirix	1	1	1			1	
DFV890	1	1	1	1		1	
Dimethyl sulfoxide (DSMO)	1				1		
Domase alfa (inh)	1			1		1	
Doubase C	1						
Dupilumab	1	1					
Edaravone	1	1	1				
Endothelial dysfunction protocol	1	1	1			1	
Etesunam	1			1			
Enoxaparin	1	1				1	
Ensovibep	1	1		1		1	
Enzalutamide	1	1	1			1	
Ethanol (inhaled)	1	1		1		1	



Intervention	Overall number of studies including the intervention, n=737	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Febuxostat	1						1
Fenofibrate	1	1	1			1	1
Fenretinide	1	1					
Fostamatinib	1	1		1		1	
Gabapentin +/- Montelukast	1			1		1	
GB0139 (inhaled)	1	1				1	
Gimsilumab (Anti-GM-CSF Monoclonal Antibody)	4	1		1		1	
Helium (inhaled)	1						
Hemadsorption	1	1		1		1	
Hesperidin	1	1	1	1		1	1
Hypertonic saline (inhaled)	1	1					
IgVSF-v13	1	1		1		1	
Ibrutinib	1	1	1			1	
Icosapent ethyl	1			1			
IFN-alpha2b + IFN-gamma	1						
Imatinib	1	1	1			1	
Indomethacin	1	1	1			1	
Infliximab	1	1		1		1	
INM005 (equine antibodies)	1	1	1	1		1	
Interferon beta-1a (inhaled)	1	1	1	1		1	
Interferon gamma	1						
Interferon kappa + TFF2	1	1				1	
Interferon-2	1	1		1		1	
Iodthymol	1	1					
Itolizumab	1	1	1			1	
Ivermectin (inhaled)	1			1			
Ixekizumab	1	1		1		1	
KB109	1	1		1		1	
L-arginine	1	1				1	
Lactococcus Lactis (intranasal)	1			1		1	
Lenzilumab	1	1	1			1	
Leylimab	1	1	1	1		1	
Lincomycin	1						
Lithium	1	1				1	
Mavrilimumab	1	1	1	1		1	
Mefenamic acid	1	1				1	1
Metoprolol	1						
Methylene blue	1	1					
Metoprolol	1	1					
Metronidazole	1			1			
Montelukast	1	1					
Nigadolimab	1					1	
Mycobacterium w	1	1					
Nafamostat mesylate	1	1				1	
Namilumab	1	1		1		1	
Nano-curcumin	1					1	
Neem (Azadirachta Indica A. Juss)	1				1		
Nicotine patches	1	1				1	
Nimotuzumab-nimotuz	2	1				1	1
Norelgestromin and Ethinylestradiol	1						
Novaferon	1						
NSAIDS	1	1		1		1	
Nutritional support	1	1	1				
OP-101	1	1	1			1	
Otilimab	1	1				1	
Palmitoylethanolamide	1						
Pembrolizumab	1	1	1	1		1	
Pirfenidone	1	1	1	1		1	
Pitidapsin	1	1	1			1	
PN8001 (CCK-A antagonist)	1	1		1			
Polymerized type I collagen (PTC)	1						1
Potassium Canrenoate	1	1				1	
Povidone iodine	1	1				1	1
Progesterone	1	1	1			1	
Proteclin-M	1	1	1			1	
Propolis	1	1	1	1			
Prostacyclin	1	1				1	
Prostacyclin (inhaled)	1	1					

Intervention	Overall number of studies including the intervention: n=787	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Pyridostigmine	1	1	1	1		1	
Ralstonia	1	1				1	
Ramipril	1	1			1		
RO-X19 (light therapy)	1			1			
Recombinant Super-Compound IFN	1	1		1			
Remdesivir (inhaled)	1						1
Reparixin	1	1	1			1	
Ribavirin	1						
Ribavirin + interferon beta-1b	1						
rhG-CSF	1	1		1		1	
rhG-CSF (inhaled)	1	1	1	1		1	
rhu-pGSN	1	1	1			1	
Salbutamol	1	1				1	
Secukinumab	1	1	1			1	
Somcaspc	1	1					
Sertindx	1					1	1
Short-wave diathermy	1	1		1		1	
Sildenafil	1	1	1			1	
Silymarin	1			1		1	
Siltuximab	1	1	1	1			
Sirolgopin	1	1	1				
Sprvan	NEW	1					
Stem cell nebulization	1	1		1		1	
Subdexide	1	1	1			1	1
Tahnoquine	1			1		1	1
TD-0903 (inhaled JAK inhibitor)	1	1				1	
ThymoQuinone	1					1	
Tranilast	1	1		1			
Trazodone	1	1		1		1	
TXA-127	1	1	1				
Ultraviolet light phototherapy	1	1				1	
Verapamil	1	1	1			1	
Vildagliptin calcium	1	1	1	1		1	
Vitamin E	1						
WV115 (oral remdesivir)	NEW					1	
XAV-19 (swine polyclonal antibodies)	1	1				1	
Zafirlukast	1	1					
Zilucoplan	1	1				1	
α-Lipoic acid	1	1					

(*) Based on low risk of bias subgroup of studies; (†) Major bleeding or clinically important bleeding; (**) Observed results apply mostly to hospitalized patients with moderate to critical disease. The COLCORONA trial that included patients with recent onset mild disease showed a tendency to less hospitalizations, less mortality and less mechanical ventilation requirements. However the certainty on those potential benefits was low because of very serious imprecision as the number of events was low; (##) Subgroup of seronegative patients; (@) High dose schemes (i.e. dexamethasone 12 mg a day) are probably not more effective than standard dose schemes (i.e dexamethasone 6 mg a day); (@@) Excluding high risk of bias studies; (§) Observed effects would probably be considered important in patients with very high hospitalization risk (>10%); (**) Effect vs. SOC assumed from indirect comparison.

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No significant effect		
Harmful effect		
Uncertain effect		
No evidence or no estimable effect		

Table 2. List of non-RCTs of interventions for COVID-19 with primary outcome measures and certainty (n=7). (interactive online version)

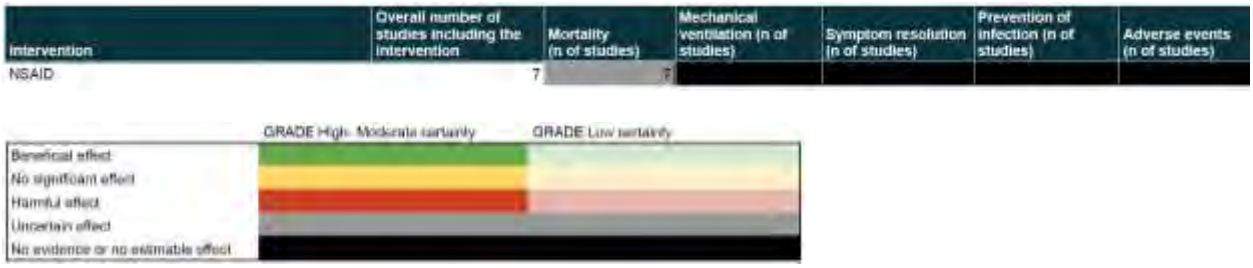


Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=243), as at 30 January 2023

	Intervention	Summary of findings
1	**99mTc-MDP**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Adalimumab**	Uncertainty in potential benefits and harms. Further research is needed.
3	**ACEIs or ARBs**	Continuing or initiating ACEIs or ARBs in patients with COVID-19 may increase mortality. However, the certainty of the evidence was low. Further research is needed.
4	**Alpha-1 antitrypsin**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Amiodarone**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Ammonium chloride**	Uncertainty in potential benefits and harms. Further research is needed.
7	**AMP5A (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Anakinra**	Anakinra may not reduce mortality or increase severe adverse events. However, the certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

	Intervention	Summary of findings
9	**Anticoagulants**	There are specific recommendations on the use of antithrombotic agents for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) probably does not decrease mortality in comparison with prophylactic dose (i.e., enoxaparin 40 mg a day). Anticoagulants in full dose decrease venous thromboembolic events but increase major bleeding in comparison with prophylactic dose. In mild ambulatory patients, anticoagulants in prophylactic dose, may not importantly improve time to symptom resolution or reduce hospitalizations.
10	**APMV2020 (aspirin, promethazine, micronutrients)**	Uncertainty in potential benefits and harms. Further research is needed.
11	**Aprepitant**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Aprotinin**	Uncertainty in potential benefits and harms. Further research is needed.
13	**Arbidol**	Uncertainty in potential benefits and harms. Further research is needed.
14	**ArtemiC (artemisinina, curcumina, frankincense, and vitamin C):**	Uncertainty in potential benefits and harms. Further research is needed.
15	**Artemisinin**	Uncertainty in potential benefits and harms. Further research is needed.
16	**Aspirin**	Aspirin probably does not reduce mortality, or mechanical ventilation and probably does not increase symptom resolution or improvement.
17	**Atazanavir/ritonavir**	Uncertainty in potential benefits and harms. Further research is needed.
18	**Atovaquone**	Uncertainty in potential benefits and harms. Further research is needed.
19	**Auxora**	Auxora may not increase severe adverse events. The effects of auxora on other important outcomes are uncertain. Further research is needed.

	Intervention	Summary of findings
20	**Avdoralimab**	Uncertainty in potential benefits and harms. Further research is needed.
21	**Aviptadil**	Uncertainty in potential benefits and harms. Further research is needed.
22	**Ayush-64**	Uncertainty in potential benefits and harms. Further research is needed.
23	**AZD1656**	AZD1656 may improve time to symptom resolution. The effects of AZD 1656 on other important outcomes are uncertain. Further research is needed.
24	**Azelastine**	Uncertainty in potential benefits and harms. Further research is needed.
25	**Azithromycin**	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
26	**Azvudine**	Uncertainty in potential benefits and harms. Further research is needed.
27	**Baricitinib**	In patients with moderate to critical disease, baricitinib reduces mortality, probably reduces mechanical ventilation requirements, and probably improves time to symptom resolution, without increasing severe adverse events.
28	**Baloxavir**	Uncertainty in potential benefits and harms. Further research is needed.
29	**Bamlanivimab +/- etesevimab (monoclonal antibody)**	Bamlanivimab probably reduces hospitalizations in patients with COVID-19 and it probably reduces symptomatic infections in exposed individuals. It is uncertain if it affects mortality or mechanical ventilation requirements. Further research is needed.
30	**BCG**	Uncertainty in potential benefits and harms. Further research is needed.
31	**Bebtelovimab**	Uncertainty in potential benefits and harms. Further research is needed.
32	**Beta-glucans**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
33	**Bicarbonate (inhaled)**	Inhaled bicarbonate may reduce mortality and may not reduce hospitalizations. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.
34	**Bioven**	Uncertainty in potential benefits and harms. Further research is needed.
35	**Boswellia extract**	Uncertainty in potential benefits and harms. Further research is needed.
36	**Bromhexine hydrochloride**	Bromhexine may reduce symptomatic infections in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed.
37	**Calcitriol**	Uncertainty in potential benefits and harms. Further research is needed.
38	**Camostat mesilate**	Camostat mesilate may not improve time to symptom resolution. Further research is needed.
39	**Canakinumab**	Uncertainty in potential benefits and harms. Further research is needed.
40	**Cannabidiol**	Uncertainty in potential benefits and harms. Further research is needed.
41	**CD24Fc (soluble CD24 appended to heavy chains 2 and 3 of human immunoglobulin G1)**	CD24Fc may reduce mechanical ventilation and increase symptom resolution or improvement. However, certainty of the evidence was low for imprecision. Further research is needed.
42	**CERC-002**	Uncertainty in potential benefits and harms. Further research is needed.
43	**Chloroquine nasal drops**	Uncertainty in potential benefits and harms. Further research is needed.
44	**Chlorpheniramine (nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
45	**CIGB-325**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
46	**Clarithromycin**	Uncertainty in potential benefits and harms. Further research is needed.
47	**Clazakizumab**	Clazakizumab may reduce mechanical ventilation and improve time to symptoms resolution. However, certainty of the evidence was low. Further research is needed.
48	**Clevudine**	Uncertainty in potential benefits and harms. Further research is needed.
49	**Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)**	Uncertainty in potential benefits and harms. Further research is needed.
50	**Colchicine**	Colchicine probably does not reduce mortality, mechanical ventilation requirements or increase symptom resolution or improvement with moderate certainty. In patients with mild recent onset COVID-19 colchicine probably does not have an important effect on hospitalizations. However, the certainty of the evidence was low because of imprecision.
51	**Colchicine + rosuvastatin**	Uncertainty in potential benefits and harms. Further research is needed.
52	**Convalescent plasma**	Convalescent plasma does not reduce mortality or reduces mechanical ventilation requirements or improves time to symptom resolution with moderate to high certainty of the evidence. In patients with recent onset mild COVID-19 convalescent plasma probably does not have an important effect on hospitalizations. Convalescent plasma may not increase severe adverse events.
53	**Crizanlizumab**	Uncertainty in potential benefits and harms. Further research is needed.
54	**Curcumin + piperine**	Uncertainty in potential benefits and harms. Further research is needed.
55	**Curcumin + quercetin + vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
56	**Dapagliflozin**	Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.

	Intervention	Summary of findings
57	**Darunavir-cobicistat**	Uncertainty in potential benefits and harms. Further research is needed.
58	**Degarelix**	Uncertainty in potential benefits and harms. Further research is needed.
59	**DFV890**	DFV890 may improve time to symptom resolution. The effects of DFV890 on other important outcomes are uncertain. Further research is needed.
60	**Dimethyl sulfoxide (DSMO)**	Uncertainty in potential benefits and harms. Further research is needed.
61	**Dornase alfa (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
62	**Doubase C**	Uncertainty in potential benefits and harms. Further research is needed.
63	**Doxycycline**	Doxycycline does not increase symptom resolution or improvement and may not reduce hospitalizations.
64	**Dutasteride**	Uncertainty in potential benefits and harms. Further research is needed**.**
65	**Dupilumab**	Uncertainty in potential benefits and harms. Further research is needed**.**
66	**Edaravone**	Uncertainty in potential benefits and harms. Further research is needed**.**
67	**Electrolyzed saline**	Uncertainty in potential benefits and harms. Further research is needed.
68	**Endothelial dysfunction protocol**	Uncertainty in potential benefits and harms. Further research is needed.
69	**Enisamium**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
70	**Ensovibep**	Uncertainty in potential benefits and harms. Further research is needed.
71	**Ensitrelvir**	Uncertainty in potential benefits and harms. Further research is needed.
72	**Enzalutamide**	Uncertainty in potential benefits and harms. Further research is needed.
73	**Ethanol (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
74	**Famotidine**	Uncertainty in potential benefits and harms. Further research is needed.
75	**Favipiravir**	Favipiravir may increase mortality and mechanical ventilation requirements; it may not reduce hospitalizations and it does not improve symptom resolution. Further research is needed.
76	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
77	**Fenofibrate**	Fenofibrate may not increase severe adverse events. The effects of fenofibrate on other important outcomes are uncertain. Further research is needed.
78	**Finasteride**	Uncertainty in potential benefits and harms. Further research is needed.
79	**Fluvoxamine**	In patients with recent onset mild COVID-19 fluvoxamine probably does not have an important effect on hospitalizations, does not increase symptom resolution and may not increase severe adverse events. Certainty of the evidence was low to high. Further research is needed.
80	**Fostamatinib**	Uncertainty in potential benefits and harms. Further research is needed.
81	**Gabapentin +/- montelukast**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
82	**GB0139 (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
83	**Gimsilumab (anti-GM-CSF monoclonal antibody)**	Gimsilumab may not reduce mortality or increase symptom resolution. Further research is needed.
84	**Helium (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
85	**Hemadsorption**	Uncertainty in potential benefits and harms. Further research is needed.
86	**Hesperidin**	Hesperidin may not improve symptom resolution; however, the certainty of the evidence was low. Further research is needed.
87	**Hydroxychloroquine and chloroquine**	Hydroxychloroquine or chloroquine probably increases mortality, and probably does not reduce invasive mechanical ventilation or significantly improve time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19 it probably has no important effect on the risk of infection and in patients with mild, recent onset disease, and it may not have an important effect on hospitalizations. However, certainty of the evidence is low because of risk of bias and imprecision.
88	**Hyperbaric oxygen**	Uncertainty in potential benefits and harms. Further research is needed.
89	**Hyperimmune anti-COVID-19 intravenous immunoglobulin (C-IVIG)**	Uncertainty in potential benefits and harms. Further research is needed.
90	**Hypertonic saline (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
91	**hzVSF-v13**	Uncertainty in potential benefits and harms. Further research is needed.
92	**Ibrutinib**	Uncertainty in potential benefits and harms. Further research is needed.
93	**Icatibant**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
94	**Icosapent ethyl**	Uncertainty in potential benefits and harms. Further research is needed.
95	**Imatinib**	Imatinib may not increase severe adverse events. The effects of imatinib on other important outcomes are uncertain. Further research is needed.
96	**Indomethacin**	Uncertainty in potential benefits and harms. Further research is needed.
97	**Infliximab**	Uncertainty in potential benefits and harms. Further research is needed.
98	**INM005 (polyclonal fragments of equine antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
99	**Interferon alpha-2b and interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
100	**Interferon beta-1a**	IFN beta-1a probably does not reduce mortality, invasive mechanical ventilation requirements or improve symptom resolution. Further research is needed.
101	**Interferon beta-1a (inhaled)**	Inhaled interferon beta-1a may improve time to symptom resolution. Further research is needed.
102	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
103	**Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
104	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.
105	**Interleukin-2**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
106	**Iota-carrageenan**	Uncertainty in potential benefits and harms. Further research is needed.
107	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
108	**Ivermectin**	Although pooled estimates suggest significant benefits with ivermectin, included studies' methodological limitations and a small overall number of events result in very low certainty of the evidence. Based on the results reported by the RCTs classified as low risk of bias, ivermectin probably does not reduce mortality or improve time to symptom resolution. In patients with recent onset of the disease, ivermectin probably does not have an important effect on hospitalizations and may not increase severe adverse events. It is uncertain if it reduces symptomatic infections when used as prophylaxis.
109	**Ivermectin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
110	**IVIG (intravenous immunoglobulin)**	Uncertainty in potential benefits and harms. Further research is needed.
111	**Ixekizumab**	Uncertainty in potential benefits and harms. Further research is needed.
112	**KB109**	Uncertainty in potential benefits and harms. Further research is needed.
113	**L-arginine**	Uncertainty in potential benefits and harms. Further research is needed.
114	***Lactococcus lactis*** **(intranasal)**	Uncertainty in potential benefits and harms. Further research is needed.
115	**Lactoferrin**	Uncertainty in potential benefits and harms. Further research is needed.
116	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
117	**Lenzilumab**	Lenzilumab may reduce mechanical ventilation requirements and may not increase severe adverse events. The effects of lenzilumab on other important outcomes are uncertain. Further research is needed.

	Intervention	Summary of findings
118	**Levamisole**	Uncertainty in potential benefits and harms. Further research is needed.
119	**Levilimab**	Levilimab may improve time to symptom resolution; however, the certainty of the evidence was low. The effects of levilimab on other important outcomes are uncertain. Further research is needed.
120	**Linagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
121	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.
122	**Lithium**	Uncertainty in potential benefits and harms. Further research is needed.
123	**Lopinavir-ritonavir**	Lopinavir-ritonavir probably does not reduce mortality with moderate certainty. Lopinavir-ritonavir may not be associated with a significant increase in severe adverse events. However, the certainty is low because of risk of bias and imprecision.
124	**Low-dose radiation therapy**	Uncertainty in potential benefits and harms. Further research is needed.
125	**Mavrilimumab**	Uncertainty in potential benefits and harms. Further research is needed.
126	**Mefenamic acid**	Uncertainty in potential benefits and harms. Further research is needed.
127	**Melatonin**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
128	**Mesenchymal stem-cell transplantation**	Mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence is low. Further research is needed.
129	**Metformin**	Metformin may not reduce hospitalizations in patients with recent onset mild disease. However, certainty of the evidence is low because of imprecision. Further research is needed.
130	**Methylene blue**	Uncertainty in potential benefits and harms. Further research is needed.
131	**Metisoprinol**	Uncertainty in potential benefits and harms. Further research is needed.
132	**Metoprolol**	Uncertainty in potential benefits and harms. Further research is needed.
133	**Metronidazole**	Uncertainty in potential benefits and harms. Further research is needed.
134	**Molnupiravir**	Molnupiravir probably has no important effect on hospitalizations but probably improves time to symptom resolution in patients with recent onset mild to moderate disease, it may not increase severe adverse events.
135	**Montelukast**	Uncertainty in potential benefits and harms. Further research is needed.
136	**Mouthwash**	Mouthwash may improve time to symptom resolution. Uncertainty in potential benefits and harms on other outcomes. Further research is needed.
137	**Mupadolimab**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
138	**Mycobacterium w**	Uncertainty in potential benefits and harms. Further research is needed.
139	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.
140	**N-acetylcysteine (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
141	**Nafamostat mesylate**	Uncertainty in potential benefits and harms. Further research is needed.
142	**Namilumab**	Uncertainty in potential benefits and harms. Further research is needed.
143	**Nano-curcumin**	Uncertainty in potential benefits and harms. Further research is needed.
144	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
145	**Neem (*Azadirachta indica* A. Juss)**	Uncertainty in potential benefits and harms. Further research is needed.
146	**Niclosamide**	Uncertainty in potential benefits and harms. Further research is needed.
147	**Nicotine patches**	Uncertainty in potential benefits and harms. Further research is needed.
148	***Nigella sativa* +/- honey**	Uncertainty in potential benefits and harms. Further research is needed.
149	**Nirmatrelvir-ritonavir**	Nirmatrelvir-ritonavir probably reduces hospitalizations in patients with mild recent onset COVID-19 and risk factors for severity, and it probably does not increase severe adverse events.
150	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
151	**Nitric oxide**	Uncertainty in potential benefits and harms. Further research is needed.
152	**Non-steroidal anti-inflammatory drugs (NSAIDs)**	Current best evidence suggests no association between NSAIDs consumption and COVID-19 related mortality. However, the certainty of the evidence is very low because of the risk of bias. Further research is needed.
153	**Norelgestromin and ethinylestradiol**	Uncertainty in potential benefits and harms. Further research is needed.
154	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
155	**Nutritional support**	Uncertainty in potential benefits and harms. Further research is needed.
156	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed
157	**OP-101**	Uncertainty in potential benefits and harms. Further research is needed
158	**Opaganib**	Opaganib may not reduce mortality or mechanical ventilation, it may not increase severe adverse events but it may increase symptom resolution or improvement. Further research is needed.
159	**Otilimab**	Uncertainty in potential benefits and harms. Further research is needed
160	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
161	**P2Y12 inhibitors**	P2Y12 inhibitors may increase mortality, may not improve time to symptom resolution and may increase severe adverse events. However, certainty of the evidence was low because of imprecision. Further research is needed.

	Intervention	Summary of findings
162	**Palmitoylethanolamide**	Uncertainty in potential benefits and harms. Further research is needed.
163	**Peg-interferon alfa**	Uncertainty in potential benefits and harms. Further research is needed.
164	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
165	**Pembrolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
166	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.
167	**Pirfenidone**	Uncertainty in potential benefits and harms. Further research is needed.
168	**Plitidepsin**	Uncertainty in potential benefits and harms. Further research is needed.
169	**PNB001 (CCK-A antagonist)**	Uncertainty in potential benefits and harms. Further research is needed.
170	**Polymerized type I collagen (PT1C)**	Uncertainty in potential benefits and harms. Further research is needed.
171	**Potassium canrenoate**	Uncertainty in potential benefits and harms. Further research is needed.
172	**Povidone iodine (nasal spray)**	Uncertainty in potential benefits and harms. Further research is needed.
173	**Probiotics**	Uncertainty in potential benefits and harms. Further research is needed.
174	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
175	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed.
176	**Propolis**	Uncertainty in potential benefits and harms. Further research is needed.
177	**Prostacyclin**	Uncertainty in potential benefits and harms. Further research is needed.
178	**Prostacyclin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
179	**Proxalutamide**	Uncertainty in potential benefits and harms. Further research is needed.
180	**Pyridostigmine**	Uncertainty in potential benefits and harms. Further research is needed.
181	**Quercetin**	Uncertainty in potential benefits and harms. Further research is needed.
182	**Raloxifene**	Uncertainty in potential benefits and harms. Further research is needed.
183	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
184	**RD-X19 (light therapy)**	Uncertainty in potential benefits and harms. Further research is needed.
185	**Recombinant super-compound interferon**	Uncertainty in potential benefits and harms. Further research is needed.
186	**REGEN-COV (casirivimab and imdevimab)**	In seronegative patients with severe to critical disease, REGEN-COV probably reduces mortality and increases symptom resolution and improvement. In patients with recent onset mild disease, REGEN-COV probably reduces hospitalizations and time to symptom resolution without increasing severe adverse events, and in asymptomatic exposed individuals REGEN-COV reduces symptomatic infections.

	Intervention	Summary of findings
187	**Regdanvimab**	Regdanvimab may improve time to symptom resolution in mild to moderate patients. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.
188	**Remdesivir**	In hospitalized patients with moderate to critical disease, remdesivir probably reduces mortality and mechanical ventilation, and it may improve time to symptom resolution without increasing severe adverse events. In patients with recent onset mild COVID-19, it may reduce hospitalizations. However, the certainty is low because of risk of bias and imprecision.
189	**Remdesivir (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
190	**Reparixin**	Uncertainty in potential benefits and harms. Further research is needed.
191	**Resveratrol**	Uncertainty in potential benefits and harms. Further research is needed.
192	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.
193	**rhG-CSF (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
194	**rhu-pGSN**	Uncertainty in potential benefits and harms. Further research is needed.
195	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.
196	**Ribavirin + interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
197	**Ruxolitinib**	Ruxolitinib may reduce mortality; however, the certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
198	**Sabizabulin**	Uncertainty in potential benefits and harms. Further research is needed.
199	**Sarilumab**	Sarilumab may not reduce mortality nor mechanical ventilation requirements, and probably does not improve time to symptom resolution. Sarilumab probably does not increase severe adverse events.
200	**Secukinumab**	Uncertainty in potential benefits and harms. Further research is needed.
201	**Senicapoc**	Uncertainty in potential benefits and harms. Further research is needed.
202	**Sentinox**	Uncertainty in potential benefits and harms. Further research is needed.
203	**Short-wave diathermy**	Uncertainty in potential benefits and harms. Further research is needed.
204	**Sildenafil**	Uncertainty in potential benefits and harms. Further research is needed.
205	**Siltuximab**	Uncertainty in potential benefits and harms. Further research is needed.
206	**Silymarin**	Uncertainty in potential benefits and harms. Further research is needed.
207	**Sitagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
208	**Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir**	Sofosbuvir with or without daclatasvir or ledipasvir may increase mortality and not reduce mechanical ventilation requirements, and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.
209	**Sotrovimab**	Sotrovimab may probably reduce hospitalizations in patients with recent onset mild COVID-19.
210	**Spironolactone**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
211	**Spirulin**	Uncertainty in potential benefits and harms. Further research is needed.
212	**Statins**	Statins may reduce mortality; however, certainty of the evidence was low. Further research is needed.
213	**Stem-cell nebulization**	Uncertainty in potential benefits and harms. Further research is needed.
214	**Steroids (corticosteroids)**	Corticosteroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Corticosteroids may not significantly increase the risk of severe adverse events. Higher-dose schemes (i.e., dexamethasone 12 mg a day) are probably not more effective than standard dose schemes (i.e., dexamethasone 6 mg a day).
215	**Steroids (corticosteroids, inhaled)**	Inhaled corticosteroids may improve time to symptom resolution but probably does not have an important effect on hospitalizations. Its effects on other important outcomes are uncertain. Further research is needed.
216	**Steroids (corticosteroids, nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
217	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
218	**Tafenoquine**	Uncertainty in potential benefits and harms. Further research is needed.
219	**TD-0903 (inhaled JAK-inhibitor)**	Uncertainty in potential benefits and harms. Further research is needed.
220	**Tenofovir + emtricitabine**	Tenofovir + emtricitabine may not reduce mortality but may reduce mechanical ventilation. However, certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
221	**Thalidomide**	Uncertainty in potential benefits and harms. Further research is needed.
222	**Thymoquinone**	Uncertainty in potential benefits and harms. Further research is needed.
223	**Tissue-plasminogen activator (tPA)**	Uncertainty in potential benefits and harms. Further research is needed.
224	**Tixagevimab–cilgavimab**	Tixagevimab–cilgavimab probably reduces mortality, hospitalizations, and SARS-COV-2 infections in exposed individuals and may not increase severe adverse events.
225	**Tocilizumab**	Tocilizumab reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
226	**Tofacitinib**	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low. Further research is needed.
227	**Tranilast**	Uncertainty in potential benefits and harms. Further research is needed.
228	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.
229	**TXA-127**	Uncertainty in potential benefits and harms. Further research is needed.
230	**Ultraviolet light phototherapy**	Uncertainty in potential benefits and harms. Further research is needed.
231	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
232	**Verapamil**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
233	**Vidofludimus calcium**	Uncertainty in potential benefits and harms. Further research is needed.
234	**Vilobelimab**	Vilobelimab probably reduces mortality and probably does not increase severe adverse events.
235	**Vitamin B**	Uncertainty in potential benefits and harms. Further research is needed.
236	**Vitamin C**	Vitamin C may reduce mortality and increase symptom resolution or improvement. However, the certainty of the evidence was low. Further research is needed.
237	**Vitamin D**	Vitamin D does no reduce infections in exposed individuals and probably not reduce hospitalizations. Vitamin D effect on other important outcomes is uncertain. Further research is needed.
238	**vv116 (oral remdesivir)**	vv116 is as effective as nirmatrelvir/ritonavir in attaining symptom resolution. Its effects on other patient important outcomes are uncertain. Further research is needed.
239	**XAV-19 (swine glyco-humanized polyclonal antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
240	**Zafirlukast**	Uncertainty in potential benefits and harms. Further research is needed.
241	**Zilucoplan**	Uncertainty in potential benefits and harms. Further research is needed.
242	**Zinc**	Zinc may not improve symptom resolution. However, the certainty of the evidence was low because of imprecision. Its effects on other clinical important outcomes are uncertain. Further research is needed.
243	**α-lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to WHO International Clinical Trials Registry Platform (ICTRP), hundreds of potential interventions are being assessed in more than 10 000 clinical trials and observational studies. In this review, we identified and examined 243 therapeutic options.

• **Corticosteroids:** The body of evidence on corticosteroids, which includes 27 RCTs, shows that low- or moderate-dose treatment schemes (RECOVERY trial dose was 6 mg of oral or intravenous preparation once daily for 10 days) are probably effective in reducing mortality in patients with severe COVID-19 infection. These results remained robust after including studies in which patients with acute respiratory distress syndrome (ARDS) secondary to alternative etiologies (not COVID-19 related) were randomized to corticosteroids or placebo/no corticosteroids. Higher-dose schemes (i.e., dexamethasone 12 mg a day) are probably not more effective than standard dose schemes (i.e., dexamethasone 6 mg a day).

• **Remdesivir:** The results of 10 RCTs, including the final results of the SOLIDARITY trial, show that in hospitalized patients with moderate to critical disease, remdesivir probably reduces mortality and mechanical ventilation, and it may improve time to symptom resolution. Certainty of the evidence was moderate because of imprecision. In patients with recent onset mild COVID-19 remdesivir may reduce hospitalizations; however, the certainty of the evidence is low because of imprecision. Further research is needed.

• **vv116 (oral remdesivir):** The results of 1 RCT show that vv116 results as effective as nirmatrelvir/ritonavir in attaining symptom resolution. Its effects in other clinical important outcomes are uncertain. Further research is needed.

• **Hydroxychloroquine, lopinavir–ritonavir, and interferon beta-1a**: The body of evidence on hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a, including anticipated findings from the RECOVERY and SOLIDARITY trials, showed no benefit in terms of mortality reduction, invasive mechanical ventilation requirements or time to clinical improvement. Furthermore, the analysis showed probable mortality increment in those patients treated with hydroxychloroquine. Fourteen studies that assessed hydroxychloroquine in exposed individuals showed that probably it has no important effect in reducing infections with moderate certainty.

• **Antibiotics**: The body of evidence on azithromycin and doxycycline shows no significant benefits in patients with mild to moderate or severe to critical COVID-19.

• **Convalescent plasma:** The results of 58 RCTs assessing convalescent plasma in COVID-19, including the RECOVERY trial with 11,558 hospitalized patients, showed no mortality reduction, significant mechanical ventilation requirement reduction or time to symptom resolution improvement with moderate to high certainty of the evidence. In mild patients, convalescent plasma probably does not have an important effect on hospitalizations with moderate certainty. Convalescent plasma may not increase severe adverse events with low certainty. No significant differences were observed between patients treated early (< 4 days since symptom onset) or with more advanced disease in a subgroup analysis from the RECOVERY trial.

• **Tocilizumab:** The results of 28 RCTs assessing tocilizumab show that, in patients with severe or critical disease, tocilizumab reduces mortality and mechanical ventilation requirements without significantly increasing severe adverse events.

• **Clazakizumab:** The results of one RCT suggests that, in patients with severe or critical disease, clazakizumab may reduce mechanical ventilation requirements and improve time to symptom resolution. However, certainty of the evidence was low because of imprecision. Further research is needed.

• **Sarilumab:** The results of 11 RCTs assessing sarilumab show that, in patients with severe or critical disease, sarilumab may not reduce mortality nor mechanical ventilation requirements, and probably does not improve time to symptom resolution in patients with severe to critical disease. Sarilumab probably does not increase severe adverse events. However, certainty of the evidence was low and further research is needed to confirm these findings.

• **Anakinra:** The results of six RCTs assessing anakinra in hospitalized patients with non-severe disease, show inconsistent results on mortality and symptom resolution and suggest that anakinra may not reduce mortality or increase severe adverse events. Certainty of the evidence was low and further research is needed.

• **Tofacitinib:** The results of two RCTs assessing tofacitinib in hospitalized patients with moderate to severe disease, suggest possible increase in symptom resolution or improvement and possible increase in severe adverse events with tofacitinib. Certainty of the evidence was low and further research is needed.

• **Vilobelimab:** The results of two RCTs assessing vilobelimab show that, in patients with severe or critical disease, vilobelimab probably reduces mortality without significantly increasing severe adverse events.

• **Colchicine:** The results of 16 RCTs assessing colchicine, including the COLCORONA study that recruited 4,488 patients with recent COVID-19 diagnosis and risk factors for severity and the RECOVERY trial that recruited 11,340 hospitalized patients, show that colchicine probably does not reduce mortality, mechanical ventilation requirements, improve time to symptom resolution, or reduce hospitalizations. These findings are mainly driven by the RECOVERY study. The COLCORONA study that included outpatients with mild early COVID-19 suggest possible reduction in hospitalizations, mechanical ventilation requirements and mortality in this subgroup. However, certainty of the evidence was low because of very severe imprecision due to a small number of events.

• **Ivermectin:** Pooled estimates of 49 RCTs suggest mortality reduction with ivermectin, but the certainty of the evidence was very low because of methodological limitations and small number of events. Based on the results reported by the subgroup RCTs classified as low risk of bias, ivermectin probably does not reduce mortality or improve time to symptom resolution, and probably does not have an important effect on hospitalizations. Further research is needed to confirm these findings.

• **Favipiravir:** Twenty-nine RCTs assessed favipiravir vs SOC or other interventions. Their results suggest that favipiravir may increase mortality and mechanical ventilation requirements, it may not reduce hospitalizations and it does not improve symptom resolution. Further research is needed to confirm these findings.

• **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** Sixteen RCTs assessed sofosbuvir with or without daclatasvir, ledipasvir, or velpatasvir against standard of care or other interventions. Subgroup analysis showed significant differences between low risk of bias and high risk of bias studies. The results of the two studies classified as low risk of bias suggest that sofosbuvir alone or in combination may increase mortality and not reduce mechanical ventilation requirements, and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

• **Tenofovir + emtricitabine:** Five RCTs assessed tenofovir + emtricitabine against standard of care or other interventions. Their results suggest that tenofovir + emtricitabine may not reduce mortality and may decrease mechanical ventilation requirements. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed to confirm these findings.

• **Baricitinib:** The results of seven RCTs show that, in patients with moderate to critical disease, baricitinib reduces mortality, probably reduces mechanical ventilation requirements, and probably improves time to symptom resolution, without increasing severe adverse events.

• **Ruxolitinib:** The results of three RCTs show that, in patients with moderate to critical disease, ruxolitinib may reduce mortality. However, the certainty of the evidence was low because of imprecision and inconsistency. Further research is needed.

• **CD24Fc (soluble CD24 appended to heavy chains 2 and 3 of human immunoglobulin G1):** The results of one RCT shows that in patients with severe disease, CD24Fc may reduce mechanical ventilation and increase symptom resolution. However, the certainty of the evidence was low because of imprecision. Further research is needed.

• **REGEN-COV (casirivimab and imdevimab):** The results of 12 RCTs suggest that, in patients with severe to critical disease, overall REGEN-COV may reduce mortality and mechanical ventilation, or increase symptom resolution or improvement. However, the certainty of the evidence was low. A subgroup analysis suggests a differential effect on seronegative patients in which REGEN-COV probably reduces mortality and mechanical ventilation requirements and increases symptom resolution or improvement. In patients with recent onset mild COVID-19, REGEN-COV probably reduces hospitalizations and improves time to symptom resolution without increasing severe adverse events, and in exposed asymptomatic individuals REGEN-COV reduces symptomatic infections. One study that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab in non-severe patients with risk factors for severity, reported no important differences in hospitalizations.

• **Bamlinivimab +/- etesevimab:** The results of six RCTs suggest that bamlinivimab probably decreases hospitalizations in patients with COVID-19 and probably decreases symptomatic infection in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed. One study that compared bamlanivimab +/- etesevimab against REGEN-COV (casirivimab and imdevimab) in non-severe patients with risk factors for severity, reported no important differences in hospitalizations.

• **Sotrovimab:** The results of two RCTs show that, in patients with recent onset mild COVID-19, sotrovimab probably reduces hospitalizations and improves time to symptom resolution without increasing severe adverse events. The certainty of the evidence was moderate because of imprecision but with evidence of equipoise between sotrovimab and REGEN-COV.

• **Regdanvimab:** The results of two RCTs show that, in patients with mild to moderate disease, regdanvimab may improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision. Its effects on other important outcomes are uncertain. Further research is needed to confirm or discard these findings.

• **Tixagevimab–cilgavimab:** The results of three RCTs show that, in individuals with COVID-19, tixagevimab–cilgavimab probably reduces mortality and hospitalizations, and in those exposed to SARS-COV-2 tixagevimab–cilgavimab probably reduces symptomatic infections without increasing severe adverse events.

• **Proxalutamide:** The results of four RCTs suggest that proxalutamide may result in important benefits. However, the certainty of the evidence was very low because of very serious risk of bias, imprecision, and indirectness. Further research is needed to confirm or discard these findings.

• **Dapagliflozin:** The results of one RCT suggests that, in patients with cardiometabolic risk factors hospitalized with moderate COVID-19, dapagliflozin may reduce mortality, but probably does not increase symptom resolution. However, the certainty of the evidence was low because of imprecision. Further research is needed to confirm or discard these findings.

• **Mesenchymal stem-cell transplantation:** The results of ten RCTs show that, in patients with severe to critical, mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence was low because of imprecision. Further research is needed to confirm or discard these findings.

• **Inhaled corticosteroids:** The results of nine RCTs show that inhaled corticosteroids may improve time to symptom resolution but probably does not have an important effect on hospitalizations. Its effects on other relevant outcomes are uncertain. Further research is needed.

• **Fluvoxamine:** The results of five RCTs show that in patients with mild disease, fluvoxamine probably does not have an important effect on hospitalizations, does not increase symptom resolution and may not increase adverse events. The certainty of the evidence was high to low because of imprecision. Further research is needed.

• **Lenzilumab:** The results of one RCT suggests that lenzilumab may reduce invasive mechanical ventilation requirements in severe patients without increasing severe adverse events. However, the certainty of the evidence was low because of imprecision. Further research is needed.

• **INM005 (polyclonal fragments of equine antibodies):** Currently, there is very low certainty about the effects of INM005 on clinically important outcomes.

• **Famotidine:** Currently, there is very low certainty about the effects of famotidine on clinically important outcomes.

• **Anticoagulants:** Thromboembolic complications in patients infected with COVID-19 are relatively frequent. As for hospitalized patients with severe medical conditions current guidelines recommend thromboprophylactic measures to be adopted for inpatients with COVID-19 infection. Regarding the best thromboprophylactic scheme the results of 22 RCTs that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day) showed no differences in mortality with moderate certainty (imprecision). In mild ambulatory patients four RCTs suggest that rivaroxaban or enoxaparin in prophylactic dose may not importantly improve time to symptom resolution or reduce hospitalizations.

• **Aspirin:** Results of five RCTs inform that aspirin probably does not reduce mortality or mechanical ventilation and probably does not increase symptom resolution or improvement.

• **P2Y12 inhibitors:** The results of two RCTs suggest that P2Y12 in combination with anticoagulants in prophylactic or full dose may not reduce mortality, may not improve time to symptom resolution, and may increase severe adverse events. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

• **NSAIDs:** No association between NSAIDs exposure and increased mortality was observed. However, certainty of the evidence is very low and further research is needed to confirm these findings.

• **ACEIs or ARBs:** The results of eight low-risk of bias RCTs suggest that initiating or continuing ACEIs or ARBs in patients with COVID-19 may increase mortality. However, certainty of the evidence is low because of imprecision and further research is needed to confirm these findings.

• **Molnupiravir:** The results of 11 RCTs show that molnupiravir probably has no important effect on hospitalizations but it probably increases symptom resolution. Molnupiravir may not increase severe adverse events.

• **Nirmatrelvir-ritonavir:** The results of one RCT shows that nirmatrelvir-ritonavir probably reduces hospitalizations in patients with recent onset mild to moderate disease, and probably does not increase severe adverse events.

• **Vitamin D:** The results of 20 RCTs show that vitamin D does not reduce symptomatic infections and probably does not reduce hospitalizations. Vitamin D effects on other important outcomes are uncertain. Further research is needed.

• **Vitamin C:** The results of ten RCTs suggest that vitamin C may reduce mortality and increase symptom resolution or improvement. However, the certainty of the evidence was low. Further research is needed.

• **Probiotics:** The results of four RCTs suggest that probiotics may improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

• **Mouthwash:** The results of 14 RCTs suggest that mouthwashes may improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

• **Camostat mesilate:** The results of five RCTs suggest that camostat mesilate may not improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and indirectness, furthermore the effects on other important outcomes are uncertain. Further research is needed.

• **Opaganib:** The results of two RCTs suggest that opaganib may not reduce mortality or mechanical ventilation, it may not increase severe adverse events but it may increase symptom resolution or improvement. However, certainty of the evidence was low because of imprecision. Further research is needed.

Changes since previous edition

• **Corticosteroids:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Icatibant:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **N-acetylcysteine (inhaled):** New evidence included without significant changes.

• **Hyperbaric oxygen:** New evidence included without significant changes.

• **Hydroxychloroquine:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Bromhexine:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **vv116 (oral remdesivir):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Spirulin:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Fluvoxamine:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Anticoagulants:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Aspirin:** New evidence included without significant changes.

• **Mesenchymal stem-cell transplantation:** New evidence included without significant changes.

• **L-arginine:** New evidence included without significant changes.

Concluding remarks

• The Pan American Health Organization (PAHO) is continually monitoring ongoing research on any possible therapeutic options. As evidence emerges, then PAHO will immediately assess and update its position, particularly as it applies to any special subgroup populations such as children, expectant mothers, and those with immune conditions.

• PAHO is also mindful of the emerging differential impact of COVID-19 on ethnic and minority groups and is continuously seeking data that could help in mitigating excess risk of severe illness or death in minority subgroups. These groups are plagued by social and structural inequities that bring to bear a disproportionate burden of COVID-19 illness.

• The safety of the patient suffering from COVID-19 is a key priority to improve the quality of care in the provision of health services.

• Adequately designed and reported clinical trials are crucial for the practice of evidence-based medicine. Most of the research to date on COVID-19 has very poor methodology that is hidden and very difficult to validate. Greater transparency and better designed studies are urgently needed.

Hallazgos clave

Opciones terapéuticas: Según el portal de búsqueda de la Plataforma de Registros Internacionales de Ensayos Clínicos de la Organización Mundial de la Salud, se están investigando cientos de posibles tratamientos o sus combinaciones en más de 10.000 ensayos clínicos y estudios observacionales. En esta revisión, se examinan 243 posibles opciones terapéuticas.

• **Corticosteroides:** El conjunto de evidencia sobre los corticoesteroides incluye 27 ensayos clínicos controlados aleatorizados (ECCA) y muestra que la administración de dosis bajas y moderadas (la dosis utilizada en el estudio RECOVERY fue de 6 mg diarios de dexametasona por vía oral o intravenosa durante 10 días) probablemente reduce la mortalidad en pacientes con infección grave por SARS-CoV-2. Los resultados se mantuvieron uniformes tras agregar al análisis estudios en los que pacientes con síndrome de dificultad respiratoria aguda de otras etiologías recibieron corticosteroides o manejo estándar de forma aleatoria. Esquemas con dosis más altas (por ejemplo, 12 mg de dexametasona por día) probablemente no resulten más efectivos que los esquemas habituales (por ejemplo, 6 mg de dexametasona por día).

• **Remdesivir:** Los resultados de 10 ECCA, incluidos los resultados finales del ensayo Solidaridad, muestran que en pacientes hospitalizados con enfermedad de moderada a critica, el remdesivir probablemente reduzca la mortalidad y la necesidad de ventilación mecánica invasiva, y podría mejorar el tiempo de resolución de los síntomas. La certeza de la evidencia es moderada por imprecisión. En pacientes con enfermedad leve de comienzo reciente, el remdesivir podría reducir las hospitalizaciones, pero la certeza de la evidencia es baja por imprecisión. Se necesita más información.

• **vv116 (remdesivir oral):** Los resultados de un ECA muestran que el vv116 tiene una eficacia similar al tratamiento con nirmatrelvir y ritonavir respecto al tiempo de resolución

de los síntomas. Los efectos sobre otros desenlaces clínicos importantes son inciertos. Se necesita más información.

• **Hidroxicloroquina, interferón beta 1-a y lopinavir con ritonavir:** El conjunto de evidencia sobre la hidroxicloroquina, el interferón beta 1-a y el lopinavir con ritonavir, incluidos los resultados preliminares de los estudios RECOVERY y Solidaridad, no muestra beneficios en la reducción de la mortalidad, la necesidad de ventilación mecánica invasiva o el plazo necesario para la mejoría clínica. La evidencia sobre la hidroxicloroquina incluso sugiere que su utilización probablemente genere un incremento en la mortalidad. Catorce estudios que evaluaron la hidroxicloroquina en personas expuestas a la COVID-19 indican que probablemente no tenga un efecto importante en la reducción de las infecciones con certeza moderada.

• **Antibióticos:** El conjunto de evidencia identificado sobre la azitromicina y la doxiciclina no muestra beneficios significativos en pacientes con COVID-19 de leve a moderada o de grave a crítica.

• **Plasma de convalecientes:** Los resultados de 58 ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19, incluido el estudio RECOVERY que incorpora 11.558 pacientes, no mostraron reducción de la mortalidad, disminución de la necesidad de ventilación mecánica invasiva ni mejoría en el tiempo de resolución de los síntomas con certeza de moderada a alta. En pacientes con síntomas leves, el plasma de convalecientes probablemente no produzca ningún efecto importante sobre las hospitalizaciones con certeza moderada. El plasma de convalecientes podría no aumentar los eventos adversos graves con certeza baja. En un análisis de subgrupo del estudio RECOVERY, no se observó ningún efecto diferencial entre los pacientes tratados con rapidez (menos de 4 días desde el inicio de los síntomas) y los que presentaban enfermedad más avanzada al iniciar dicho tratamiento.

• **Tocilizumab:** Los resultados de 28 ECCA muestran que el tocilizumab reduce la mortalidad y la necesidad de ventilación invasiva sin un incremento importante de los efectos adversos graves en pacientes con enfermedad grave o crítica.

• **Clazakizumab:** Los resultados de un ECCA sugieren que el clazakizumab podría reducir la necesidad de ventilación mecánica invasiva y mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

• **Sarilumab:** Los resultados de 11 ECCA muestran que el sarilumab podría no reducir la mortalidad ni la necesidad de ventilación mecánica y probablemente no mejore el tiempo de resolución de los síntomas en pacientes con enfermedad grave o crítica. El sarilumab probablemente no aumente los eventos adversos graves. Sin embargo, la certeza de la evidencia es baja y se necesita más información para confirmar estas conclusiones.

• **Anakinra:** Los resultados de seis ECCA que evaluaron la anakinra en pacientes hospitalizados con enfermedad no grave muestran resultados incongruentes en la mortalidad y la resolución de los síntomas y sugieren que podría no reducir la mortalidad ni aumentar los eventos adversos graves. La certeza de la evidencia es baja y se necesita más información.

• **Tofacitinib:** Los resultados dos ECCA que evaluaron el tofacitinib en pacientes hospitalizados con enfermedad de moderada a grave indican una posible mejora de la resolución de los síntomas, aunque con un posible aumento de los eventos adversos graves. La certeza de la evidencia es baja y se necesita más información.

• **Vilobelimab:** Los resultados de dos ECCA muestran que el vilobelimab probablemente reduzca la mortalidad sin un incremento importante de los efectos adversos graves en pacientes con enfermedad grave o crítica.

• **Colchicina:** Los resultados de 16 ECCA —entre los que se encuentra el estudio COLCORONA, que incluyó 4488 pacientes con diagnóstico reciente de COVID-19 y factores de riesgo para enfermedad grave, y el estudio RECOVERY, que incorpora 11.340 pacientes hospitalizados— muestran que la colchicina probablemente no reduzca la mortalidad o la necesidad de ventilación mecánica, no mejore la velocidad de resolución de los síntomas ni reduzca las hospitalizaciones. Estos resultados se sustentan fundamentalmente en el estudio RECOVERY. El estudio COLCORONA, que incluyó pacientes ambulatorios con enfermedad leve, apunta una posible reducción de las hospitalizaciones, de la necesidad de ventilación mecánica y de la mortalidad en este subgrupo. Sin embargo, la certeza de la evidencia es baja por imprecisión muy grave, ya que el número de eventos fue reducido.

• **Ivermectina:** Los resultados combinados de 49 ECCA indican una reducción de la mortalidad con la ivermectina. Sin embargo, la certeza de la evidencia es muy baja por limitaciones metodológicas y un número de eventos reducido. Con base en la información facilitada por los estudios con riesgo bajo de sesgo, la ivermectina probablemente no reduzca la mortalidad ni se asocie a una mejoría en el tiempo de resolución de los síntomas, ni tampoco tenga un efecto importante sobre las hospitalizaciones. Se necesita más información para confirmar estas conclusiones.

• **Favipiravir:** Veintinueve ECCA evaluaron el favipiravir en comparación con la prestación de cuidados estándares u otras intervenciones. Los resultados sugieren que el favipiravir podría aumentar la mortalidad y la necesidad de ventilación mecánica invasiva, podría no reducir las hospitalizaciones y no mejora la resolución de los síntomas. Se necesita más información para confirmar estas conclusiones.

• **Sofosbuvir con o sin daclatasvir, ledipasvir, velpatasvir o ravidasvir:** Dieciséis ECCA evaluaron el sofosbuvir solo o en combinación con daclatasvir, ledipasvir o velpatasvir en comparación con la prestación de cuidados estándares u otras intervenciones. Los resultados de los estudios con un riesgo alto de sesgo y de los

estudios con un riesgo bajo de sesgo fueron sustancialmente diferentes. Los resultados de los dos estudios clasificados con riesgo bajo de sesgo sugieren que el sofosbuvir solo o en combinación podría aumentar la mortalidad y no reducir la necesidad de ventilación mecánica invasiva, y probablemente no mejore el tiempo de resolución de los síntomas. Se necesita más información para confirmar estas conclusiones.

• **Tenofovir y emtricitabina:** Cinco ECCA evaluaron el tenofovir y la emtricitabina en comparación con la prestación de cuidados estándares u otras intervenciones. Los resultados sugieren que podrían no reducir la mortalidad, pero probablemente reduzcan la necesidad de ventilación mecánica invasiva. Sin embargo, la certeza de la evidencia es baja por imprecisión y riesgo de sesgo. Se necesita más información para confirmar estas conclusiones.

• **Baricitinib:** Los resultados de siete ECCA muestran que, en pacientes con enfermedad de moderada a crítica, el baricitinib reduce la mortalidad, y probablemente reduzca la necesidad de ventilación mecánica invasiva y mejore el tiempo de resolución de síntomas sin aumentar los eventos adversos graves.

• **Ruxolitinib:** Los resultados de tres ECCA sugieren que, en pacientes con enfermedad de moderada a grave, el ruxolitinib podría reducir la mortalidad. Sin embargo, la certeza de la evidencia es baja por falta de congruencia e imprecisión. Se necesita más información.

• **CD24Fc (cadenas pesadas 2 y 3 de inmunoglobulina humana G1 anexadas a CD24):** Los resultados de un ECCA muestran que, en pacientes con enfermedad grave, el CD24Fc podría reducir la necesidad de ventilación mecánica invasiva y mejorar la resolución de síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

• **REGEN-COV (casirivimab e imdevimab):** Los resultados de 12 ECCA muestran que, en pacientes con enfermedad grave o crítica, el REGEN-COV podría reducir la

mortalidad y la necesidad de ventilación mecánica invasiva y mejorar la velocidad de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja. Un análisis de subgrupo mostró un efecto diferencial en pacientes con anticuerpos negativos. En este subgrupo, el REGEN-COV probablemente reduzca la mortalidad y la necesidad de ventilación mecánica e incremente la resolución de los síntomas. En pacientes con enfermedad leve de comienzo reciente, el REGEN-COV probablemente reduzca las hospitalizaciones y mejore el tiempo de resolución de los síntomas sin aumentar el riesgo de eventos adversos graves; y en personas asintomáticas, expuestas al SARS-CoV-2, el REGEN-COV reduce las infecciones sintomáticas. Un estudio que comparó el REGEN-COV (casirivimab e imdevimab) con el bamlanivimab con o sin etesevimab en pacientes con síntomas leves y factores de riesgo para enfermedad grave notificó ausencia de diferencias importantes en las hospitalizaciones.

• **Bamlinivimab con o sin etesevimab:** Los resultados de seis ECCA indican que el bamlanivimab probablemente reduzca las hospitalizaciones en pacientes con COVID-19 y probablemente disminuya las infecciones sintomáticas en personas expuestas. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información. Un estudio que comparó el bamlanivimab con o sin etesevimab con el REGEN-COV (casirivimab e imdevimab) en pacientes con síntomas leves y factores de riesgo para enfermedad grave notificó ausencia de diferencias importantes en las hospitalizaciones.

• **Sotrovimab:** Los resultados de dos ECCA muestran que, en pacientes con enfermedad leve de comienzo reciente, el sotrovimab probablemente reduzca las hospitalizaciones y mejore el tiempo de resolución de los síntomas sin aumentar el riesgo de eventos adversos graves. La certeza de la evidencia es moderada por imprecisión, pero incluye hallazgos de eficacia similar entre el sotrovimab y el REGEN-COV.

• **Regdanvimab:** Los resultados de dos ECCA muestran que, en pacientes con enfermedad leve a moderada, el regdanivimab podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Sus

efectos sobre otros desenlaces importantes son inciertos. Se necesita más información para confirmar o descartar estas conclusiones.

• **Tixagevimab y cilgavimab:** Los resultados de tres ECCA muestran que el tixagevimab y el cilgavimab probablemente reduzcan la mortalidad, las hospitalizaciones y las infecciones sintomáticas en personas expuestas al SARS-CoV-2 y podrían no aumentar los eventos adversos graves.

• **Proxalutamida:** Los resultados de cuatro ECCA sugieren un efecto favorable asociado a la proxalutamida. Sin embargo, la certeza de la evidencia es muy baja por riesgo muy grave de sesgo, imprecisión e información indirecta. Se necesita más información para confirmar o descartar estas conclusiones.

• **Dapagliflozina:** Los resultados de un ECCA muestran que, en pacientes con factores de riesgo cardiometabólicos hospitalizados por COVID-19 moderada, la dapagliflozina podría reducir la mortalidad, pero probablemente no mejore la resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.

• **Trasplante de células madre mesenquimatosas:** Los resultados de diez ECCA apuntan que, en pacientes con enfermedad de grave a crítica, el trasplante de células madre mesenquimatosas podría reducir la mortalidad. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.

• **Corticosteroides inhalados:** Los resultados de nueve ECCA muestran que los corticosteroides inhalados podrían mejoran el tiempo de resolución de los síntomas, pero probablemente no afecten las hospitalizaciones de forma considerable. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Fluvoxamina:** Los resultados de cinco ECCA muestran que, en pacientes con enfermedad leve, la fluvoxamina probablemente no tenga un efecto importante sobre las hospitalizaciones ni aumente la resolución de los síntomas y podría no incrementar los eventos adversos. La certeza de la evidencia es de baja a alta por imprecisión. Se necesita más información.

• **Lenzilumab:** Los resultados de un ECCA sugieren que el lenzilumab podría reducir la necesidad de ventilación mecánica invasiva en pacientes graves sin aumentar los eventos adversos graves. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

• **INM005 (fragmentos policlonales de anticuerpos equinos):** Por el momento, la certeza de la evidencia sobre los efectos del INM005 en desenlaces clínicos importantes es muy baja.

• **Famotidina:** Por el momento, la certeza de la evidencia sobre los efectos de la famotidina en desenlaces clínicos importantes es muy baja.

• **Anticoagulantes:** Las complicaciones tromboembólicas en pacientes con COVID-19 son relativamente frecuentes. Al igual que en pacientes hospitalizados por afecciones médicas graves, las directrices vigentes indican que los pacientes hospitalizados por COVID-19 sean tratados con medidas tromboprofilácticas. En relación con el mejor esquema tromboprofiláctico, excluidos cuatro estudios clasificados con riesgo alto de sesgo, los resultados de 22 ECCA que compararon los anticoagulantes en dosis intermedias (p. ej., 1 mg/kg de enoxaparina por día) o dosis completas (p. ej., 1 mg/kg de enoxaparina cada 12 h por día) frente a dosis profilácticas (p. ej., 40 mg de enoxaparina por día) no mostraron diferencias en la mortalidad con certeza moderada (imprecisión). Los resultados de cuatro ECCA sugieren que, en pacientes ambulatorios con enfermedad leve, el rivaroxabán o la enoxaparina en dosis profilácticas podrían no

mejorar el tiempo de resolución de los síntomas de forma considerable ni reducir las hospitalizaciones.

• **Aspirina:** Los resultados de cinco ECCA informan que la aspirina probablemente no reduzca la mortalidad o la necesidad de ventilación mecánica ni mejore el tiempo de resolución de los síntomas.

• **Inhibidores P2Y12:** Los resultados de dos ECCA sugieren que el tratamiento con P2Y12 combinado con anticoagulantes en dosis profilácticas o completas podría no reducir la mortalidad ni mejorar el tiempo de resolución de los síntomas, y podría aumentar los eventos adversos graves. Sin embargo, la certeza de la evidencia es baja y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Antiinflamatorios no esteroideos (AINE):** Hasta el momento, el uso de los AINE no está asociado con un incremento de la mortalidad. Sin embargo, la certeza de la evidencia es muy baja, por lo que se necesita más información para confirmar estas conclusiones.

• **IECA y ARB:** Los resultados de ocho ECCA con riesgo bajo de sesgo sugieren que el inicio o continuación de los IECA y los ARB en pacientes con COVID-19 podría aumentar la mortalidad. Sin embargo, la certeza de la evidencia es baja, por lo que se necesita más información para confirmar estas conclusiones.

• **Molnupiravir:** Los resultados de 11 ECCA muestran que el tratamiento con molnupiravir probablemente no tenga un efecto importante en las hospitalizaciones pero probablemente mejore el tiempo de resolución de los síntomas. El molnupiravir podría no aumentar los eventos adversos graves.

• **Nirmatrelvir y ritonavir:** Los resultados de un ECCA muestran que el tratamiento con nirmatrelvir y ritonavir probablemente reduzca las hospitalizaciones en pacientes con

enfermedad de leve a moderada de comienzo reciente y probablemente no aumente los eventos adversos graves.

• **Vitamina D:** Los resultados de 20 ECCA muestran que el tratamiento con vitamina D no reduce las infecciones sintomáticas y probablemente no reduzca las hospitalizaciones. Los efectos de la vitamina D sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Vitamina C:** Los resultados de diez ECCA sugieren que el tratamiento con vitamina C podría reducir la mortalidad y mejorar la resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja. Se necesita más información.

• **Probióticos:** Los resultados de cuatro ECCA sugieren que el tratamiento con probióticos podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Enjuague bucal:** Los resultados de 14 ECCA sugieren que el tratamiento con enjuagues bucales podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Mesilato de camostat:** Los resultados de cinco ECCA sugieren que el tratamiento con mesilato de camostat podría no mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión e información indirecta, y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Opaganib:** Los resultados de dos ECCA sugieren que el opaganib podría no reducir la mortalidad ni la necesidad de ventilación mecánica invasiva y probablemente no incremente los eventos adversos graves, pero podría mejorar el tiempo de resolución de

los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

Cambios respecto a la versión anterior

• **Corticosteroides:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Icatibant:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **N-acetilcisteína (inhalada):** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

• **Oxigeno hiperbárico:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

• **Hidroxicloroquina:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Bromhexina:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **vv116 (remdesivir oral):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Espirulina:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Fluvoxamina:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Anticoagulantes:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Aspirina:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

• **Trasplante de células madre mesenquimatosas:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

• **L-arginina:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

Conclusiones

• La Organización Panamericana de la Salud (OPS) hace seguimiento en todo momento de la evidencia en relación con cualquier posible intervención terapéutica. A medida que se disponga de evidencia nueva, la OPS la incorporará con rapidez y actualizará sus recomendaciones, especialmente si dicha evidencia se refiere a grupos en situación de vulnerabilidad como los niños y niñas, las mujeres embarazadas, las personas mayores o los pacientes inmunocomprometidos, entre otros.

• La OPS también tiene en cuenta las diferencias en el impacto de la COVID-19 sobre las minorías y los diferentes grupos étnicos. En consecuencia, la Organización recopila constantemente información que pueda servir para mitigar el exceso de riesgo de enfermedad grave o muerte de estas minorías. Estos grupos sufren inequidades sociales y estructurales que conllevan una carga de enfermedad desproporcionada.

• La seguridad de los pacientes afectados por la COVID-19 es una prioridad clave de la mejora de la calidad de la atención y los servicios de salud.

• La importancia de los ensayos clínicos controlados aleatorizados con un diseño adecuado es fundamental en la toma de decisiones basadas en la evidencia. Hasta el momento, la mayoría de la investigación en el campo de la COVID-19 tiene muy baja calidad metodológica, lo que dificulta su identificación y validación. Urge incrementar la transparencia y plantear estudios de más calidad.

Systematic review of therapeutic options for treatment of COVID-19

Background

The vast amount of data generated by clinical studies of potential therapeutic options for COVID-19 presents important challenges. This new information must be interpreted quickly so that prescribers can make optimal treatment decisions with as little harm to patients as possible, and so that medicines manufacturers can scale-up production rapidly and bolster their supply chains. Interpreting new data quickly will save lives by ensuring that reportedly successful drugs can be administered to as many patients as possible as quickly as possible. Moreover, if evidence indicates that a medication is not effective, then ongoing clinical trials could change focus and pivot to more promising alternatives. Since many physicians are currently using treatments that rely on compassionate-use exemptions or off-label indications to treat patients with COVID-19,[1] it is crucial that they have access to the most up-to-date research evidence to inform their treatment decisions.

To address this evidence gap, we compiled the following database of evidence on potential therapeutic options for COVID-19. We hope this information will help investigators, policy makers, and prescribers navigate the flood of relevant data to ensure that management of COVID-19 at both individual and population levels is based on the best available knowledge. We will endeavor to continually update this resource as more research is released into the public space.

Methods

We used the Living OVerview of Evidence (L·OVE; https://iloveevidence.com) platform to identify studies for inclusion in this review. This platform is a system that maps PICO (Patient–Intervention–Comparison–Outcome) questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in electronic databases, preprint servers, trial registries, and other resources relevant to COVID-19. The latest version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on the L·OVE website.[2]

Search strategy

We systematically searched in L·OVE for COVID-19. The search terms and databases covered are described on the L·OVE search strategy methods page available at: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&section=methods. The repository is continuously updated, and the information is transmitted in real-time to the L·OVE platform. It was last checked for this review on 30 January 2023. The searches covered the period from the inception date of each database, and no study design, publication status or language restriction was applied.

Study selection

The results of the searches in the individual sources were de-duplicated by an algorithm that compares unique identifiers (database identification number, digital object identifier (DOI), trial registry identification number), and citation details (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract). Then, the information matching the search strategy was sent in real-time to the L·OVE platform where at least two authors independently screened the titles and abstracts yielded against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis and then decided about their inclusion.

Inclusion criteria

We aimed to find all available RCTs for potential therapeutic pharmacological interventions for COVID-19 with study designs that included head-to-head comparisons, or control groups with no intervention or a placebo. Target patient populations included both adults and children exposed to or with confirmed or suspected COVID-19. We focused on comparative effectiveness studies that provide evidence on outcomes of crucial importance to patients (mortality, invasive mechanical ventilation, symptom resolution or improvement, infection [prophylaxis studies] and severe adverse events).[3] In addition to RCTs, we included comparative non-RCTs that report on effects of NSAID consumption on mortality. We only incorporated non-RCTs that included at least 100 patients. We presented results of RCTs and non-RCTs separately.[4]

Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform provides instant notification of articles with a high likelihood of being eligible. The authors review them, decide upon inclusion, and update the living web version of the review accordingly. If meta-analytical pooling is possible from retrieved evidence, we will do this to derive more precise estimates of effect and derive additional statistical power.

The focus has been on RCTs studies for all included therapeutic pharmacological interventions (adults and children). Adults and children exposed to or with confirmed or suspected COVID-19 were and will be included. Trials that compare interventions head-to-head or against no intervention or placebo is the focus. We have focused on comparative effectiveness studies that provide evidence on patient-important outcomes (mortality, invasive mechanical ventilation, symptom resolution or improvement, infection (prophylaxis studies), hospitalization (studies that included patients with non-severe disease) and severe adverse events).[3] For studies that assessed thromboprophylactic interventions we also assessed venous thromboembolic events and major bleeding. For the outcome "hospitalization" we included information from studies reporting the number of hospitalizations or the number of hospitalizations combined with the number of deaths without hospitalization. We did not include information from studies reporting a combination of hospitalizations and medical consultations. No electronic database search restrictions were imposed.

For any meta-analytical pooling, if and when data allow, we pool all studies and present the combined analysis with relative and absolute effect sizes. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). We extracted mortality and invasive mechanical ventilation baseline risks from the ISARIC cohort as of 18 December 2020.[5,6] For baseline infection risk in exposed to COVID-19 we used estimates from a SR on physical distancing and mask utilization,[7] and for adverse events and symptom resolution/improvement we used the mean risk in the control groups from included RCTs until 18 December 2020. For venous thromboembolic events and major bleeding baseline risk we used the mean risk in the control groups from included RCTs until 25 March 2021. For hospitalization baseline risk we used the median risk in the control groups from included RCTs until 23 December 2021. We continuously monitor baseline risks by assessing the mean risk of every outcome in the control groups of included RCTs. When substantial changes to baseline risks are detected, we update

the estimates used for absolute effects calculations. For mortality, there were some drug instances whereby we provide systematic-review (meta-analysis) evidence indirectly related to patients with COVID-19, e.g., corticosteroids in patients with ARDS.

For result interpretations and imprecision assessment we used a minimally contextualized approach which considers whether the 95%CI includes the null effect, or, when the point estimate is close to the null effect, whether the 95%CI lies within the boundaries of small but important benefit and harm that corresponds to every outcome assessed.[8,9]

We used the following thresholds to define important benefits and harms: Mortality, +/- 1%; Mechanical ventilation, +/- 2%; Symptom resolution or improvement, +/- 5%; Symptomatic infection in exposed individuals, +/- 5%; Hospitalization in patients with mild recent COVID-19, +/- 1.9%; Severe adverse events, +/- 3%.

For some interventions when we found significant heterogeneity, we performed subgroup analysis considering: 1) risk of bias (high/moderate vs low risk of bias); 2) disease severity (mild, moderate, severe, or critical); and 3) intervention's characteristics (i.e., different doses or administration schemes). When we observed significant differences between subgroups, we presented individual subgroup's estimates of effect and certainty of the evidence assessment.

A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect (Table 4).[10] For non-RCTs, potential residual confounding was assumed in all cases and certainty of the evidence was downgraded twice for risk of bias. The GRADE approach was used to assess the certainty on the body of evidence for every comparison on an outcome basis (Table 5).[11] Risk of bias judgments were compared against other similar projects (Drug treatments for covid-19: living systematic review and network meta-

analysis and The COVID-NMA initiative). Significant discrepancies were discussed until a final decision was reached.

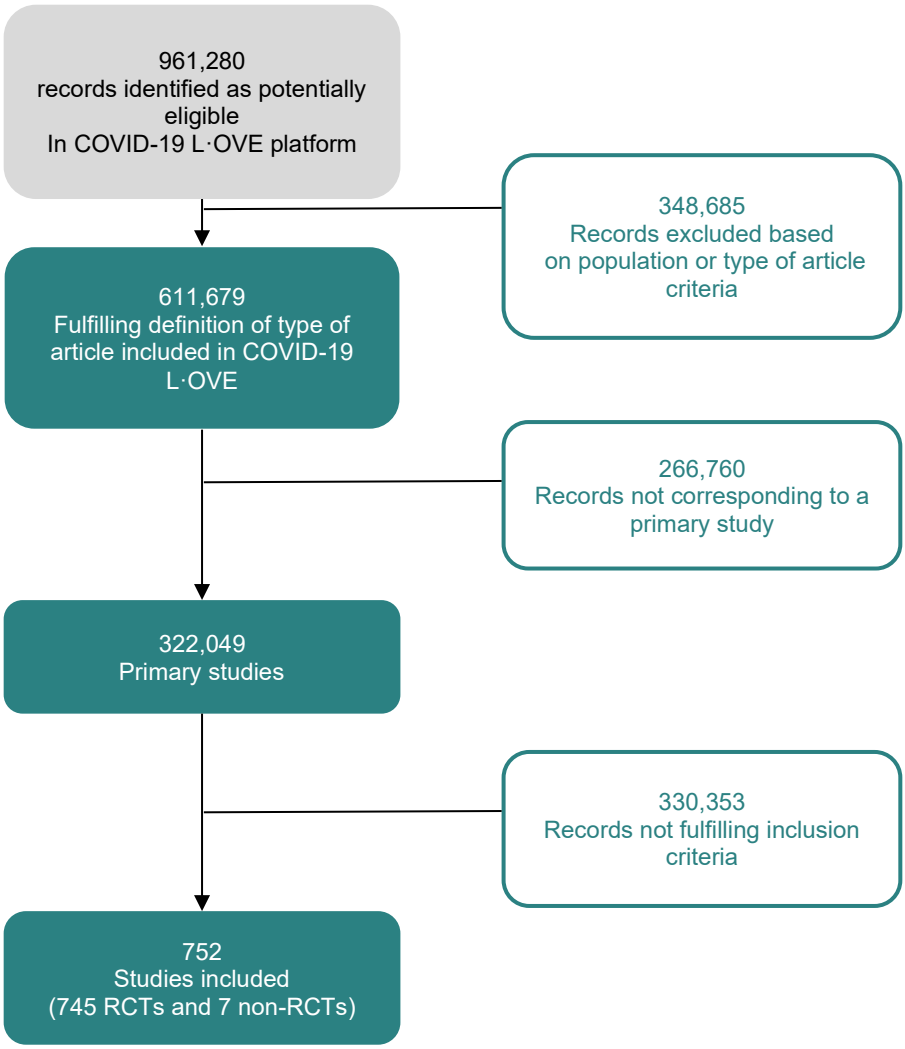
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in Figure 1. A total of 752 studies were selected for inclusion, 745 RCTs and 7 non-RCTs. A list of excluded studies is available upon request.

Figure 1. Study identification and selection process



Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs resulted in high risk of bias due to suboptimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal. For the observational studies, we had concerns with the representativeness of study groups (selection bias) and imbalance of the known and unknown prognostic factors (confounding). Many studies are also at risk of being confounded by indication. Most are not prospective in nature and the outcome measures are mainly heterogeneous with wide variation in reporting across the included studies. In general, follow-up was short and as mentioned, confounded potentially by the severity of disease, comorbidities, and previous or concomitant COVID-19 treatment. The risk of bias assessment of each RCT is presented in Table 4.

Table 4. Risk of bias of included RCTs

Study						Overall Risk-of-bias judgement	
						Mortality and invasive mechanical ventilation	Symptoms, infection and adverse events
RECOVERY - Dexa	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
RECOVERY - Hydroxychloroquine	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
BCN PEP CoV-2	Low	Some Concerns	Some Concerns	Some Concerns	Low		Some Concerns
ACTT-1	Low	Low	Low	Some Concerns	Low	Low	Low
COVID-19 PEP	Low	Low	High	Low	Low		High
Cavalcanti et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kamran SM et al	High	Some Concerns	Low	High	Low		High
COVID-19 PET	Low	Low	Low	Low	Low	Low	Low
SIMPLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BCN PEP CoV-2	High	Some Concerns	Low	High	Low		High
Chen C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CAP-China remdesivir 2	Low	Low	Low	Low	Low	Low	Low
LOTUS China	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Tang et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hung IF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
GRECCO-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Li L et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RAISTAVI	Low	Some Concerns	Low	High	Low		High
Chen, Zeng et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Chuan Li C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zheng et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ELACOI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVICOVID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
GLUCOCOVID	High	Some Concerns	Low	Low	Low	High	High
ObiloCOVID19	Low	Low	Low	Some Concerns	Low	Low	Low
Cavouet-Monfared et al	High	Some Concerns	Low	Low	Low	High	High
Chen et al	High	Some Concerns	Low	Low	Low	High	High
Davoodi L et al	High	Some Concerns	Low	Low	Low	High	High
Ivashchenko AA et al	High	Some Concerns	Low	Low	Low	High	High
Chen et al	High	Some Concerns	Low	Low	Low	High	High
Gao Y et al	Low	Some Concerns	Low	Low	Low	Low	Low
Chen PC et al	High	Some Concerns	Low	Low	Low	High	High
HC-nCoV	High	Some Concerns	Low	Low	Low	High	High
Lou Y et al	High	Some Concerns	Low	Low	Low	High	High
Vitar APJ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Gawronski O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Huang et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Yuan et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ren Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mehboob R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zheng et al	Low	Some Concerns	Low	Low	Low	Low	High
Skiadas et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Hu K, Wang M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ESPERANZA	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopez et al	High	Low	Low	Low	Low	High	High
Duarte M et al	High	High	High	Some Concerns	Some Concerns	High	High
Metovid	Low	Low	Low	Low	Low	Low	Low
Mansour E et al	Low	Low	Low	Some Concerns	Low	Low	High
Zhang J et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - Lopinavir-Ritonavir	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
CAREDA	Low	Low	Low	Low	Low	Low	Low
Abbasinazar Kangarlı H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sadeghi A et al	High	Some Concerns	Low	Low	Low	High	High
Sfuri L et al	High	Some Concerns	Low	Some Concerns	Low	High	High
SIMPLE 2	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
Abd-Elsalam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sekhavati E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shaoran et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahmani H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ConPlas-19	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
DEXA-COVID19							
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Steroids-SARI							
COVID STEROID							
CoDEX	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVIDIOL	High	Some Concerns	Low	Some Concerns	Low	High	High
CAPE COVID	Low	Low	Low	Low	Low	Low	Low
COVACTA	Low	Low	Low	Low	Low	Low	Low
COALITION II	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Li T et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Wang D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Chowdhury et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLACID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
Ghandilaghi N et al	High	Low	Low	Low	Low	Some Concerns	Some Concerns
TX-COVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
Cheng LL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Farahani R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kamali KS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATENEA-Co-300	High	Some Concerns	Low	Some Concerns	Low	High	High
Wu X et al	Low	Low	Low	Low	Low	Low	Low
Balcells ME et al (Pontificia Universidad Catolica de Chile)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Eqtesadi M et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PREP	Low	Low	Low	Low	Low	Low	Low
Wang M, Hu R. et al (Renmin Hospital of Wuhan University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Ota Y et al (Fujita Health University Hospital)	High	Some Concerns	Low	Some Concerns	Low	High	High
Pedde et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
TEACH	High	Low	Low	Some Concerns	Low	High	High

Hajizadeh et al (Iran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
PREP_COVID	Low	Low	Low	Low	Low	Low	Low	
de Almeida JCG et al (Universidade de São Paulo)	Low	Low	Low	Low	Low	Low	Low	
Fu W et al (Shanghai Public Health Clinical Center)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Salehzadeh F (Ardabil University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Dabbous H et al (Ain Shams University)	High	Some Concerns	Low	Some Concerns	Low	High	High	
PATCH	Low	Low	Low	Low	Low	Low	Low	
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
PLASMA-AR	Low	Low	Low	Low	Low	Low	Low	
COVID-19-MCS	Low	Low	Low	Some Concerns	High	Low	High	
Mahmud et al	Low	Low	Low	Low	Low	Low	Low	
Ansarin K (Tabriz University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High	
WHO SOLIDARITY - HCQ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
Vellmeitra V et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Shi L et al	Low	Low	Low	Low	Low	Low	Low	
RCT-TCS-COVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
BACC Bay Tocilizumab Trial	Low	Low	Low	Low	Low	Low	Low	
SARITA-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High	
Ghasemiftam S et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High	
COVID-19 PEP (University of Washington)	Low	Low	Low	Low	Low	NA	Low	
Hashim HA et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
ILBS-COVID-02	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High	
PRINCECOVID	High	Some Concerns	Low	Some Concerns	Low	High	High	
Pedrosabihkan U et al (Medical Education and Drugs Department)	High	Low	Low	Low	Low	High	High	
Alqahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Khamis F et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
BLAZE-1	High	Low	Low	Low	Low	High	High	
PETAL	Low	Low	Low	Low	Low	Low	Low	
Lazzeri G et al	High	Low	Low	Low	Low	High	High	
Ruzhentsova T et al (R-Pharm)	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Lassi E et al	Low	Low	Low	Low	Low	Low	Low	
Mikki P et al	Low	Low	Low	Low	Low	Low	Low	
HHADE trial	High	Some Concerns	Low	Some Concerns	Low	High	High	
Yakovlt M et al (Pharmo Corporate)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Ghoreishari S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
HAHPS	Low	High	Low	Some Concerns	Low	High	High	
Elgazzar et al (mild)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Elgazzar et al (severe)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Elgazzar et al (prophylaxis)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Talaimi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
FAVIS2020 (Promomed, LLC)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Munsi H et al (University of Sao Paulo)	Low	Low	Low	Low	Low	Low	Low	
Udwadia ZF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
CORIMUNO-TOCI 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
EMPACTA	Low	Low	Low	Low	Low	Low	Low	
HYCOVID	Low	Low	Low	Low	Low	Low	Low	
Krolewiecki et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
ILIAD	Low	Low	Low	Low	Low	Low	Low	
AB-DRUG-SARS-004	High	Low	Low	Low	Low	High	High	
Q-PROTECT	Low	Low	Low	Low	Low	Low	Low	
Hasnain M et al	High	Low	Low	Low	Low	High	High	
FundacionINFANT-Plasma	Low	Low	Low	Low	Low	Low	Low	
COVID-Lambda	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Naseri et al	Some Concerns	Some Concerns	Low	Some Concerns	Low	High	High	
PICP19	High	Some Concerns	Low	Some Concerns	Low	High	High	
Mukhtar K et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Ahmed et al	High	Low	Low	Low	Low	High	High	
TCELICI9-021-00	High	Some Concerns	Low	Some Concerns	Low	High	High	
Abd Elsalam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High	
Prevelin-M	High	Some Concerns	Low	Some Concerns	Low	High	High	
Maldonado I et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
GARGLES	High	Some Concerns	Low	Some Concerns	Low	High	High	
ERSul	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns	
Chaccour et al	Low	Low	Low	Low	Low	Low	Low	
ACTT-2	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns	
RECOVERY	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
EIDD-2801-1001	Low	Low	Low	Low	Low	Low	Low	
Weinreich	Low	Low	Low	Low	Low	Low	Low	
Roozbeh F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
ACTIV-3/TICO	Low	Low	Some Concerns	Low	Low	Low	High	
Chachar et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
BabyAova LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Balduzzi et al	Low	Low	Low	Low	Low	Low	Low	
REMAP-CAP - tocilizumab	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Abdelmokaoud AA et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Rahi et al	Low	Low	Low	Low	Low	Low	Low	
Rahmati P et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
PAVIA-004-Cov2020	High	Low	Low	Low	Low	High	High	
Chahla et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
COVIFERON	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
RECOVERY-Plasma	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
Interferon in COVID (Alavi Darazam I et al)	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
AB-DRUG-SARS-004 (Cadegiani FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High	
JamaMaghsoudiGolrokal S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Sedighiyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Roostaei A et al	High	Low	Low	Low	Low	High	High	
Ren-Covid	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
SECT	High	Some Concerns	Low	Some Concerns	Low	High	High	
Mohan et al	Low	Low	Low	Low	Low	Low	Low	
Shahsavarpad et al	Low	Low	Low	Low	Low	Low	Low	
Saporito et al	High	Some Concerns	Low	Some Concerns	Low	High	High	

Santana et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Bukhari et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Okumus et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Vega	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
Gottlieb	Low	Low	Low	Low	Low	Low	Low	
RIVALTE CORONA	Low	Some Concerns	Some Concerns	Low	Low	Low	High	
CORIMUNO-ANA-1	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Thakar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Ortiz H et al	High	High	Low	Some Concerns	Low	High	High	
Tang X et al	Low	Some Concerns	Low	Low	Low	Low	Low	
COLCORONA	Low	Some Concerns	Low	Low	Low	Low	Low	
Lopardo	Low	Low	Low	Low	Low	Low	Low	
Ostrosse HM et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
ATTRACT	Low	Some Concerns	Low	Low	Low	Low	Low	
Ramirez K et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns	
EAT-OUTA AndreGuV	Low	Low	High	Low	Low	High	High	
Farrokhi S et al	Some Concerns	Some Concerns	High	Some Concerns	Low	High	High	
Khalili H et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Rokkiavitev VP et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
KALIPI	High	Some Concerns	Low	Some Concerns	Low	High	High	
HYDRA	Low	Some Concerns	Low	Low	Low	Low	Low	
Sell S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
RETPGMD2GR	High	Some Concerns	Low	Some Concerns	Low	High	High	
SJU-MED-CHTH-H-00001	High	Some Concerns	Low	Some Concerns	Low	High	High	
STOIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Borges M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
RECOVERY-TCZ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
COVIDAtoZ -Zinc	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
COVID-19 Early Treatment	Low	Some Concerns	Low	Low	Low	Low	Low	
Shogenova LV et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
EPC16844	Low	Some Concerns	Low	Low	Low	Low	Low	
ARTL-H	High	Some Concerns	Low	Some Concerns	Low	High	High	
Puneet	High	Some Concerns	Low	Some Concerns	Low	High	High	
VB-II-IVIG-COVID-167320-CT1	High	Some Concerns	Low	Some Concerns	Low	High	High	
Jamaati H et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Beltran-HCQ	High	Some Concerns	Low	Some Concerns	Low	High	High	
ZINC COVID	Low	Some Concerns	Low	Low	Low	Low	Low	
PATCH 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
AB-DRUG-SARS-064-2	High	Some Concerns	Low	Some Concerns	Low	High	High	
Nouri-Vaskeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Lopez-Medina et al	Low	Low	Low	Low	Low	Low	Low	
Lalukreddy M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Silva	High	Some Concerns	Low	Some Concerns	Low	High	High	
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High	
Bennato Guiati et al	Low	Low	Low	Low	Low	Low	Low	
Piotr-Junac et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Mikhaylov	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
3GAMMACOVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High	
AAAS9924	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns	
Tolouian et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
ElZein R et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
PEGI 20 000	High	Some Concerns	Low	Some Concerns	Low	High	High	
MAIIH-COVID	Low	Some Concerns	Low	Low	Low	Low	Low	
INSPIRATION	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	
Zarychanski	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	
Santos PSS et al	Low	Some Concerns	Low	Low	Low	Low	Low	
Soleymani-Dodaran M et al	Low	Some Concerns	Low	Low	Low	Low	Low	
TD-0903-B168	High	Some Concerns	Low	Some Concerns	Low	High	High	
DISCOVER	Low	Some Concerns	Low	Low	Low	Low	Low	
HUHG-2020-20682	Low	Some Concerns	Low	Low	Low	Low	Low	
Alavi-Moghaddam M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
CT-PSI 1.2	Low	Some Concerns	Low	Low	Low	Low	Low	
Vahabikashani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
BBCovid	Low	Some Concerns	Low	Low	Low	Low	Low	
Hanna Huang Y et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Gopinkhova VV et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
KDH-120	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Beltran Gonzalez JL et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Dowd S et al	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High	
COVID-AIV	High	Some Concerns	Low	Some Concerns	Low	High	High	
Arora S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Rijadovi AR et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Kishoria N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
CERC-080-COVID-01	High	Low	High	Some Concerns	Low	High	High	
Mahajan L et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns	
Rouhollahi M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
HBOTCOVID19	High	Some Concerns	Low	Some Concerns	Low	High	High	
RESIST	High	Some Concerns	Low	Some Concerns	Low	High	High	
RESIST	High	Some Concerns	Low	Some Concerns	Low	High	High	
CARN-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Seet	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
SBU-COVID19-ConvalescentPlasma	Low	Some Concerns	Low	Low	Low	Low	Low	
TOGETHER	Low	Some Concerns	Low	Low	Low	Low	Low	
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
OSCAR	Low	Some Concerns	Low	Low	Low	Low	Low	
POLYCOR	Low	Some Concerns	Low	Low	Low	Low	Low	
Vanguard	Low	Some Concerns	Low	Low	Low	Low	Low	
Siemieniuk RR et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
CamCOVID	Low	Some Concerns	Low	Low	Low	Low	Low	
BCR-PNB-001	High	Some Concerns	Low	Some Concerns	Low	High	High	
AYDMEC	Low	Some Concerns	Low	Some Concerns	Low	Low	High	

Stem 2 et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
CLORO-TRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High	
PROBCO	High	Some Concerns	Low	Some Concerns	Low	High	High	
Nasiri TM et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
PISCO	High	Some Concerns	Low	Some Concerns	Low	High	High	
HMS-COVID-PK	Low	Some Concerns	Low	Low	Low	Low	Low	
Rashed A et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
More M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
FACOT	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
COV-BARRIER	Low	Some Concerns	Low	Low	Low	Low	Low	
LIVE-AIR	Low	Some Concerns	Low	Low	Low	Low	Low	
PreToVid	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Mahmoudi M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
AGILE	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Hamdy Salman O et al	Low	Some Concerns	Low	Low	Low	Low	Low	
COVID-RT-01	Low	Some Concerns	Low	Low	Low	Low	Low	
COVID-AIR	High	Some Concerns	Low	Some Concerns	Low	High	High	
Peresu U et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Zarychanski-Non-critical	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	
Santormalo-COVID19 Study	Low	Some Concerns	Low	Low	Low	Low	Low	
DAPSID	High	Some Concerns	Low	Some Concerns	Low	High	High	
CHEER	High	Some Concerns	Low	Some Concerns	Low	High	High	
RECOVERY - Colchicine	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
Silva Mendez-Flores S et al	High	Low	Low	Low	Low	High	High	
SAVE-MORE	Low	Some Concerns	Low	Low	Low	Low	Low	
Winchester S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Elgohary MAS et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
ARMY-1	Low	Some Concerns	Low	Low	Low	Low	Low	
Hamidi-Alamdari D et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Zammarchi L et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Abd-Elsalam S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Siber et al	Low	Low	Some Concerns	Low	Low	Low	Low	
Faital et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
SOVIECOD	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
ACTION	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	
BLAZE-2	Low	Low	Low	Low	Low	Low	Low	
PrePAC-COVID	Low	Low	Low	Low	Low	Low	Low	
Tian F et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
RECOVERY - ABA	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
HONEST	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
COMET-ICE	Low	Low	Low	Low	Low	Low	Low	
PSMMSCOVID19	Low	Low	Low	Low	Low	Low	Low	
SERTAD-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
SEV-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High	
CATALYST	High	Some Concerns	Low	Some Concerns	Low	High	High	
Ali S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
RECOVERY - REGEN-COV	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
Sahin A et al	High	Low	Low	Low	Low	High	High	
ACEI-COVID	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
Covid-19 Phase 3 Prevention Trial	Low	Low	Low	Low	Low	Low	Low	
EECI-2001-2003	Low	Low	Low	Low	Low	Low	Low	
REMAP-CAP	Low	Some Concerns	Low	Low	Low	Low	Some Concerns	
STOP-COVID	Low	Low	Low	Low	Low	Low	Low	
Vallejos et al	Low	Low	Low	Low	Low	Low	Low	
CONCOR-1	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
ALBERTA HOPE-Covid19	Low	Low	Low	Low	Low	Low	Low	
Hamed DM et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
COUNTER-COVID	Low	Low	Low	Low	Low	Low	Low	
Abdulamir AS et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
RP-DRUG-SARS-883	High	Low	Low	Low	Low	High	High	
Ayat ZF et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Di Pietro F et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
ARD-CORONA	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
ARCHITECTS	Low	Low	Low	Low	Low	Low	Low	
CORIMUNO-TOCI-ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
COV-AID	Low	Low	Low	Low	Low	Low	Low	
COVIDOSE-2	Low	Low	Low	Low	Low	Low	Low	
COVIDSTORM	Low	Low	Low	Low	Low	Low	Low	
COVITOZ-01	Low	Low	Low	Low	Low	Low	Low	
HMO-0224-20	High	Low	Low	Low	Low	High	High	
REMDACTA	Low	Low	Low	Low	Low	Low	Low	
ItenCoVA	Low	Low	Low	Low	Low	Low	Low	
Davoudian N et al	Low	Low	Low	Low	Low	Low	Low	
TOCOVID	Low	Low	Low	Low	Low	Low	Low	
COVINTOC	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
CORIMUNO-SAR	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
CORIMUNO-SAR-ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
SARCOVID	Low	Low	Low	Low	Low	Low	Low	
SARCOR	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
SARTRE	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
COV-AID-2	Low	Low	Low	Low	Low	Low	Low	
REGENERON Sao Pl	Low	Some Concerns	Low	Low	Low	Low	Low	
COPEP	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
RAPID	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	
Wang Q et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Hosseinzadeh A et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
BLAZE-1	Low	Low	Low	Low	Low	Low	Low	
Naimeddin F et al	Low	Low	Low	Low	Low	Low	Low	
CAN-COVID	Low	Low	Low	Low	Low	Low	Low	
Eduardo FP et al	Low	Low	Low	Low	Low	Low	Low	
ABARIG-SARS-080	High	Low	Low	Low	Low	High	High	
COVID STEROID 2	Low	Low	Low	Low	Low	Low	Low	

ACTION	Low	Low	High	Low	Low	Some Concerns	Some Concerns
Gildar-Duarte HG et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Sabico S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PLACOVID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
UMIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BISHOP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Avadapoya K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ravichandran et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DARE-19	Low	Low	Low	Low	Low	Low	Low
DGIYCOv	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PRINCIPLE	Low	Low	Low	Low	Low	Low	Low
Parikh D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Covid-19 Phase 3 Prevention Trial - Exploratic	Low	Low	Low	Low	Low	Low	Low
Three C	Low	Low	Low	Low	Low	Low	Low
COVIDIT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
KUMC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Abbasi S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CIPC	Low	Low	Low	Low	Low	Low	Low
Kosak et al	High	Some Concerns	Low	Some Concerns	Low	High	High
TOGETHER-Fluvoxamine	Low	Low	Low	Low	Low	Low	Low
TOGIDEX	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Fakhoran A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HERO-HCQ	Low	Low	Low	Low	Low	Low	Low
Alcalden Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Bhutiani S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
VASCEPA COVID-19 CARDIOLINK-3	High	Some Concerns	Low	Some Concerns	Low	High	High
Sfakia M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rodriguez C et al	Low	Low	Low	Low	Low	Low	Low
Mirzaani ZA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Stroh	Low	Low	Low	Low	Low	Low	Low
MADRID-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
JZW-MC-PVAA	Low	Low	Low	Low	Low	Low	Low
DAWn-Plasma	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
OPTIMISE-C19	Low	Low	Low	Low	Low	Low	Low
Cosorio	High	Low	Low	Low	Low	High	High
ALV-020-001	Low	Low	Low	Low	Low	Low	Low
Gattis MR-RESPOND-1	Low	Low	Low	Low	Low	Low	Low
ACTIV-2	High	Some Concerns	Low	Some Concerns	Low	Low	Low
CAFCWI	Low	Low	Low	Low	Low	Low	Low
Sicorifilte et al	Low	Low	Low	Low	Low	Low	Low
McCreary M et al	Low	Low	Low	Low	Low	Low	Low
Gamel M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Meakin et al	Low	Low	Low	Low	Low	Low	Low
COL-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE - Colchicine	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hasanvazad M et al	High	Low	Low	Low	Low	High	High
Ramachandran R et al	Low	Low	Low	Low	Low	Low	Low
CPI-009-002	High	Low	Low	Low	Low	High	High
Di-Domênico MB et al	High	Low	Some Concerns	Low	Low	High	High
CT-P59 1.3	Low	Low	Low	Low	Low	Low	Low
ABC-19	Low	Low	Low	Low	Low	Low	Low
CORONA	Low	Low	Low	Low	Low	Low	Low
STARS	High	Some Concerns	Low	Some Concerns	Low	High	High
ARTAIC'19	High	Low	High	Low	Low	High	High
Bafaloni DE et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESPERIDIN	Low	Low	Low	Low	Low	Low	Low
Recolalfr	Low	Low	Low	Low	Low	Low	Low
Azizi H et al	High	Low	High	Low	Low	High	High
FIGHT-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
CANDIDATE	Low	Low	Low	Low	Low	Low	Low
REMACOV	High	Some Concerns	Low	Some Concerns	Low	High	High
HEP-COVID	Low	Low	Low	Low	Low	Some Concerns	Some Concerns
ACTIV-4B	Low	Low	Low	Low	Low	Low	Low
COV-BARRIER-MV	Low	Low	Low	Low	Low	Low	Low
DEFINE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEV-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
SARPAC	High	Some Concerns	Low	Some Concerns	Low	High	High
Diana YM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PRODOV-19-2020	High	Some Concerns	Low	Some Concerns	Low	High	High
Haghighi S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RUKOCVID	Low	Low	Low	Low	Low	Low	Low
ACTT-3	Low	Low	Low	Low	Low	Low	Low
Amico A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Maghbool Z et al	High	Low	Low	Low	Low	High	High
INTEREST	Low	Low	Low	Low	Low	Low	Low
Olaniyi O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
EB-PTS-01	Low	Low	Low	Low	Low	Low	Low
Mibarak S et al	Low	Low	Low	Low	Low	Low	Low
Lalli F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zhu R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CONTAIN	Low	Low	Low	Low	Low	Low	Low
COV-AID-3	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Somersan Karakaya	Low	Low	Low	Low	Low	Low	Low
COVID-19-MCS	High	Low	Low	Low	Low	High	High
Yildiz E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CYTOCOV-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Algahtani FD et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ALPS-COVID	Low	Low	Low	Low	Low	Low	Low
R10933-10987-COVA-20145	Low	Low	Low	Low	Low	Low	Low
VCACS	High	Some Concerns	Low	Some Concerns	Low	High	High
CVD-04-CD-001	Low	Low	Low	Low	Low	Low	Low

PrevCOP2	High	Some Concerns	Low	Some Concerns	Low	High	High	
Tosgai N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Hal F et al	Low	Low	Low	Low	Low	Low	Low	
MOVe-OUT	Low	Low	Low	Low	Low	Low	Low	
Weinreich_C	Low	Low	Low	Low	Low	Low	Low	
Bakpa-Hammad MT et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Sathish RM et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
AP-014	High	Some Concerns	Low	Some Concerns	Low	High	High	
Aagerbom M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Khazzoni AS et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
COMBAT-COVID	Low	Low	Low	Low	Low	Low	Low	
ACPRECOV	Low	Low	Low	Low	Low	Low	Low	
X-Covid-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Hoblitzel M et al	Low	Low	Low	Low	Low	Low	Low	
Malaysian Flavipiravir Study	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
George C et al	Low	Low	Low	Low	Low	Low	Low	
TSUNAMI	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
CORV-ert & CoV-Early	Low	Low	Low	Low	Low	Low	Low	
Raghavan K et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Shirkoh et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
CSSC-004	Low	Low	Low	Low	Low	Low	Low	
Camelliotto M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
CRITICAL	Low	Low	Low	Low	Low	Low	Low	
Reglkersa_Part2								
RIMETREE	Low	Low	Low	Low	Low	Low	Low	
BUCOSARS	Low	Low	Low	Low	Low	Low	Low	
BK-CoV-251	High	Some Concerns	Low	Some Concerns	Low	High	High	
HIGHLOWDEXA	High	Some Concerns	Low	Some Concerns	Low	High	High	
DEFINE	High	Some Concerns	Low	Some Concerns	Low	High	High	
Ahmadi S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Pradakis et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Baxter AL et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
PAVI-COV-US251	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Kazemipour et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Rangel B et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
WINCOVID	High	Some Concerns	Low	Some Concerns	Low	High	High	
Pollidi ML et al	Low	Low	High	Low	Low	High	High	
COFOS	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
WHP COVID-19	Low	Low	Low	Low	Low	Low	Low	
TOGETHER 2	Low	Low	Low	Low	Low	Low	Low	
CONTAIN COVID-19	Low	Low	Low	Low	Low	Low	Low	
COVIBENZA	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
COLCOVID	Low	Low	Low	Low	Low	Low	Low	
Alkofton M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
OPTIMIST-C19	Low	Low	Low	Low	Low	Low	Low	
COVID-OmegaF	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Majidi N et al	High	Low	Low	Low	Low	High	High	
ICU-VR	High	Some Concerns	Low	Some Concerns	Low	High	High	
ALLIANCE	High	Some Concerns	Low	Some Concerns	Low	High	High	
PROTECT-EHIC	Low	Low	Low	Low	Low	Low	Low	
UMAB-083	High	Some Concerns	Low	Some Concerns	Low	High	High	
Tobiasen R et al	Low	Low	Low	Low	Low	Low	Low	
INSPIRATION4RESPIRATION-S	Low	Low	Low	Low	Low	Low	Low	
Abuzeida R et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Hu D et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
AviMild	Low	Low	Low	Low	Low	Low	Low	
APLICOV-PC	Low	Low	Low	Low	Low	Low	Low	
MARIPOSA	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
IMPACT	High	Some Concerns	Low	Some Concerns	Low	High	High	
Covid19IOPPN	High	Some Concerns	Low	Some Concerns	Low	High	High	
ABB-COVID19	Low	Low	Low	Low	Low	Low	Low	
COVID MED	Low	Low	Low	Low	Low	Low	Low	
Naik NB et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
ACTIV-4a	Low	Low	Low	Low	Low	Low	Low	
CATCO	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
MEFECOVID-19	Low	Low	Low	Low	Low	Low	Low	
Piordanelli M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
De Santis GC et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Murugesan H et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Manomaiphiboon A et al	Low	Low	Low	Low	Low	Low	Low	
DOXPREVENT ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
Pisanbakel G et al	High	Some Concerns	Low	Some Concerns	Low	High	High	
Chupp G et al	Low	Low	Low	Low	Low	Low	Low	
NADOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
MEDIC-LAUMC	High	Low	Low	Low	Low	High	High	
RISeCue	Low	Low	Low	Low	Low	Low	Low	
TTAC	Low	Low	Low	Low	Low	Low	Low	
EPIC-HR	Low	Low	Low	Low	Low	Low	Low	
I-TECH	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
FORCE	Low	Low	Low	Low	Low	Low	Low	
Cerra DM et al	Low	Low	Low	Low	Low	Low	Low	
PHYDRA	Low	Low	Low	Low	Low	Low	Low	
Nakoulkar Z et al	Low	Low	Low	Low	Low	Low	Low	
RAAS-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High	
SpiroCOVID19	Low	Low	Low	Low	Low	Low	Low	
CR216-21	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
EPICOS	Low	Low	Low	Low	Low	Low	Low	
COPERNICO	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
PROTECT-Patient Inst	High	Some Concerns	Low	Some Concerns	Low	High	High	
Singh H et al	Low	Low	Low	Low	Low	Low	Low	
Blazin Tond S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	
RECOVERY	High	Some Concerns	Low	Some Concerns	Low	High	High	

RUXCOVID-DEVENT	Low	Low	Low	Low	Low	Low	Low
SAC-COVID	Low	Low	Low	Low	Low	Low	Low
YUSKH2020	Low	Low	Low	Low	Low	Low	Low
Shakoor M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORTIVID	Low	Low	Low	Low	Low	Low	Low
COVERAGE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hakenkord M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
#BEATHE	Low	Low	Low	Low	Low	Low	Low
Kamboj TL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
MaCOVID	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
COVID-VIT-D	High	Some Concerns	Low	Some Concerns	Low	High	High
TOGETHER - Ivermectin	Low	Low	Low	Low	Low	Low	Low
FLARE	Low	Low	Low	Low	Low	Low	Low
Brennan CM et al	Low	Low	Some Concerns	Low	Low	High	High
IRB 3935	Low	Low	Low	Low	Low	Low	Low
Tebbas P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Fathi-Kazerooni M et al	High	Low	Low	Low	Low	High	High
Rabenato CK et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
LIFESAVER	Low	Low	Low	Low	Low	Low	Low
RECOVER	Low	Low	Low	Low	Low	Low	Low
LACCPT	Low	Low	Low	Low	Low	Low	Low
CPC-SARS	Low	Low	Low	Low	Low	Low	Low
Helmik J et al	Low	Low	Low	Low	Low	Low	Low
Tobin G et al	Low	Low	Low	Low	Low	Low	Low
Chowdhury FR et al	Low	Low	Low	Low	Low	Low	Low
PLACO-COVID	Low	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Low	Low	Low	Low	Low
Co-CLARITY	Low	Low	Low	Low	Low	Low	Low
Reyo FM et al	Low	Low	Low	Low	Low	Low	Low
PERUCONPLASMA	Low	Low	Low	Low	Low	Low	Low
CP-COVID-19	Low	Low	Low	Low	Low	Low	Low
CONFIDENT	Low	Low	Low	Low	Low	Low	Low
PCKOVID-19	Low	Low	Low	Low	Low	Low	Low
COF-COVID-19	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
OCAP	Low	Low	Low	Low	Low	Low	Low
OOOPCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COPE – Coelllan V	Low	Low	Low	Low	Low	Low	Low
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ostenesoll	High	Some Concerns	Low	Some Concerns	Low	High	High
CORONAVIT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Seo H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Gulati PI et al	High	Some Concerns	Low	Some Concerns	Low	High	High
IMpaCLRT	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIPOC	High	Some Concerns	Low	Some Concerns	Low	High	High
SafeDrop	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
Redondo-Calvo FJ et al	Low	Low	Some Concerns	Low	Low	High	High
CANDLE	Low	Low	Low	Low	Low	Low	Low
COVID-Compromise	Low	Low	Low	Low	Low	Low	Low
HITCH	Low	Low	Low	Low	Low	Low	Low
Kumar D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19-HSG	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVASE	High	Some Concerns	Low	Some Concerns	Low	High	High
RCT-MP-COVID-19	Low	Low	Low	Low	Low	Low	Low
COPLA-II	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Cowcock D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedavi M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
I-PROVENT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pahwani S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mustafaie A et al						NA	NA
SILVERBULLET						NA	NA
R 2020-755-178						NA	NA
GS-US-553-4620						NA	NA
DAWN-AZITHRO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
DW-MISC	Low	Low	Low	Low	Low	Low	Low
QuVIP	Low	Low	Low	High	High	High	High
Alizadeh N et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
TNK-	Low	Low	Low	Low	Low	Low	Low
ACTT-4	Low	Low	Low	Low	Low	Low	Low
Nicastri E et al	Low	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVID-HBI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
STU-2020-0797	Low	Low	Low	Low	Low	Low	Low
MANTICO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CSSC-251	Low	Low	Low	Low	Low	Low	Low
Mukau H et al	Low	Low	Low	Low	Low	Low	Low
ZILU-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahman SMA et al	High	Low	Low	Low	Low	High	High
TACTIC-COVID	Low	Low	Low	Low	Low	Low	Low
INSPIRE	Low	Low	Low	Low	Low	Low	Low
MSC-001	Low	Low	Low	Low	Low	Low	Low
REPRVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
NO COV-ED	High	Some Concerns	Low	Some Concerns	Low	High	High
Villasis-Keever MA et al	High	Low	High	Low	Low	High	High
CARED-TRIAL	Low	Low	Low	Low	Low	Low	Low
Lorzie BE et al	Low	Low	Low	Low	Low	Low	Low
STRUCK	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV-6	Low	Low	Low	Low	Low	Low	Low
Recai_Mild	Low	Low	Low	Low	Low	Low	Low
Recai_Severe	Low	Low	Some Concerns	Low	Low	High	High
Angkuwekwinai_Treat	Low	Low	Low	Low	Low	Low	Low
Angkuwekwinai_Prev	Low	Low	Low	Low	Low	Low	Low

Mirahmadizadeh et al	Low	Low	Low	Low	Low	Low	Low
George et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rojas et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Bergey-Lleonart et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ETHIC	High	Some Concerns	Low	Some Concerns	Low	High	High
OVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mukae H et al	Low	Low	Low	Low	Low	Low	Low
Khan et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mostervi et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Stamboul et al	Low	Low	Low	Low	Low	Low	Low
Stamboul et al	Low	Low	Low	Low	Low	Low	Low
Alemany et al	Low	Low	Low	Low	Low	Low	Low
McMahon et al	Low	Low	Low	Low	Low	Low	Low
Karampitsakos et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Carvalho Nleumschwander et al	Low	Low	Low	Low	Low	Low	Low
Amouattahi et al	High	Low	Low	Low	Low	High	High
Castro-Rodriguez et al	High	Some Concerns	High	Some Concerns	Low	High	High
Tanada et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Medhat et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Prasenohadi et al	Low	Low	Low	Low	Low	Low	Low
TACKLE	Low	Low	Low	Low	Low	Low	Low
TICO	Low	Low	Low	Low	Low	Low	Low
Labro et al	Low	Low	Low	Low	Low	Low	Low
Askari H et al	Low	Low	Low	Low	Low	Low	Low
Dine et al	High	Low	Low	Low	Low	High	High
Cocconi et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Tirupakuzhi et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Lau et al	Low	Low	Low	Low	Low	Low	Low
COVIT-TRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High
Karonova	High	Some Concerns	Low	Some Concerns	Low	High	High
Benchegroun	Low	Low	Low	Low	Low	Low	Low
Panatto	High	Some Concerns	Low	Some Concerns	Low	High	High
UW 20-535	High	Some Concerns	Low	Some Concerns	Low	High	High
Barnette	High	Low	Low	Low	Low	High	High
Saviano	High	Some Concerns	Low	Some Concerns	Low	High	High
Tobback	Low	Low	Low	Low	Low	Low	Low
Barrueco	Low	Low	Low	Low	Low	Low	Low
Zayad	High	Some Concerns	Low	Some Concerns	Low	High	High
Self	Low	Low	Low	Low	Low	Low	Low
Kumar	High	Some Concerns	Low	Some Concerns	Low	High	High
Zou	High	Some Concerns	Low	Some Concerns	Low	High	High
Tandon	Low	Low	Low	Low	Low	Low	Low
COVIDICUS	Low	Low	Low	Low	Low	Low	Low
Dastenae	High	Some Concerns	Low	Some Concerns	Low	High	High
Rabbani	High	Some Concerns	Low	Some Concerns	Low	High	High
Bharti	Low	Low	Some Concerns	Low	High	High	High
Ojeda	High	Low	Low	Low	Low	High	High
Bozorgmehr R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Romero-Barguengolta	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV-6 - Fluticazone	Low	Low	Low	Low	Low	Low	Low
BLAZE-4	Low	Low	Low	Low	Low	Low	Low
PRANA	Low	Low	Low	Low	Low	Low	Low
Aryan	High	Low	Low	Low	Low	High	High
Cervero	High	Some Concerns	Low	Some Concerns	Low	High	High
Abroug	High	Low	Low	Low	Low	High	High
PLATCOV - Iver	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PLATCOV - Regen	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Fogleman C et al	Low	Low	Low	Low	Low	Low	Low
PanCOVID19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AGILE	Low	Low	Low	Low	Low	Low	Low
G-COVID	High	Low	Low	Low	Low	High	High
IRICT	Low	Low	Low	Low	Low	Low	Low
Choudhary R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khodashahi R et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AAAT0636	Low	Low	Low	Low	Low	Low	Low
ACTIV-3/TICO	Low	Low	Low	Low	Low	Low	Low
Soltani R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ANACONDA	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BTI-202	Low	Low	Low	Low	Low	Low	Low
ReCOVery-SIRIO	High	Some Concerns	Low	Some Concerns	Low	High	High
MOVe-IN	Low	Low	Low	Low	Low	Low	Low
MOVe-OUT - ph2	Low	Low	Low	Low	Low	Low	Low
FERMIN	Low	Low	Low	Low	Low	Low	Low
Nimitvilai S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Spuch C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Dalil N et al	High	Some Concerns	Low	Some Concerns	Low	High	High
OMMETCOV19-2	Low	Low	Low	Low	Low	Low	Low
COVER HCW	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
COVID-OUT	Low	Low	Low	Low	Low	Low	Low
Chung R et al	NA						
PROTECT	NA						
Tavakol ASJ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zhang FQ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
TACOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Brunvoll	Low	Low	Low	Low	Low	Low	Low
Golan	Low	Low	Low	Low	Low	Low	Low
Siribaphat	High	Some Concerns	Low	Some Concerns	Low	High	High
PANAMO_vilobelimab	Low	Low	Low	Low	Low	Low	Low
Fessler	High	Low	Low	Low	Low	High	High
ARCADIA	Low	Low	Low	Low	Low	Low	Low
Madurka	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
Van Helmond	High	High	Low	High	Low	High	High

Majidi	High	Low	Low	Low	Low	High	High
PANORAMIC_Molnu	Low	Low	Low	Low	Low	Low	Low
Vahreschild	High	Low	Low	Low	Low	High	High
INTENSE-COV	Low	Low	Low	Low	Low	Low	Low
ACCROS	High	Some Concerns	Low	Some Concerns	Low	High	High
Madoiko	High	High	Low	High	Low	High	High
Kumar	High	Low	Low	Low	Low	High	High
MEDEAS	Low	Low	Low	Low	Low	Low	Low
Abdallah	Low	Low	Low	Low	Low	Low	Low
Ameri	High	High	Low	High	Low	High	High
COLVID	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
El-Baklawy	High	High	Low	High	Low	High	High
Golberg	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
Ghobain	Low	Low	Low	Low	Low	Low	Low
LF-COVID	Low	Low	Low	Low	Low	Low	Low
ESCAPE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY_Steroid_Dose	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
ICAT-COVID	High	High	Low	High	Low	High	High
Panahi et al	High	High	Low	High	Low	High	High
Sieviera	High	High	Low	High	Low	High	High
Dhibar	Low	Low	Low	Low	Low	Low	Low
Vila Mendez	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Cao	Low	Low	Low	Low	Low	Low	Low
Javid	Low	Low	Low	Low	Low	Low	Low
ACTIV-6 - Fluvoxamine	Low	Low	Low	Low	Low	Low	Low
ASCOT - Antithrombotics	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Makueka	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Muralidharan	Low	Low	Low	Low	Low	Low	Low

Main findings

Corticosteroids

See Summary of findings Table 1, Appendix 1

We identified 17 RCTs including 9,485 participants in which systemic corticosteroids (dexamethasone, methylprednisolone, or hydrocortisone) were compared against standard of care or other treatments. Thirteen of these trials provided information on mortality for the corticosteroids against standard of care comparison. The RECOVERY trial was the biggest with 2,104 patients assigned to dexamethasone and 4,321 to standard of care. Sixteen studies included patients with severe to critical disease, as shown by the fact that mortality in the control groups ranged from 14.2% to 61.4%, and one study included hospitalized patients without respiratory failure. In the RECOVERY trial, a subgroup analysis which stratified patients by the amount of baseline respiratory support they received, showed significant differences favoring those with oxygen requirements. However, as mortality was high in the subgroup of patients that did not receive baseline oxygen treatment (14%), we decided to adopt a conservative approach and include the primary analysis considering all randomized patients. In addition, we

identified ten studies including 4,439 patients in which different corticosteroid dosage schemes were compared and one study including 42 patients in which high dose steroids were compared to tocilizumab. Our results showed:

- Corticosteroids probably reduce mortality, RR 0.90 (95%CI 0.80 to 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate certainty ⊕⊕⊕◯ (Figure 2)
- Corticosteroids probably reduce invasive mechanical ventilation requirement, RR 0.87 (95%CI 0.73 to 1.04); RD -2.2% (95%CI -4.7% to 0.7%); Moderate certainty ⊕⊕⊕◯
- Corticosteroids may improve time-to-symptom resolution, RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⊕⊕◯◯
- Corticosteroids may not significantly increase the risk of severe adverse events, RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕◯◯
- Results were consistent with trials in which corticosteroids were used to treat non COVID-19 patients with ARDS. No significant differences between subgroups of studies using different corticosteroids were observed. (Figures 3 and 4)
- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) probably does not reduce mortality compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 1 (95%CI 0.82 to 1.21); RD 0% (95%CI -2.9% to 3.4%); Moderate certainty ⊕⊕⊕◯ (Figure 5)
- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) may not reduce mechanical ventilation compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 1.11 (95%CI 0.61 to 2.01); RD 1.9% (95%CI -6.7% to 17.5%); Low certainty ⊕⊕◯◯
- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) does not increase symptom resolution or improvement compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.98 (95%CI 0.9 to 1.02); RD -1.2% (95%CI -4.2% to 1.2%); High certainty ⊕⊕⊕⊕

- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) may not increase severe adverse events compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.82 (95%CI 0.6 to 1.11); RD -1.8% (95%CI -4.1% to 1.1%); Low certainty ⊕⊕◯◯

Figure 2. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19

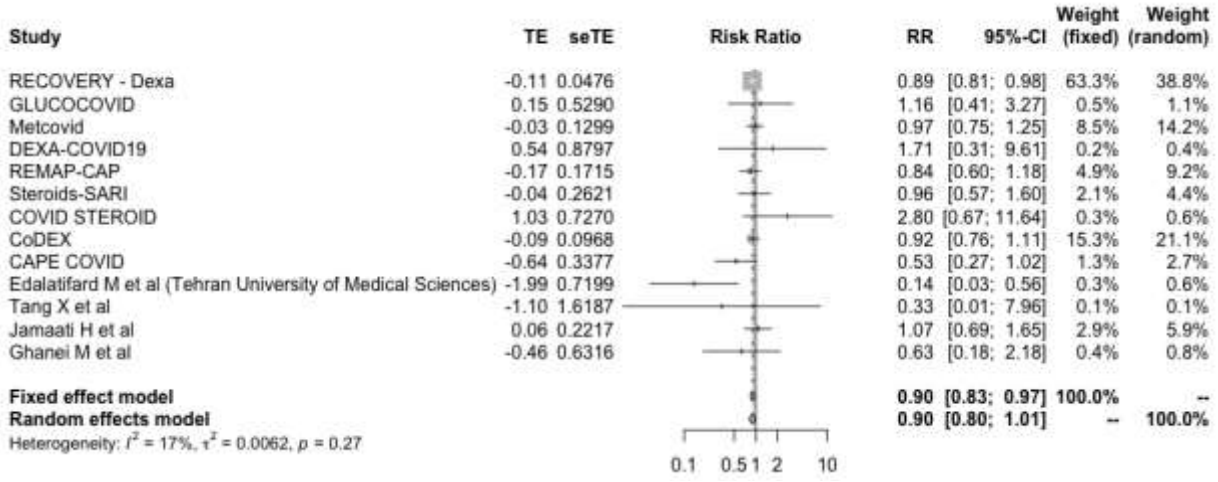


Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

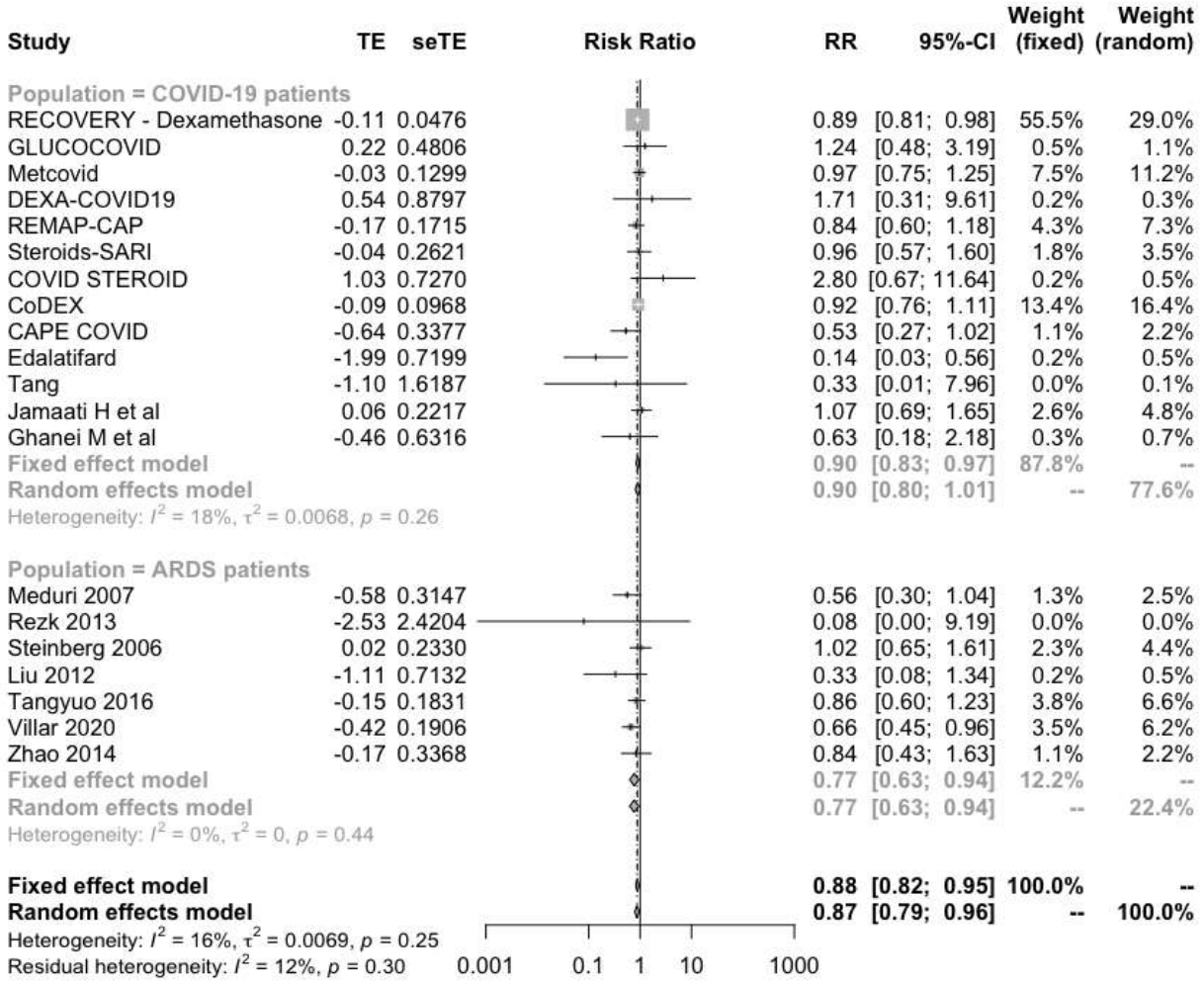


Figure 4. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

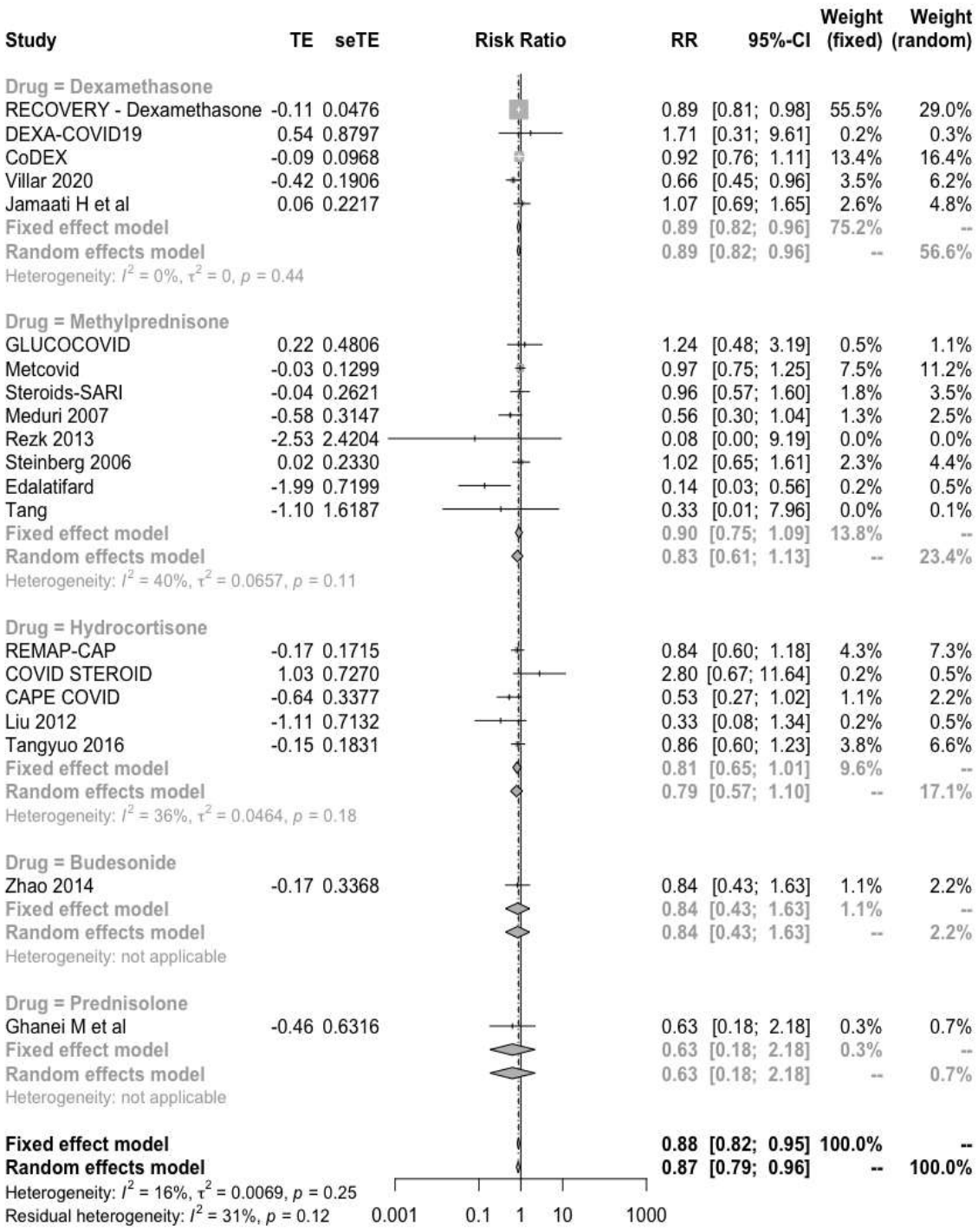
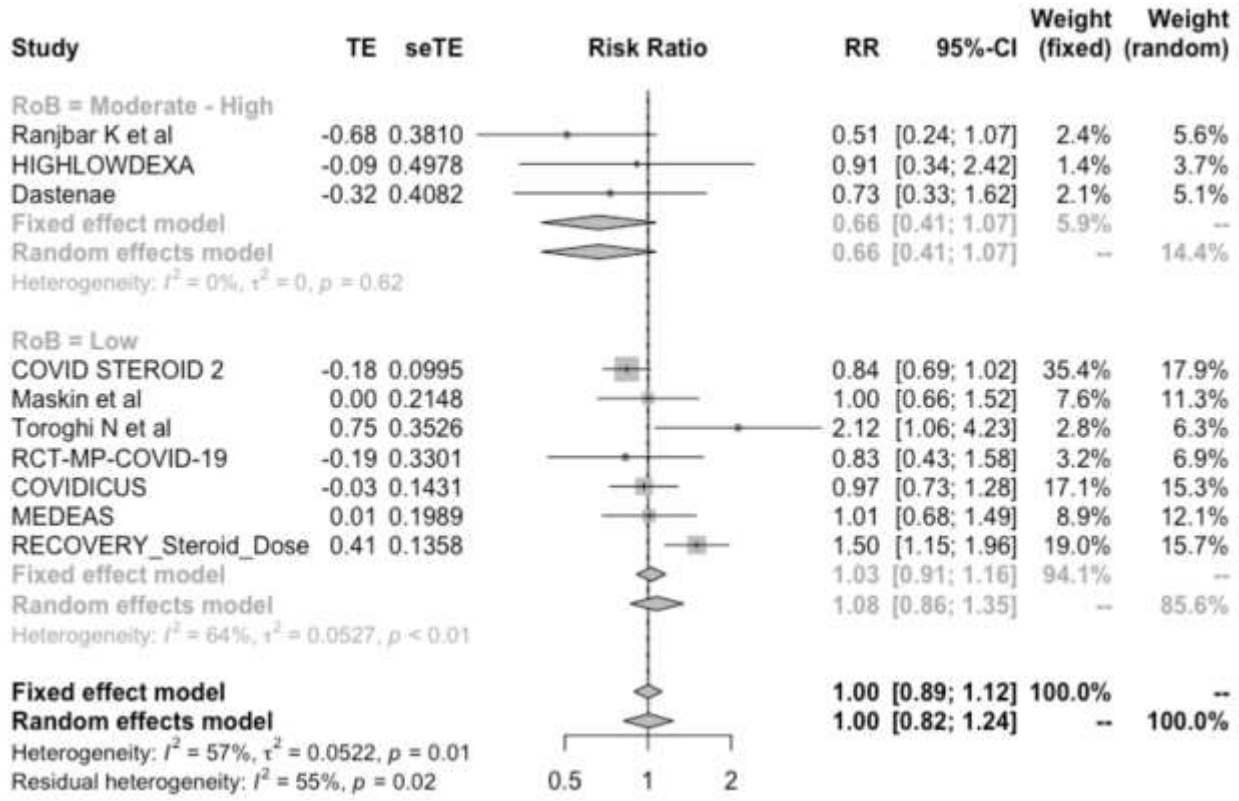


Figure 5. All-cause mortality in RCTs comparing high-dose corticosteroids (i.e., dexamethasone 12 mg a day) with standard-dose corticosteroids (i.e., dexamethasone 6 mg a day) in patients with COVID-19



In addition, one study that compared high dose corticosteroids (dexamethasone 20 mg a day) to tocilizumab reported higher mortality in patients treated with high dose corticosteroids.

Remdesivir

See Summary of findings Table 2, Appendix 1

We identified ten RCTs including 11,814 patients in which remdesivir was compared against standard of care or other treatments. In addition, we identified one study that compared different remdesivir dosage schemes. The WHO SOLIDARITY trial was the

biggest with 4,146 patients assigned to remdesivir and 4,129 to standard of care. Five studies included patients with severe disease as shown by the fact that mortality in the control groups ranged from 8.3% to 12.6%, and three studies included non-severe patients with 2% or less mortality in the control arm. Our results showed:

- Remdesivir probably reduces mortality, RR 0.93 (95%CI 0.89 to 1.03); RD -1.1% (95%CI -1.8% to 0.5%); Moderate certainty ⊕⊕⊕◯ (Figure 6)
- Remdesivir probably reduces invasive mechanical ventilation requirement, RR 0.76 (95%CI 0.56 to 1.04); RD -4.2% (95%CI -7.6% to 0.7%); Moderate certainty ⊕⊕⊕◯ (Figure 7)
- Remdesivir may improve time to symptom resolution, RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low certainty ⊕⊕◯◯ (Figure 8)
- Remdesivir may reduce hospitalizations in patients with recent onset mild, RR 0.28 (95%CI 0.11 to 0.75); RD -3.4% (95%CI -4.3% to -1.2%); Low certainty ⊕⊕◯◯
- Remdesivir may not increase the risk of severe adverse events, RR 0.77 (95%CI 0.46 to 1.29); RD -2.3% (95%CI -5.5% to 3%); Low certainty ⊕⊕◯◯

Figure 6. All-cause mortality with remdesivir use vs. standard of care in randomized control trials including COVID-19 patients

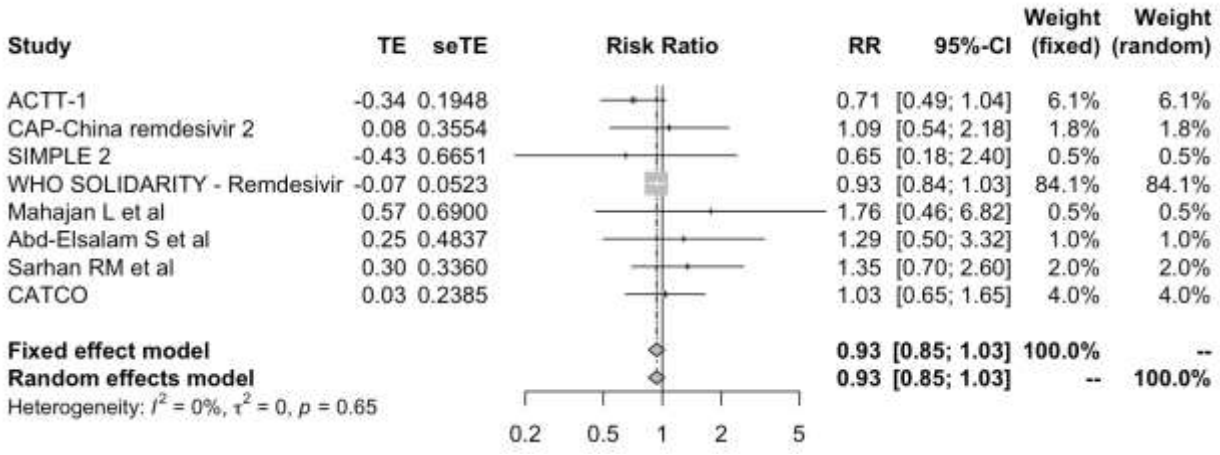


Figure 7. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

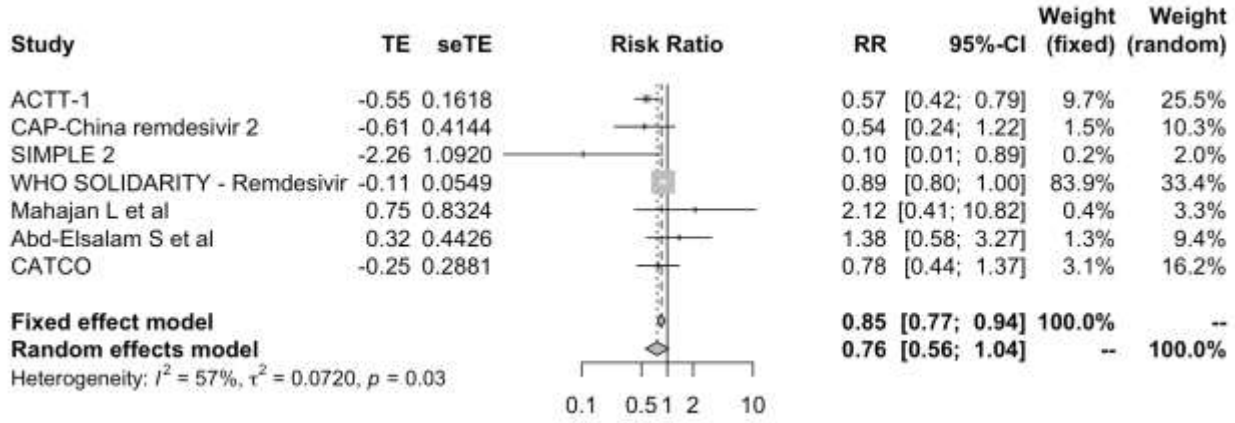
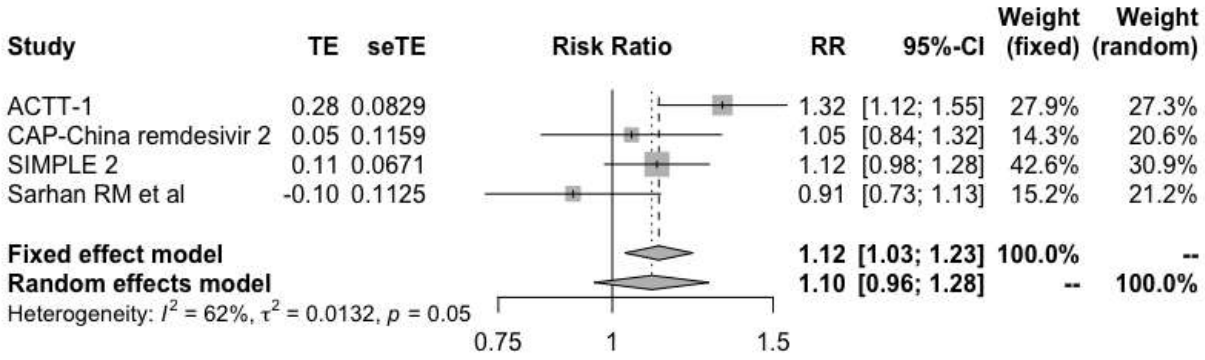


Figure 8. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 63 RCTs including 27,403 patients in which hydroxychloroquine or chloroquine were compared against standard of care or other treatments. The RECOVERY trial was the biggest with 1,561 patients assigned to dexamethasone and 3,155 to standard of care. In both the RECOVERY and SOLIDARITY trials, patients had severe disease as shown by the high mortality risk in control arms (24.9% and 9.2%, respectively). The remaining studies included patients with non-severe disease, as shown

by the lower mortality risk in control arms, ranging from 0 to 5.2%. Additionally, we identified nine studies in which hydroxychloroquine was used in healthy persons to prevent COVID-19 infection. Our results showed:

- Hydroxychloroquine or chloroquine probably does not increase mortality, RR 1.09 (95%CI 1 to 1.19); RD 1.4% (95%CI 0% to 3%); Moderate certainty ⊕⊕⊕◯ (Figure 9)
- Hydroxychloroquine or chloroquine probably does not reduce invasive mechanical ventilation requirement; RR 1.08 (95%CI 0.93 to 1.25); RD 1.4% (95%CI -1.2% to 4.3%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine probably does not improve time to symptom resolution, RR 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% to 6.1%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine probably not have an important effect on COVID-19 symptomatic infection in exposed individuals, RR 0.85 (95%CI 0.73 to 0.98); RD -2.6% (95%CI -4.6% to -0.4%); Moderate certainty ⊕⊕⊕◯ (Figure 10) (based on low risk of bias studies)
- Hydroxychloroquine or chloroquine may not significantly increase the risk of severe adverse events, RR 0.90 (95%CI 0.66 to 1.22); RD -1% (95%CI -3.5% to 2.2%); Low certainty ⊕⊕◯◯
- Hydroxychloroquine or chloroquine may not have an important effect on hospitalizations in patients with mild COVID-19, RR 0.82 (95%CI 0.61 to 1.1); RD -0.9% (95%CI -1.9% to 0.5%); Low certainty ⊕⊕◯◯

Figure 9. All-cause mortality in RCTs comparing hydroxychloroquine or chloroquine with standard of care in patients with COVID-19

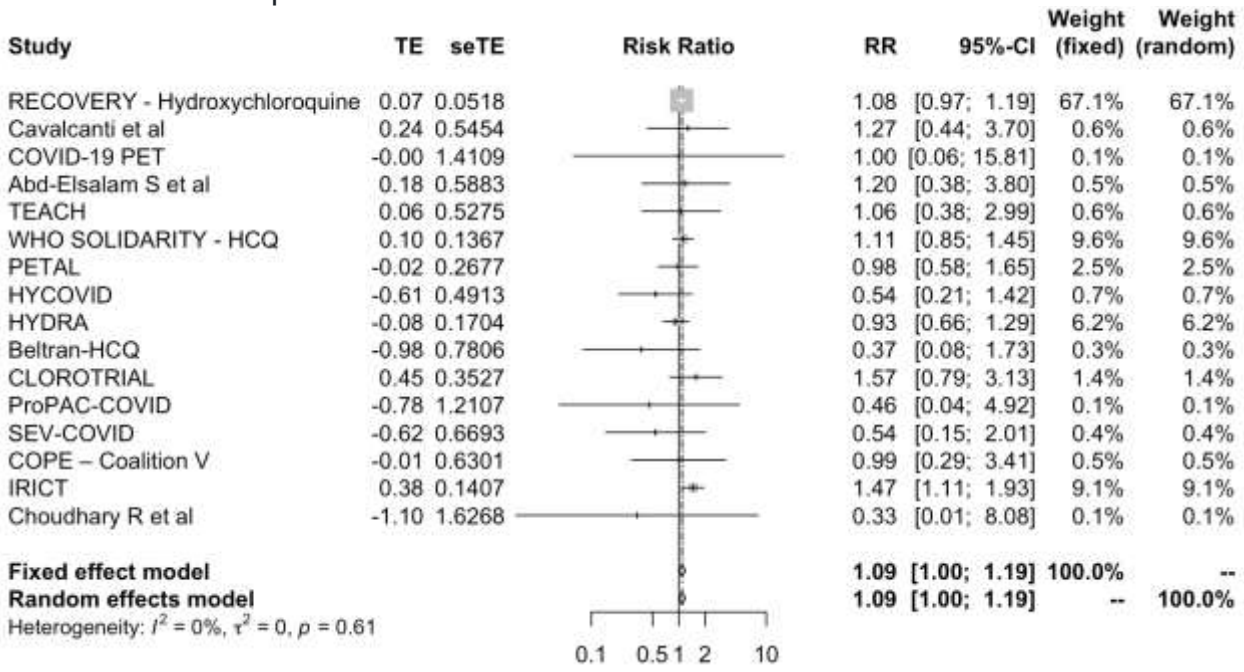
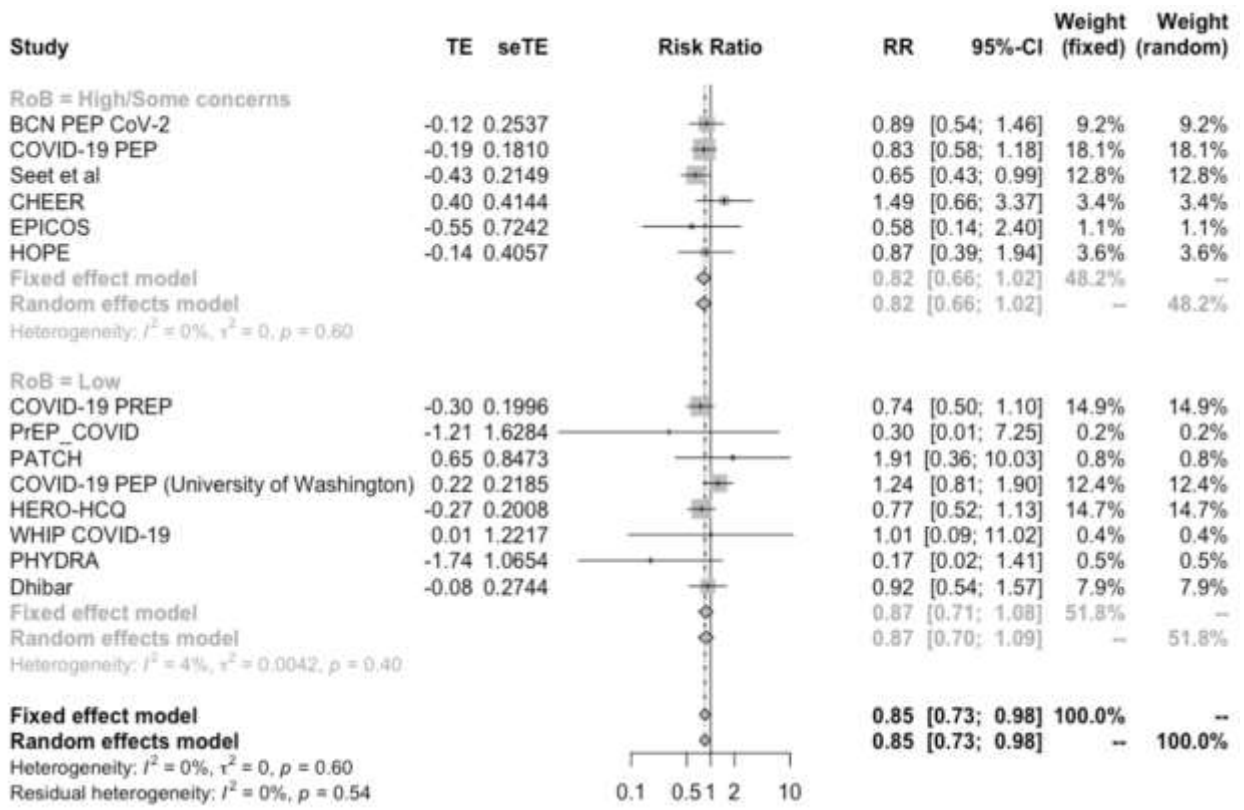


Figure 10. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



In addition, we identified a systematic review[12] that included 12 unpublished studies providing information on mortality outcome. Overall pooled estimates did not differ when including unpublished information (OR 1.08, 95%CI 0.99 to 1.18).

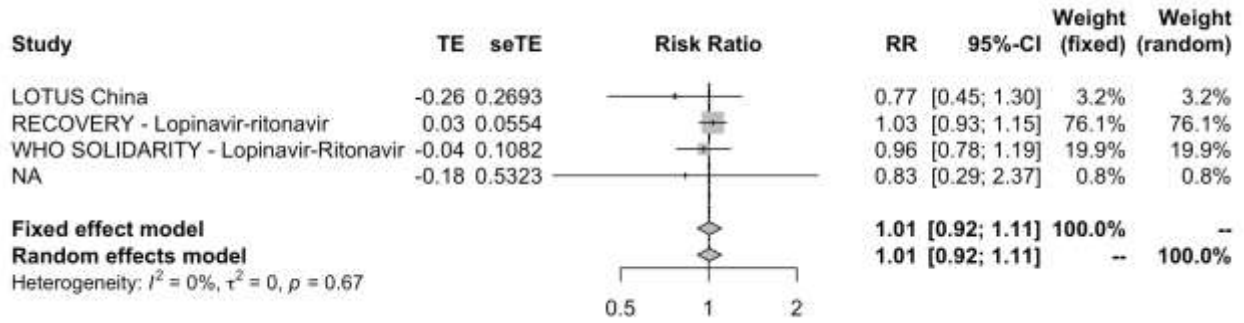
Lopinavir-ritonavir

See Summary of findings Table 4, Appendix 1

We identified 21 RCTs including 10,697 patients in which lopinavir-ritonavir was compared against standard of care or other treatments. The RECOVERY trial was the biggest with 1,616 patients assigned to dexamethasone and 3,424 to standard of care. Three studies provided information on mortality outcome, all of which included patients with severe disease, as shown by the mortality risk in control arms, which ranged from 10.6% to 25%. Our results showed:

- Lopinavir-ritonavir probably does not reduce mortality, RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -1.3% to 1.8%); Moderate certainty ⊕⊕⊕◯ (Figure 11)
- Lopinavir-ritonavir does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕
- Lopinavir-ritonavir probably does not improve symptom resolution or improvement; RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯
- Lopinavir-ritonavir may not increase the risk of severe adverse events, RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -6.5% to -0.2%); Low certainty ⊕⊕◯◯
- It is uncertain if lopinavir-ritonavir increases or decreases symptomatic infections in exposed individuals, RR 1.40 (95%CI 0.78 to 2.54); RD 1.8% (95%CI -3.8% to -26.8%); Very low certainty ⊕◯◯◯
- It is uncertain if lopinavir-ritonavir increases or decreases hospitalizations, RR 1.22 (95%CI 0.61 to 2.47); RD 1.1% (95%CI -1.9% to -7.1%); Very low certainty ⊕◯◯◯

Figure 11. All-cause mortality in RCTs comparing lopinavir–ritonavir with standard of care for treatment of patients with COVID-19



Convalescent plasma

See summary of findings Table 5 in appendix 1

We identified 58 RCTs including 24,753 patients in which convalescent plasma was compared against standard of care or other treatments. RECOVERY was the largest study including 11,588 patients. Most studies (52/58) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 5.5% to 53%. The remaining studies included patients with recent onset symptoms and reported a control-arm mortality rate of 0.4% to 6.6%, or non-infected exposed individuals. Convalescent plasma was administered in one to three infusions to symptomatic patients in all cases. Our results showed:

- Convalescent plasma does not reduce mortality, RR 0.98 (95%CI 0.93 to 1.03); RD -0.3% (95%CI -1.1% to 0.5%); High certainty ⊕⊕⊕⊕ (Figure 12)
- Convalescent plasma does not significantly reduce invasive mechanical ventilation requirements, RR 1.03 (95% CI 0.94 to 1.11); RD 0.5% (95%CI -1% to 1.9%); High certainty ⊕⊕⊕⊕
- Convalescent plasma probably does not improve symptom resolution or improvement, RR 0.99 (95% CI 0.95 to 1.02); RD -0.6% (95%CI -3% to 1.2); High certainty ⊕⊕⊕⊕

- It is uncertain if convalescent plasma reduces symptomatic infections in exposed individuals, RR 0.92 (95% CI 0.32 to 2.62); RD -1.4% (95%CI -11.8% to 28.2); Very low certainty ⊕◯◯◯
- Convalescent plasma may not increase severe adverse events, RR 1.05 (95% CI 0.90 to 1.22); RD 0.5% (95%CI -1% to 2.2%); Low certainty ⊕⊕◯◯
- Convalescent plasma probably has no important effect on hospitalizations, RR 0.77 (95% CI 0.57 to 1.03); RD -1.1% (95%CI -2.1% to 0.1%); Moderate certainty ⊕⊕⊕◯ (Figure 13). The observed effect would probably be considered important in patients with very high hospitalization risk.

Figure 12. All-cause mortality in RCTs comparing convalescent plasma with standard of care for treatment of patients with COVID-19

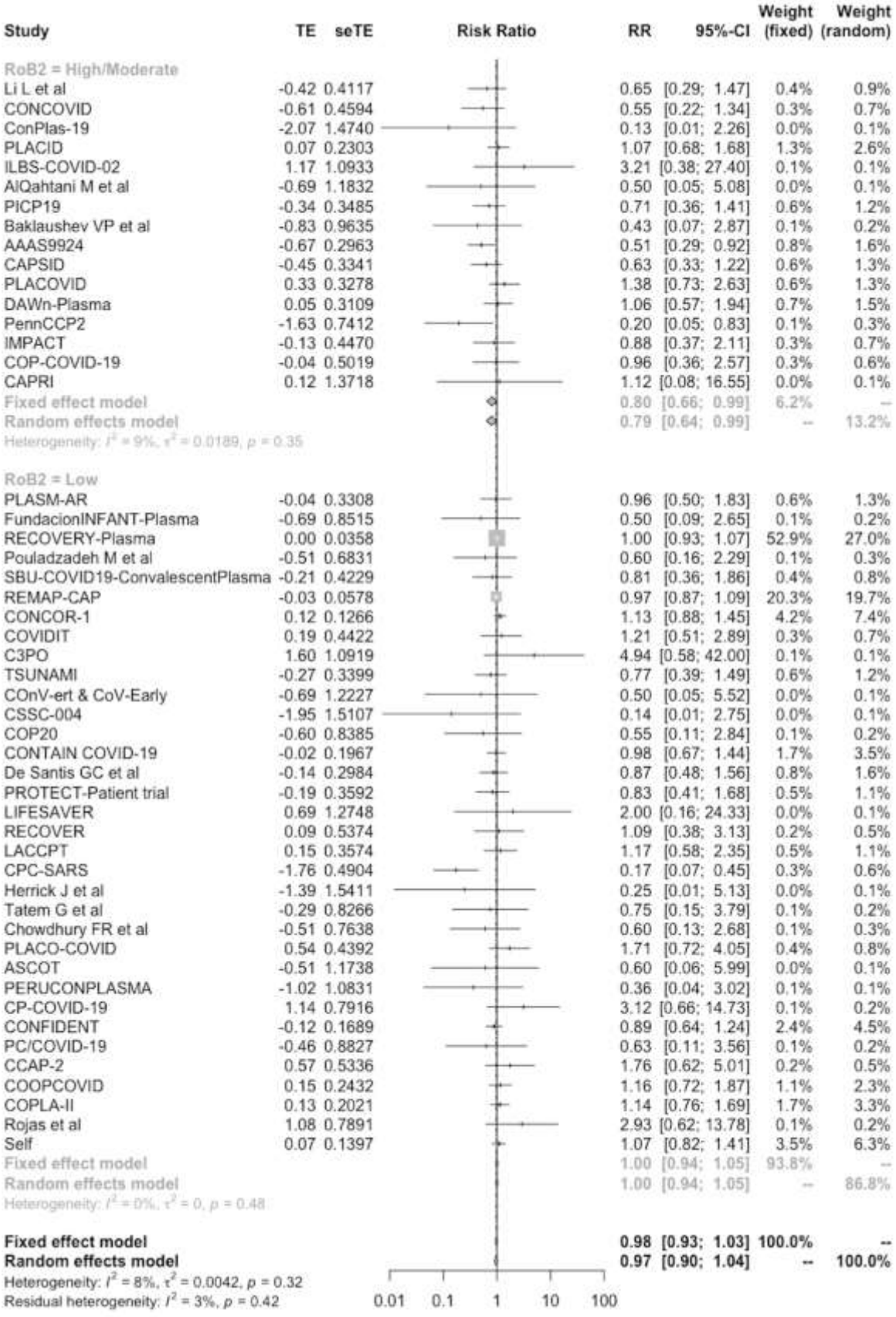
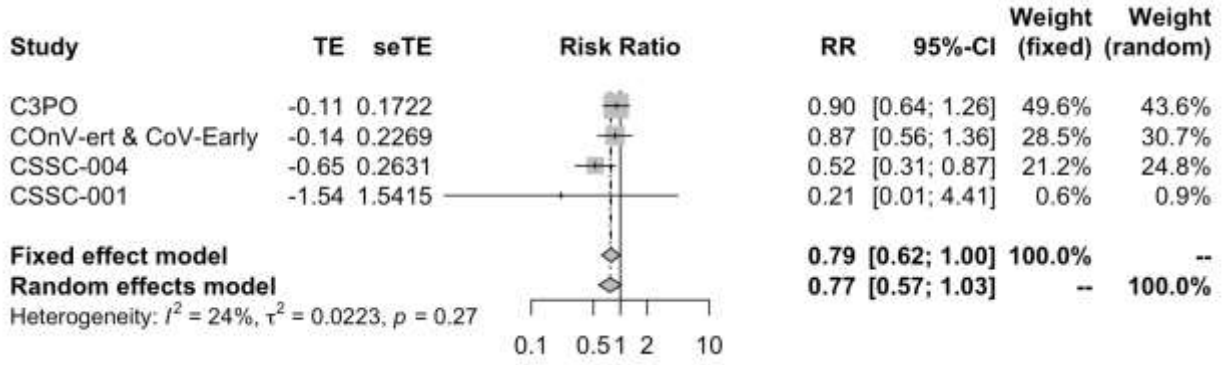


Figure 13. Hospitalizations comparing convalescent plasma with standard of care for treatment of patients with COVID-19



In one of the studies, 58 patients were randomized to early administration of convalescent plasma (at the time they were randomized) or late administration (only if clinical deterioration was observed). All patients in the early arm received the treatment, while just 43.3% of patients received it in the late arm. Results showed no mortality reduction (OR 4.22, 95%CI 0.33 to 53.57) or reduction in the need for invasive mechanical ventilation requirement reduction (OR 2.98, 95%CI 0.41 to 21.57) with early infusion. However, the certainty of the evidence was very low ⊕◯◯◯ because of imprecision. In addition, no significant differences were observed in the subgroup of patients treated early (< 4 days since the beginning of symptoms) versus late (> 4 days since the beginning of symptoms) with convalescent plasma, in the RECOVERY trial.

Tocilizumab

See Summary of findings Table 6 in Appendix 1

We identified 29 RCTs including 9,466 patients in which tocilizumab was compared against standard of care or other interventions. Twenty studies reported on the mortality outcome, including the RECOVERY study that recruited 4,116 patients. All studies

included severe patients, but some excluded critical patients. The proportion of critical patients in those studies that included them was 16.5% to 47.5%. Our results showed:

- Tocilizumab reduces mortality, RR 0.86 (95%CI 0.79 to 93); RD -2.2% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕ (Figure 14)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.84 (95%CI 0.79 to 0.91); RD -2.8% (95%CI -3.6% to -1.6%); High certainty ⊕⊕⊕⊕ (Figure 15)
- Tocilizumab may improve time to symptom resolution, RR 1.08 (95%CI 1.02 to 1.14); RD 4.8% (95%CI 1.2% to 8.5%); Low certainty ⊕⊕◯◯
- Tocilizumab probably does not significantly increase severe adverse events at 28-30 days, RR 0.95 (95%CI 0.87 to 1.04); RD -0.5% (95%CI -1.3% to 0.4%); Moderate certainty ⊕⊕⊕◯

Figure 14. All-cause mortality in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19

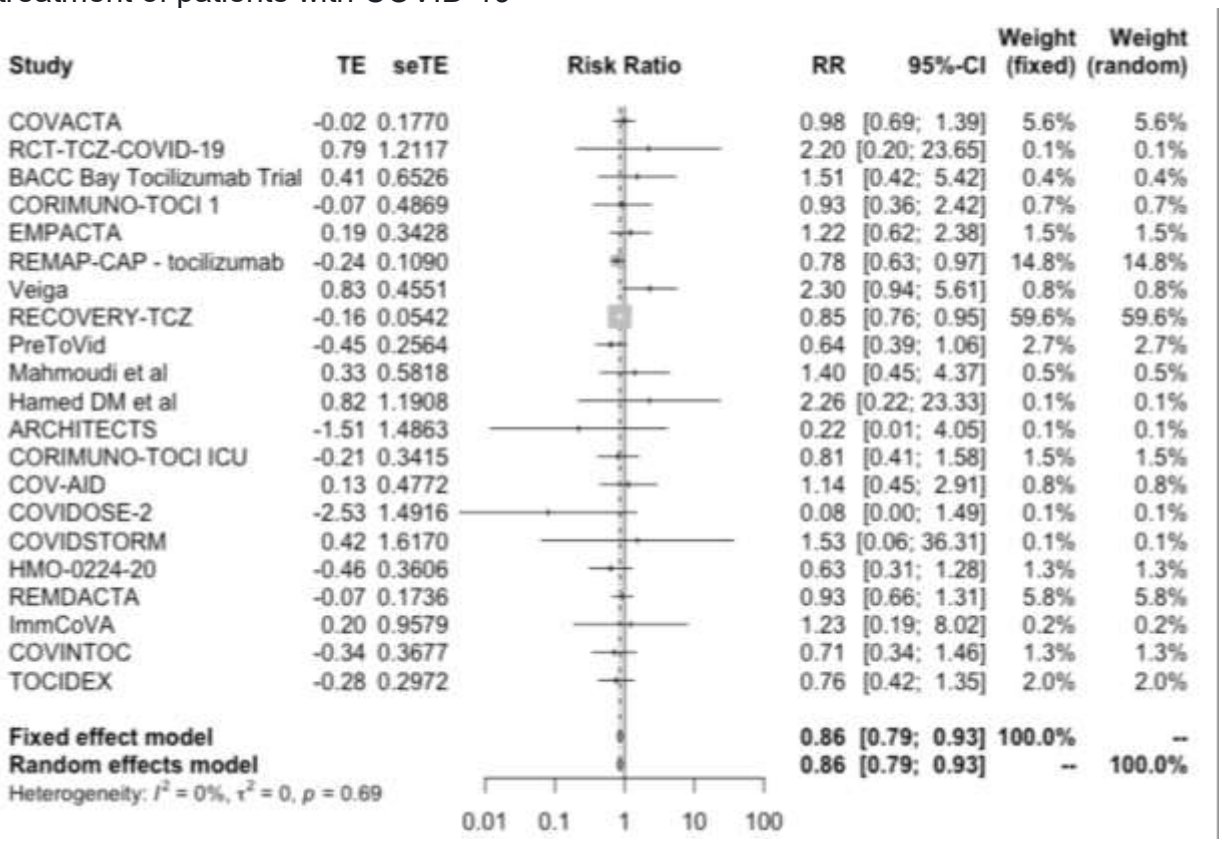
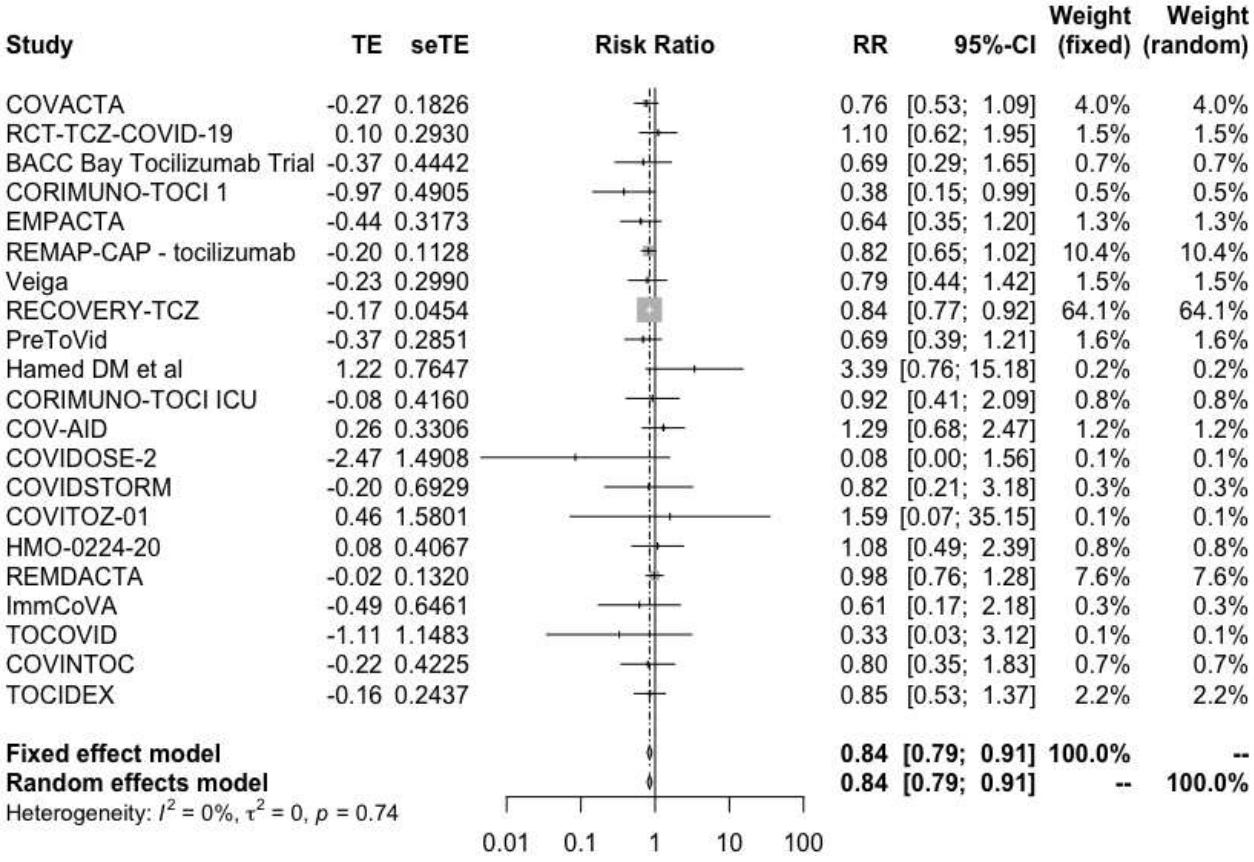


Figure 15. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



A subgroup analysis, performed in the RECOVERY trial, comparing the effect of tocilizumab in severe and critical patients, did not suggest a subgroup modification effect according to baseline disease severity (p=0.52).

In addition, one study that compared standard dose (4 mg/kg) versus high dose (8 mg/kg) found no significant differences and one study that compared baricitinib versus tocilizumab reported no significant differences in mortality or mechanical ventilation. However, the certainty of the evidence was low because of imprecision.

Anticoagulants

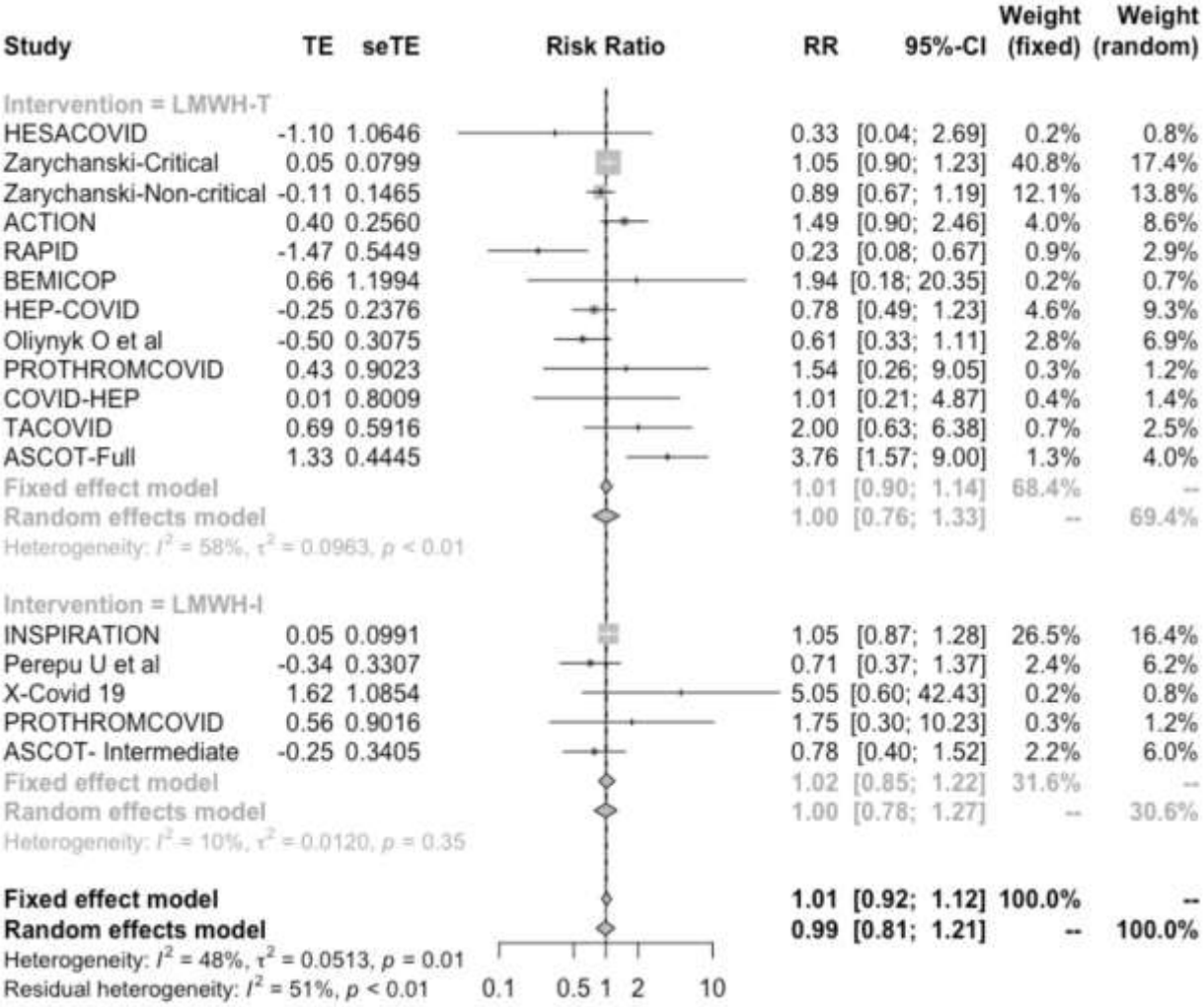
See Summary of findings Table 7, Appendix 1

Thromboembolic complications in patients infected with COVID-19 are relatively frequent.[13] As for hospitalized patients with severe medical conditions, current guidelines recommend thromboprophylaxis measures should be used for inpatients with COVID-19 infection.[14] Regarding the best thromboprophylactic scheme, we identified 22 RCTs including 9,976 patients that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day), or anticoagulants versus standard of care in patients with mild ambulatory disease. In addition, we identified one study that compared rivaroxaban and enoxaparin in hospitalized patients. All studies included hospitalized patients with COVID-19. Our results showed:

- In moderate to critical patients, anticoagulants in intermediate dose or full dose probably does not reduce mortality in comparison with prophylactic dose, RR 0.99 (95%CI 0.81 to 1.21); RD -0.2% (95%CI -3% to 3.4%); Moderate certainty ⊕⊕⊕◯ (Figure 16)
- In moderate to critical patients, anticoagulants in intermediate dose may reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.82 (95%CI 0.46 to 1.46); RD -1.2% (95%CI -3.7% to 3.2%); Low certainty ⊕⊕◯◯
- In moderate to critical patients, anticoagulants in full dose reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.56 (95%CI 0.44 to 0.72); RD -3.1% (95%CI -3.9% to -2%); High certainty ⊕⊕⊕⊕
- In moderate to critical patients, anticoagulants in intermediate dose or full dose increase major bleeding in comparison with prophylactic dose, RR 1.63 (95%CI 1.16 to 2.33); RD 1.2% (95%CI 0.3% to 2.5%); High certainty ⊕⊕⊕⊕

- In mild ambulatory patients, anticoagulants in prophylactic dose may not improve time to symptom resolution, RR 1.08 (95%CI 0.92 to 1.27); RD 4.8% (95%CI -4.8% to 16.4%); Low certainty ⊕⊕◯◯
- In mild ambulatory patients, anticoagulants in prophylactic dose may not reduce hospitalizations, RR 0.94 (95%CI 0.55 to 1.59); RD -0.3% (95%CI -2.2% to 2.8%); Low certainty ⊕⊕◯◯
- In mild ambulatory patients it is uncertain if anticoagulants in prophylactic dose increase or decrease clinically important bleeding and hospitalization; Very low certainty ⊕◯◯◯

Figure 16. All-cause mortality in RCTs using anticoagulants in therapeutic dose, intermediate dose or prophylactic dose for treatment of hospitalized patients with COVID-19



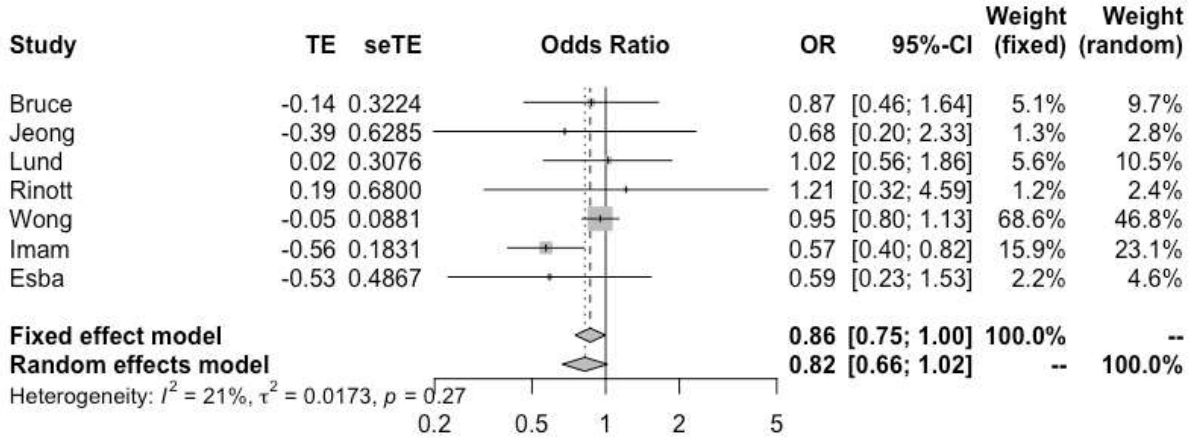
NSAIDs

See Summary of findings Table 8, Appendix 1

We identified seven non-RCTs including at least 100 patients in which COVID-19 mortality risk was compared between groups of patients exposed to NSAIDs and those that were not. Populations varied between studies. For example, Wong et al. included individuals exposed to COVID-19 (living in a region affected by the pandemic) while other studies included only patients with confirmed COVID-19 infection. Our results showed:

- No association between NSAID exposure and mortality, OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕◯◯◯ (Figure 17)

Figure 17. All-cause mortality in non-RCTs comparing exposure to NSAIDs with no exposure in individuals exposed to or infected with COVID-19



Interferon Beta-1a

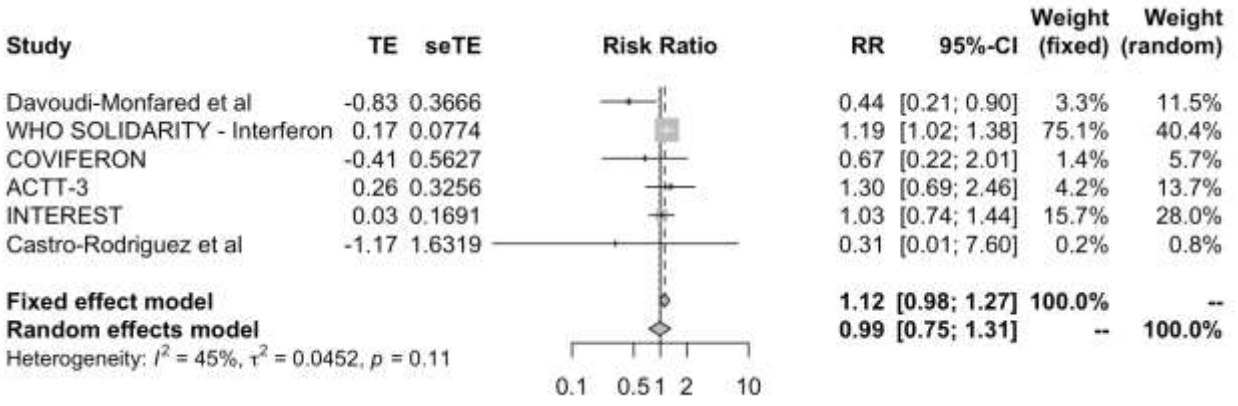
See Summary of findings Table 9, Appendix 1

We identified seven RCTs including 7,017 patients in which interferon beta-1a was compared against standard of care or other treatments and informed on mortality outcome. The WHO SOLIDARITY trial was the biggest, with 2,144 patients assigned to

intervention and 2,147 to control. The studies included severe patients, as shown by the fact that mortality in the control arms ranged from 10.5% to 45%. Our results showed:

- Interferon beta-1a (subcutaneous) probably does not reduce mortality, RR 0.99 (95%CI 0.75 to 1.31); RD -0.2% (95%CI -4% to 5%); Moderate certainty ⊕⊕⊕◯ (Figure 18)
- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 1.01 (95%CI 0.87 to 1.18); RD 0.2% (95%CI -2.2% to 3.1%); Moderate certainty ⊕⊕⊕◯
- Interferon beta-1a (subcutaneous) probably does not increase symptom resolution or improvement; RR 0.96 (95%CI 0.92 to 0.99); RD -2.6% (95%CI -4.8% to -3.2%); Moderate certainty ⊕⊕⊕◯
- Interferon beta-1a probably does not increase severe adverse events, RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕◯
- Interferon beta-1a (inhaled) may improve time to symptom resolution, HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯

Figure 18. All-cause mortality with IFN beta-1a vs. standard of care in randomized studies including COVID-19 patients



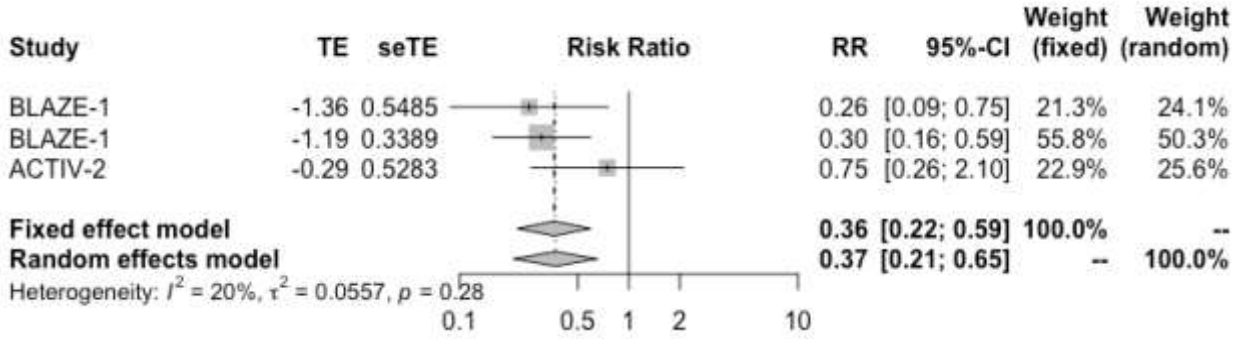
Bamlanivimab +/- etesevimab (monoclonal antibody)

See Summary of findings Table 10, Appendix 1

We identified nine RCTs including 5,939 patients in which bamlanivimab was compared against standard of care or other treatments. Eight studies included patients with mild to moderate COVID-19 and one included exposed individuals and assessed bamlanivimab as a prophylactic intervention. Our results showed:

- It is uncertain if bamlanivimab reduces mortality or mechanical ventilation requirements; RR 0.68 (95%CI 0.17 to 2.8); RD -5.1% (95%CI -13.2% to 2.8%); Very low certainty ⊕◯◯◯
- Bamlanivimab probably does not significantly improve time to symptom resolution, RR 1.02 (95%CI 0.99 to 1.06); RD 1.2% (95%CI 3.6% to 5.4%); Moderate certainty ⊕⊕⊕◯
- Bamlanivimab probably decreases symptomatic infection in exposed individuals, RR 0.56 (95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Moderate certainty ⊕⊕⊕◯
- Bamlanivimab may not increase severe adverse events; RR 1.12 (95%CI 0.75 to 1.66); RD 1.2% (95%CI -2.5% to -6.7%); Low certainty ⊕⊕◯◯
- Bamlanivimab probably reduces hospitalizations in patients with non-severe disease; RR 0.37 (95%CI 0.21 to 0.65); RD -3% (95%CI -3.8% to -1.7%); Moderate certainty ⊕⊕⊕◯ (Figure 19)

Figure 19. Hospitalizations with bamanivimab vs. standard of care in randomized studies including COVID-19 patients



In addition, one study that compared bamlanivimab +/- etesevimab against REGEN-COV (casirivimab and imdevimab) in non-severe patients with risk factors for severity reported no important differences in hospitalizations.

Favipiravir

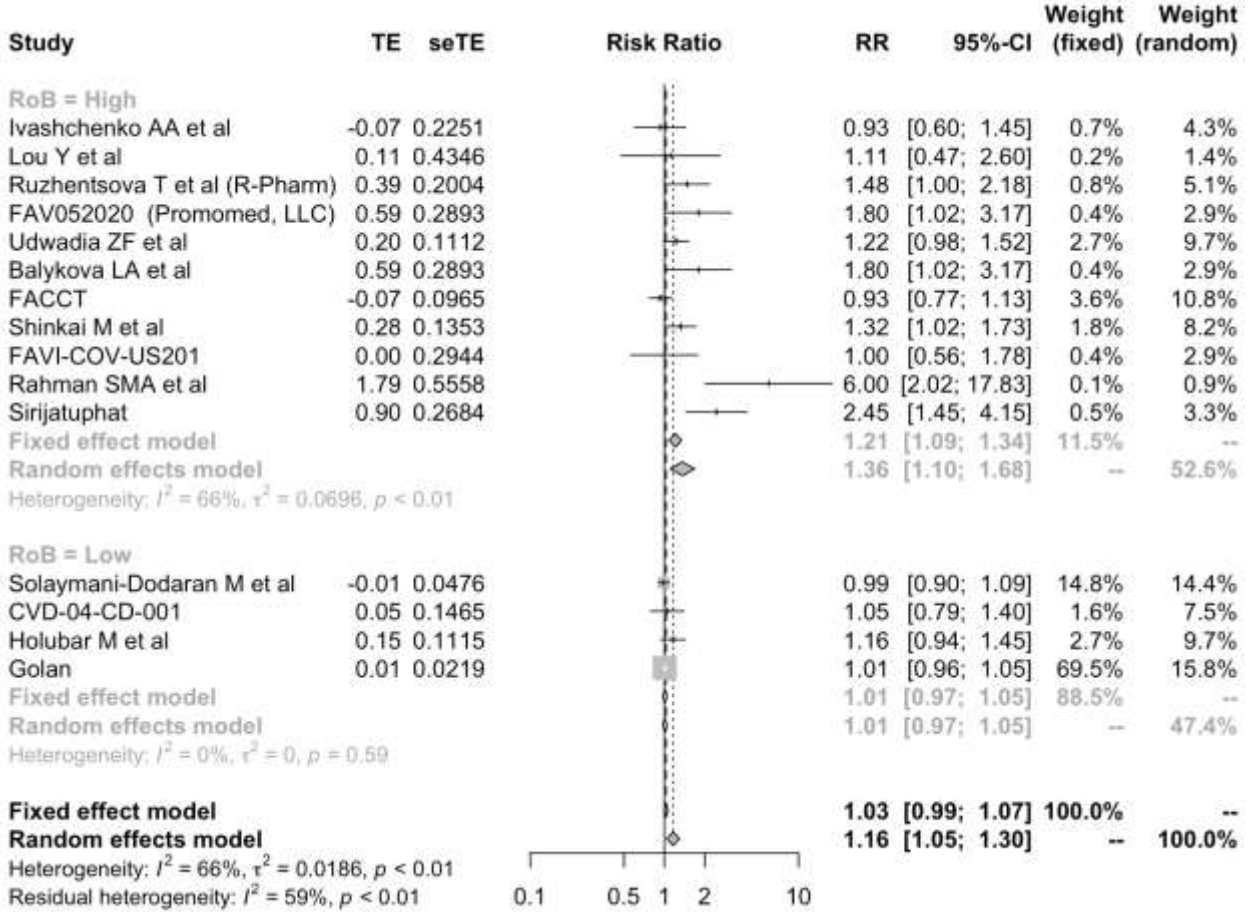
See Summary of findings Table 11, Appendix 1

We identified 29 RCTs including 4,624 patients in which favipiravir was compared against standard of care or other treatments. Seventeen studies reported on favipiravir with or without HCQ versus standard of care, two studies reported on favipiravir vs HCQ or CQ, two study reported on favipiravir vs lopinavir ritonavir and the remaining studies compared favipiravir against other active interventions. As there is moderate to high certainty that HCQ and lopinavir-ritonavir are not related to significant benefits, we assumed those interventions as equivalent to standard of care. Our results showed:

- Favipiravir may increase mortality; RR 1.08 (95%CI 0.77 to 1.52); RD 1.3% (95%CI -3.7% to 8.3%); Low certainty ⊕⊕◯◯
- Favipiravir may increase mechanical ventilation requirements; RR 1.27 (95%CI 0.91 to 1.76); RD 4.7% (95%CI -1.6% to 13.1%); Low certainty ⊕⊕◯◯
- Favipiravir probably does not increase symptom resolution or improvement, RR 1.01 (95%CI 0.97 to 1.05); RD 0.6% (95%CI -1.8% to 3%); High certainty ⊕⊕⊕⊕ (Figure 20) (based on low risk of bias studies)

- It is uncertain if favipiravir increases the risk of severe adverse events; RR 0.92 (95%CI 0.56 to 1.52); RD -0.8% (95%CI -4.5% to 5.3%); Very low certainty ⊕○○○
- Favipiravir may not reduce hospitalizations in patients with non-severe disease; RR 1.33 (95%CI 0.64 to 1.78); RD 1.6% (95%CI -1.7% to 3.7); Low certainty ⊕⊕○○

Figure 20. Symptom resolution at 7-28 days in randomized studies comparing favipiravir with standard of care in patient with COVID-19



Ivermectin

See Summary of findings Table 12, Appendix 1

We identified 49 RCTs including 13,326 patients in which ivermectin was compared against standard of care or other treatments. Studies included patients with mild to severe disease, as shown by the mortality rates in the control arms, which ranged from 0% to 42%. Most studies did not report on clinical important outcomes and most of the ones that did have important methodological limitations including inappropriate randomization process and lack or unclear report of allocation concealment. Our results showed:

- Ivermectin probably does not reduce mortality, RR 1 (95%CI 0.8 to 1.24); RD -0% (95%CI -3.2% to 3.8%); Moderate certainty ⊕⊕⊕◯ (Figure 21) (based on low risk of bias studies)
- It is uncertain if ivermectin affects mechanical ventilation, RR 0.82 (95%CI 0.58 to 1.17); RD -3.1% (95%CI -7.3% to 2.9%); Very low certainty ⊕◯◯◯ (based on low risk of bias studies)
- Ivermectin probably does not improve symptom resolution or improvement, RR 1.04 (95%CI 0.98 to 1.1); RD 2.4% (95%CI -1.2% to 6%); Moderate certainty ⊕⊕⊕◯ (Figure 22) (based on low risk of bias studies).
- It is uncertain if ivermectin affects symptomatic infection, RR 1.01 (95%CI 0.54 to 1.89); RD 0.2% (95%CI -8% to 15.5%); Very low certainty ⊕◯◯◯ (based on low risk of bias studies)
- Ivermectin may not increase severe adverse events, RR 1.05 (95%CI 0.69 to 1.62); RD 0.5% (95%CI -3.2% to 6.3%); Low certainty ⊕⊕◯◯
- Ivermectin probably does not have an important effect on hospitalizations in patients with recent onset non-severe disease, RR 0.90 (95%CI 0.74 to 1.1); RD -0.5% (95%CI -1.2% to 0.5%); Moderate certainty ⊕⊕⊕◯ (based on low risk of bias studies). The observed effect would probably be considered important in patients with very high hospitalization risk (>10%).

Figure 21. Mortality in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19

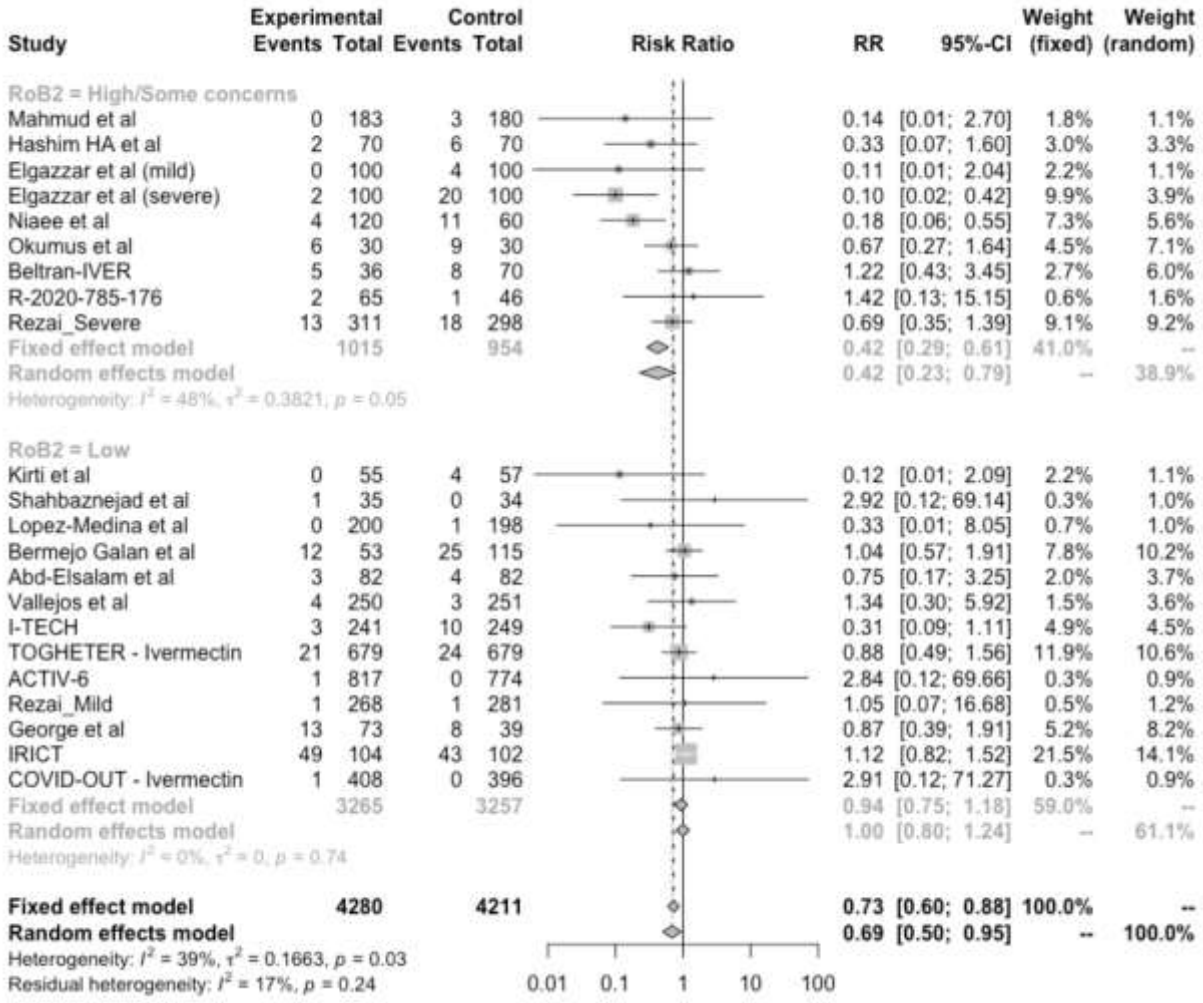
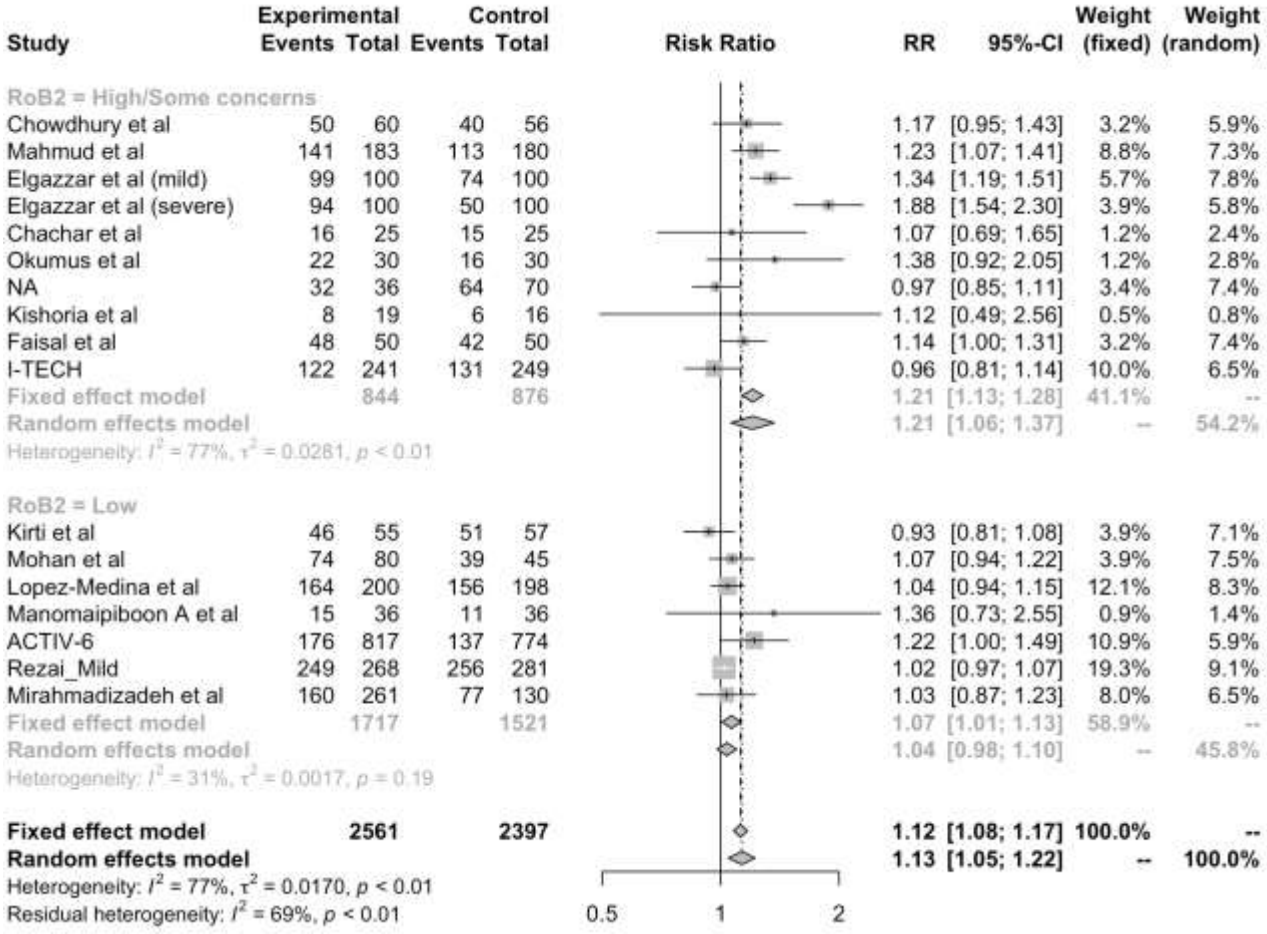


Figure 22. Symptom resolution or improvement in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



Although pooled estimates suggest significant benefits with ivermectin for some critical outcomes, these are mainly driven by studies with important methodological limitations. Furthermore, results of the studies classified as low risk of bias significantly differ from those classified as high risk of bias which results in significant uncertainty about ivermectin effects. Further research is needed to confirm or discard those findings.

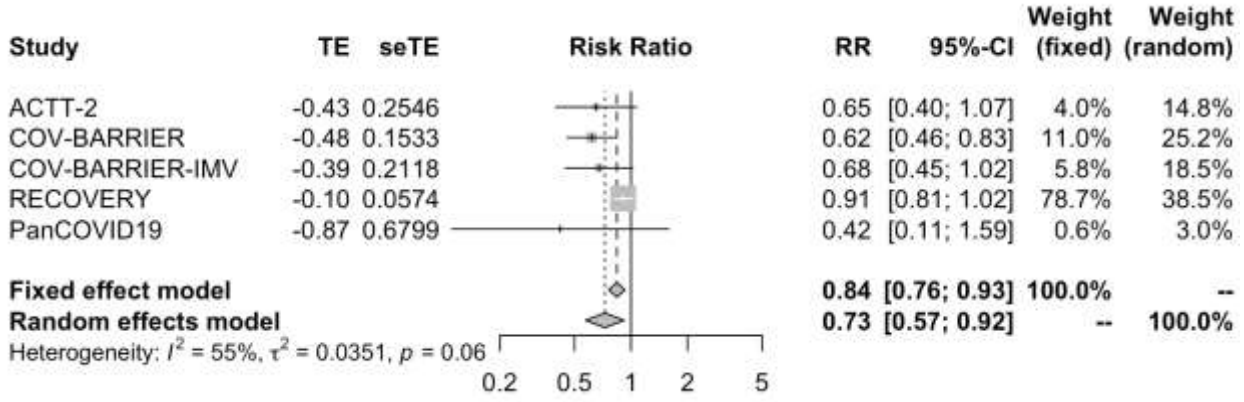
Baricitinib

See Summary of findings Table 13, Appendix 1

We identified seven RCTs including 12,363 patients in which baricitinib was compared against standard of care or other treatments. All studies included moderate to severe hospitalized patients. Critical patients were excluded. Our results showed:

- Baricitinib reduces mortality, RR 0.73 (95%CI 0.57 to 0.92); RD -4.3% (95%CI -6.9% to -1.3%); High certainty ⊕⊕⊕⊕ (Figure 23)
- Baricitinib probably reduces mechanical ventilation, RR 0.83 (95%CI 0.66 to 1.04); RD -2.9% (95%CI -5.9% to 0.7%); Moderate certainty ⊕⊕⊕◯
- Baricitinib probably improves time to symptom resolution, RR 1.27 (95%CI 1.13 to 1.42); RD 16.4% (95%CI 7.9% to 25.5%); Moderate certainty ⊕⊕⊕◯
- Baricitinib probably does not increase severe adverse events, RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⊕⊕⊕◯

Figure 23. Mortality in randomized studies comparing baricitinib with standard of care in patients with COVID-19



In addition one study that compared baricitinib versus tocilizumab reported no significant differences in mortality or mechanical ventilation. However, the certainty of the evidence was low because of imprecision.

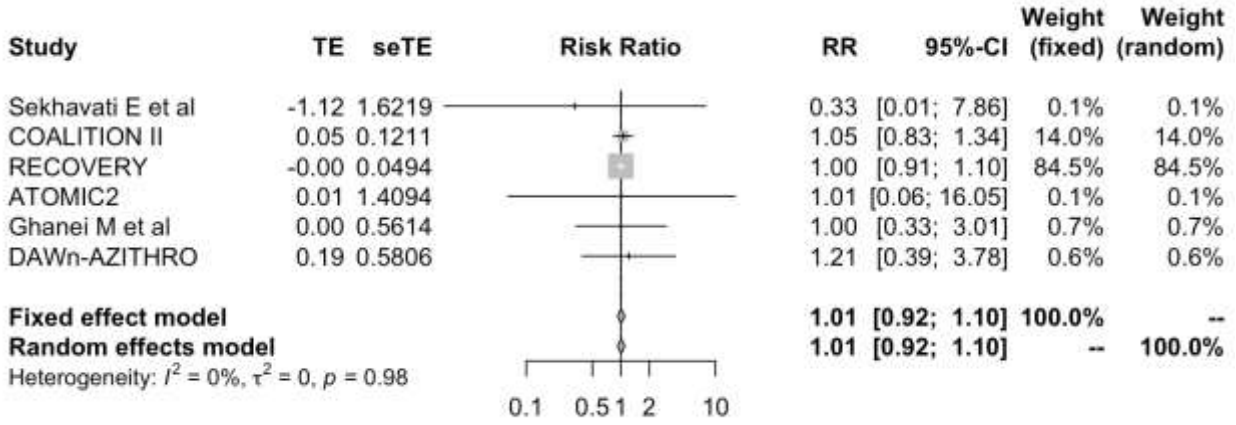
Azithromycin

See Summary of findings Table 14, Appendix 1

We identified 11 RCTs including 10,612 patients in which azithromycin was compared against standard of care or other treatments. RECOVERY trial was the biggest study including 7,762 patients with severe disease (mortality in the control arm 19%). Our results showed:

- Azithromycin probably does not reduce mortality, RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ (Figure 24)
- Azithromycin probably does not reduce mechanical ventilation requirements, RR 0.92 (95%CI 0.77 to 1.1); RD -1.4% (95%CI -4% to 1.7%); Moderate certainty ⊕⊕⊕◯
- Azithromycin does not improve time to symptom resolution, RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕
- It is uncertain if azithromycin increases severe adverse events, RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯
- Azithromycin may not reduce hospitalizations, RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -2.3% to 4.1%); Low certainty ⊕⊕◯◯

Figure 24. Mortality in randomized studies comparing azithromycin with standard of care in patients with COVID-19

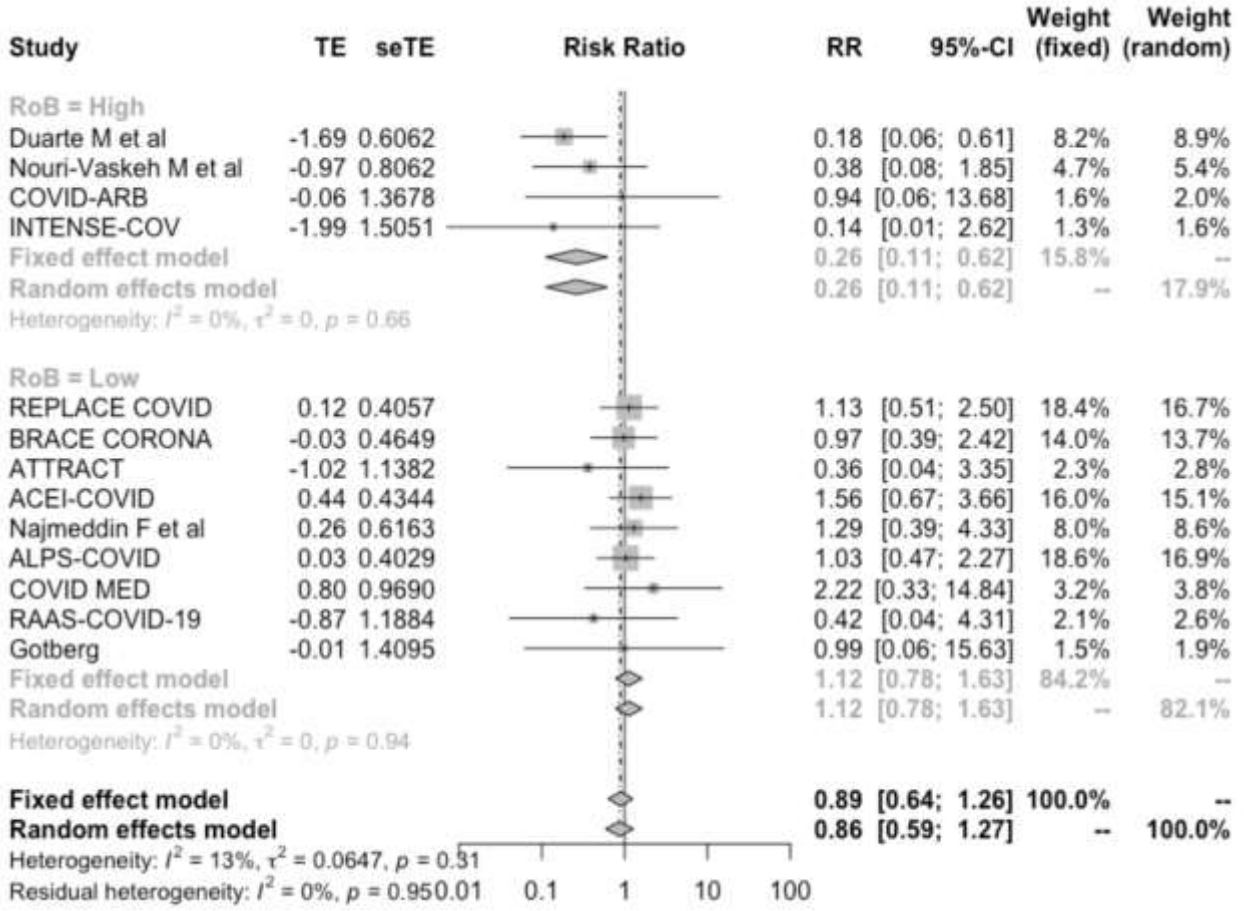


ACEI/ARB initiation or continuation

We identified 14 RCTs including 2,308 patients in which patients with COVID-19 were randomized to initiate or continue ACEI/ARB treatment and compared to standard of care or discontinue ACEI/ARB. Our results showed:

- ACEI/ARB initiation or continuation may increase mortality, RR 1.12 (95%CI 0.78 to 1.63); RD 1.9% (95%CI -3.5% to 10.1%); Low certainty ⊕⊕◯◯ (Figure 25) (based on low risk of bias studies)
- ACEI/ARB discontinuation may reduce mechanical ventilation requirements, RR 0.99 (95%CI 0.75 to 1.29); RD -0.2% (95%CI -4.3% to 5%); Low certainty ⊕⊕◯◯

Figure 25. Mortality in randomized studies comparing initiation or continuation vs standard of care o discontinuation of ACEI/ARB in patients with COVID-19



Colchicine

See Summary of findings Table 15, Appendix 1

We identified 16 RCTs including 18,757 patients in which colchicine was compared against standard of care or other treatments. The COLCORONA trial was the biggest including mild ambulatory patients, with 2,235 patients assigned to intervention and 2,253 to control, and the RECOVERY trial was the biggest including moderate to critical hospitalized patients, with 5,610 patients assigned to intervention and 5,730 assigned to control. Our results showed:

- Colchicine probably does not reduce mortality, RR 0.99 (95%CI 0.92 to 1.06); RD -0.2% (95%CI -1.3% to 1%); Moderate certainty ⊕⊕⊕◯ (Figure 26)
- Colchicine probably does not reduce mechanical ventilation requirements, RR 0.98 (95%CI 0.89 to 1.07); RD -0.3% (95%CI -1.9% to 1.2%); Moderate certainty ⊕⊕⊕◯ (Figure 27)
- Colchicine does not increase symptom resolution or improvement, RR 1 (95%CI 0.98 to 1.02); RD 0% (95%CI -1.2% to 1.2%); High certainty ⊕⊕⊕⊕
- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕
- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕◯◯◯
- Colchicine probably has no important effect on hospitalizations in patients with recent onset disease, RR 0.81 (95%CI 0.63 to 1.04); RD -0.9% (95%CI -1.8% to 0.2%); Moderate certainty ⊕⊕⊕◯

Figure 26. Mortality in randomized studies comparing colchicine vs standard of care in patients with COVID-19

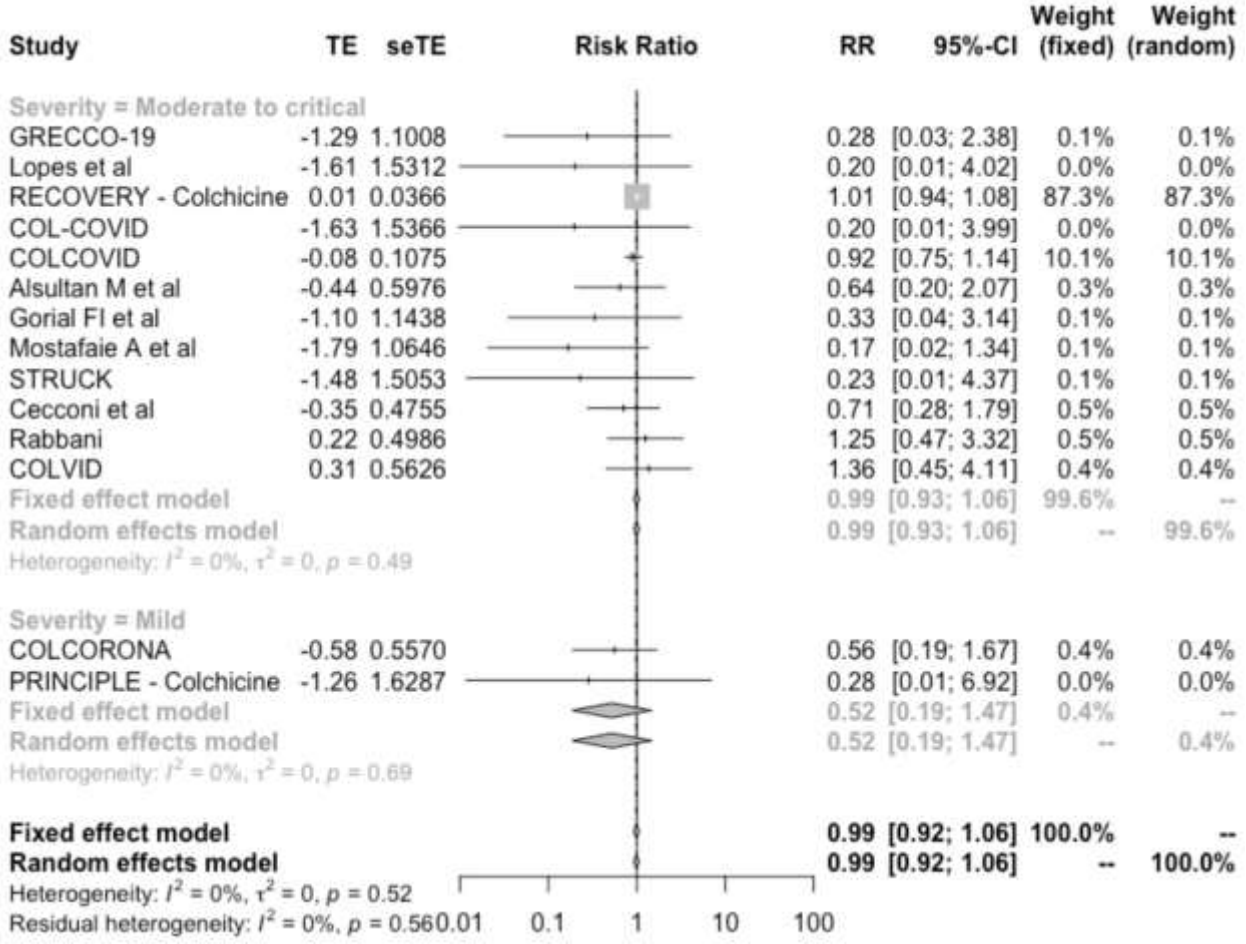
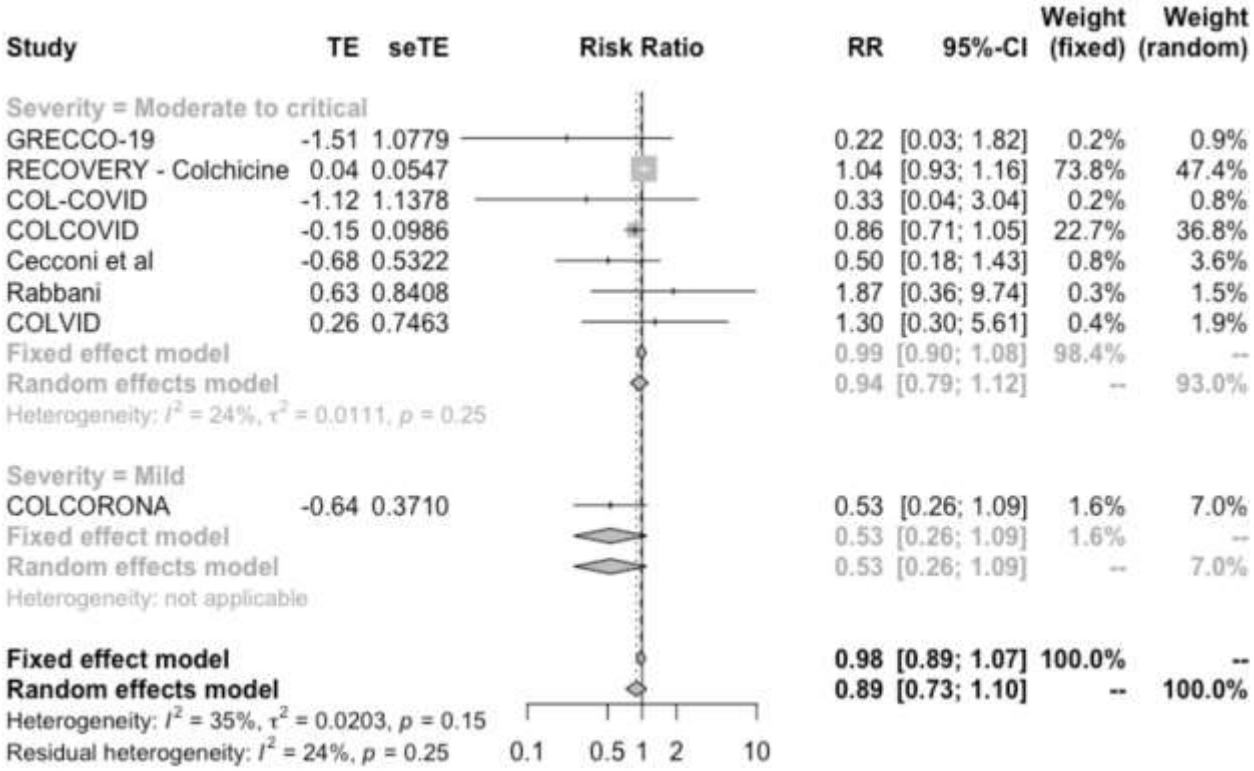


Figure 27. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



Observed results apply mostly to hospitalized patients with moderate to critical disease. The COLCORONA trial that included patients with recent onset mild disease showed a tendency to less hospitalizations, less mortality and less mechanical ventilation requirements. However, the certainty on those potential benefits was low because of very serious imprecision because of a small number of events.

Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir

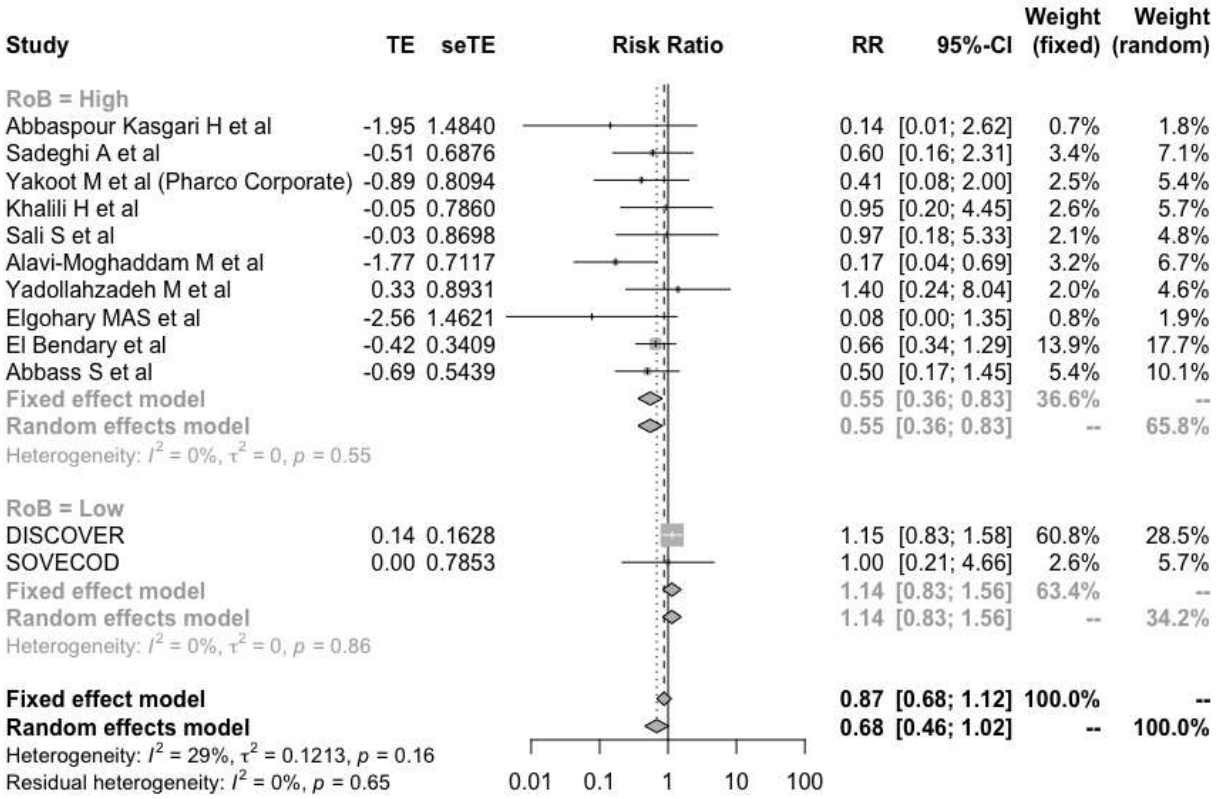
See Summary of findings Table 16, Appendix 1

We identified 16 RCTs including 3,061 patients in which sofosbuvir alone or in combination with daclatasvir or ledipasvir was compared against standard of care or other treatments. Two studies compared sofosbuvir alone vs. standard of care, one study compared sofosbuvir alone vs. lopinavir-ritonavir, seven studies compared sofosbuvir +

daclatasvir vs. standard of care, three studies compared sofosbuvir + daclatasvir vs. lopinavir-ritonavir, and three studies compared sofosbuvir + ledipasvir vs. standard of care. As there is moderate to high certainty that lopinavir-ritonavir is not related to significant benefits, we assumed that intervention as equivalent to standard of care. The DISCOVER trial was the biggest, with 1,083 patients and the only one categorized as with low risk of bias. Studies included patients with mild to severe disease. Our results showed:

- Sofosbuvir +/- daclatasvir or ledipasvir may increase mortality, RR 1.14 (95%CI 0.83 to 1.56); RD 2.2% (95%CI -2.7% to 9%); Low certainty ⊕⊕◯◯ (Figure 28) (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mechanical ventilation requirements, RR 1.02 (95%CI 0.59 to 1.76); RD 0.3% (95%CI -7.1% to 13.1%); Low certainty ⊕⊕◯◯ (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir probably does not improve time to symptom resolution, RR 1.01 (95%CI 0.95 to 1.08); RD 0.6% (95%CI -3% to 4.8%); Moderate certainty ⊕⊕⊕◯ (based on low risk of bias studies)
- It is uncertain if sofosbuvir +/- daclatasvir or ledipasvir affects symptomatic infections in exposed individuals, RR 0.52 (95%CI 0.30 to 0.89); RD -8.3% (95%CI -12.1% to -1.9%); Very low certainty ⊕◯◯◯
- It is uncertain if sofosbuvir +/- daclatasvir or ledipasvir increases severe adverse events, RR 0.35 (95%CI 0.06 to 2.19); RD -6.6% (95%CI -9.6% to 12.1%); Very low certainty ⊕◯◯◯

Figure 28. Mortality in randomized studies comparing sofosbuvir +/- daclatasvir or ledipasvir vs standard of care in patients with COVID-19



REGEN-COV (casirivimab and imdevimab)

See Summary of findings Table 17, Appendix 1

We identified 12 RCTs including 25,207 patients in which REGEN-COV (casirivimab and imdevimab) was compared against standard of care, or other treatments, in patients with recent onset COVID-19. The RECOVERY trial was the biggest, included severe to critical patients and reported differential effect in seronegative patients at baseline. Eight of the other nine studies included mild patients with recent onset disease or exposed individuals with negative PCR. Our results showed:

- Overall REGEN-COV may decrease mortality, RR 0.83 (95%CI 0.63 to 1.09); RD -2.7% (95%CI -5.9% to 1.4%); Low certainty ⊕⊕◯◯
- In seronegative patients REGEN-COV probably decreases mortality, RR 0.79 (95%CI 0.71 to 0.89); RD -3.4% (95%CI -4.6% to -1.8%); Moderate certainty ⊕⊕⊕◯ (Figure 29)
- Overall REGEN-COV may decrease mechanical ventilation, RR 0.79 (95%CI 0.54 to 1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕◯◯
- In seronegative patients REGEN-COV probably reduces mechanical ventilation, RR 0.82 (95%CI 0.74 to 0.9); RD -3.1% (95%CI -4.5% to -1.7%); Moderate certainty ⊕⊕⊕◯
- Overall REGEN-COV may increase symptom resolution, RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕⊕◯
- In seronegative patients REGEN-COV probably increases symptom resolution, RR 1.1 (95%CI 1.06 to 1.14); RD 6% (95%CI 3.6% to 8.5%); Moderate certainty ⊕⊕⊕◯
- REGEN-COV reduces symptomatic infections in exposed individuals, RR 0.24 (95%CI 0.08 to 0.76); RD -13.2% (95%CI -16% to -4.2%); High certainty ⊕⊕⊕⊕
- REGEN-COV probably does not increase severe adverse events, RR 0.51 (95%CI 0.38 to 0.67); RD -5% (95%CI -6.3% to -3.4%); Moderate certainty ⊕⊕⊕◯
- REGEN-COV probably reduces hospitalization, RR 0.28 (95%CI 0.19 to 0.42); RD -3.5% (95%CI -3.9% to -2.8%); Moderate certainty ⊕⊕⊕◯ (Figure 30)

Figure 29. Mortality in randomized studies comparing REGEN-COV vs standard of care in seronegative patients with COVID-19

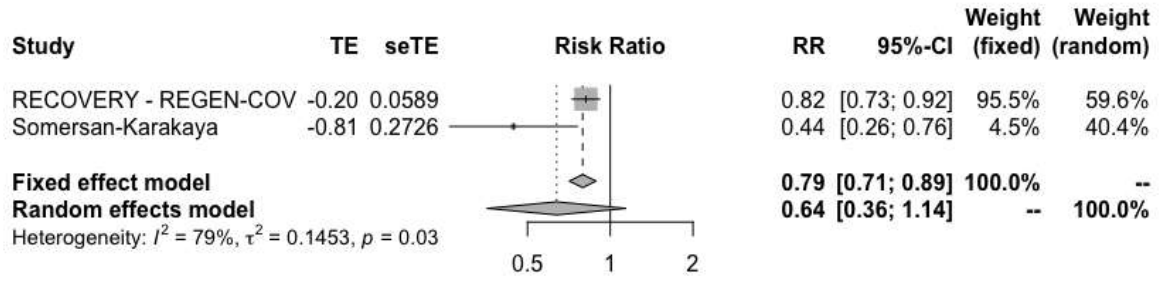
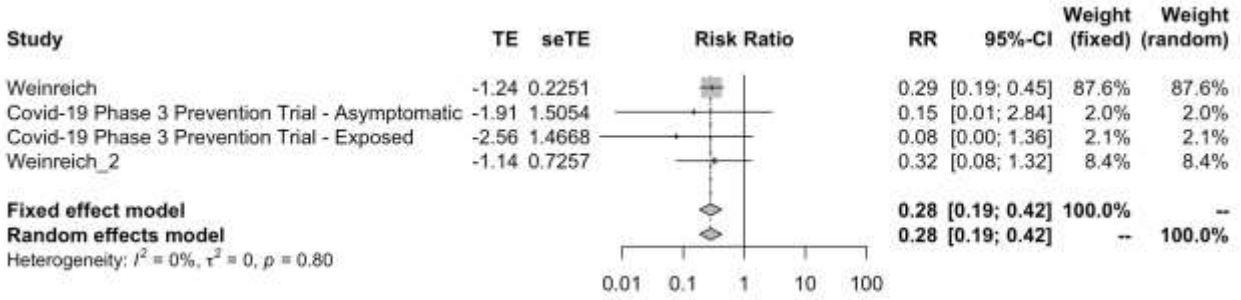


Figure 30. Hospitalization in randomized studies comparing REGEN-COV vs standard of care in patients with COVID-19



In addition, two studies that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab and sotrovimab in non-severe patients with risk factors for severity reported no important differences in hospitalizations.

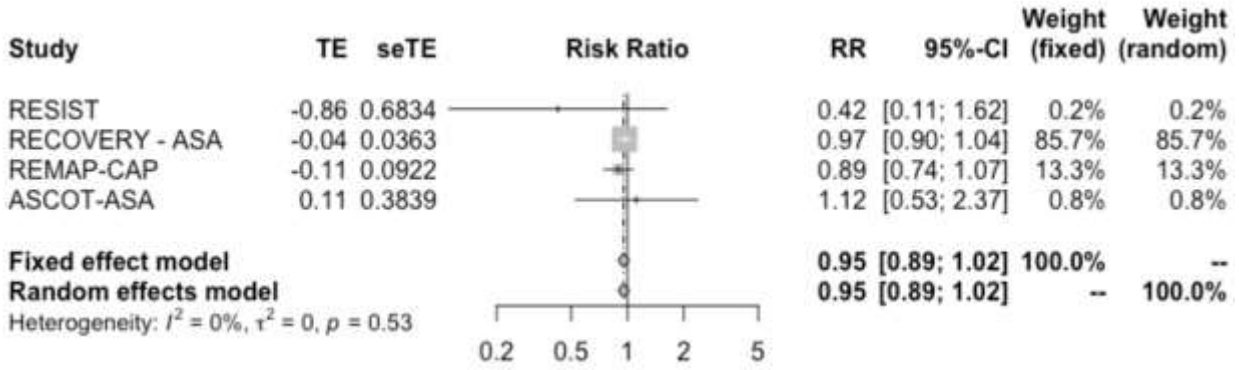
Aspirin

We identified five RCTs including 17,573 patients in which aspirin was compared against standard of care in patients with COVID-19. Our results showed:

- Aspirin probably does not reduce mortality, RR 0.95 (95%CI 0.89 to 1.02); RD -0.8% (95%CI -1.8% to 0.3; Moderate certainty ⊕⊕⊕◯ (Figure 31)
- Aspirin probably does not reduce mechanical ventilation, RR 0.95 (95%CI 0.87 to 1.04); RD -0.9% (95%CI -2.2% to 0.7); Moderate certainty ⊕⊕⊕◯

- Aspirin probably does not increase symptom resolution or improvement, RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕◯

Figure 31. Mortality in randomized studies comparing aspirin vs standard of care in patients with COVID-19



Sotrovimab

See Summary of findings Table 18, Appendix 1

We identified three RCTs including 4,934 patients with recent onset mild COVID-19 and risk factors for severe disease, in which sotrovimab was compared against standard of care or other interventions. Our results showed:

- Sotrovimab probably reduces hospitalizations, RR 0.20 (95%CI 0.08 to 0.48); RD -3.8% (95%CI -4.6% to -2.5%); Moderate certainty ⊕⊕⊕◯ (certainty upgraded because of evidence of equipoise of sotrovimab and REGEN-COV)
- Severe adverse events, RR 0.34 (95%CI 0.16 to 0.68); RD -6.7% (95%CI -8.6% to -3.3%); Moderate certainty ⊕⊕⊕◯

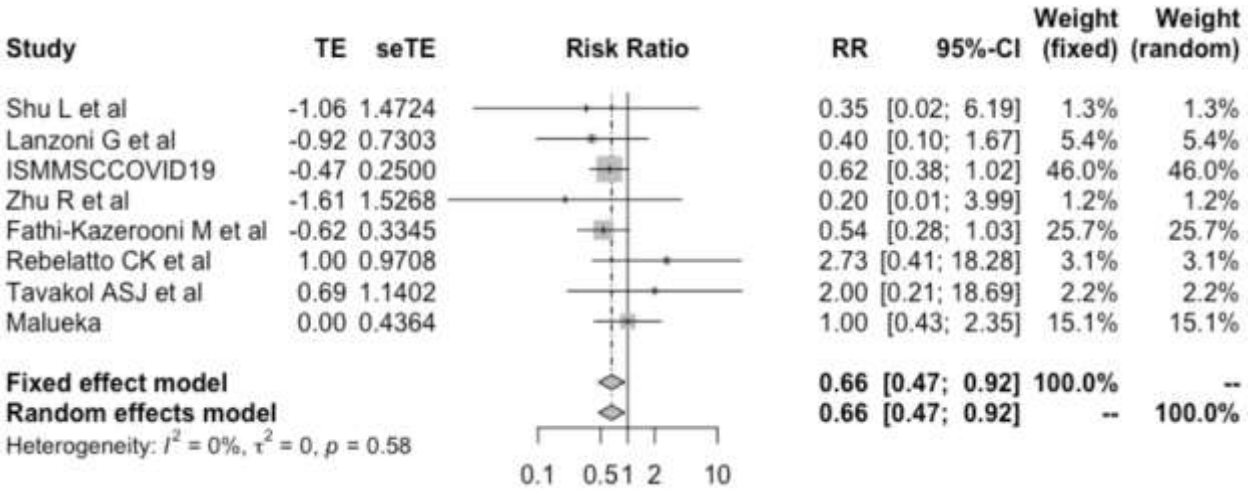
One study that compared REGEN-COV and sotrovimab in mild to moderate patients showed similar hospitalization rates (RR 0.93 95%CI, 0.77 to 1.13)

Mesenchymal stem-cell transplantation

We identified ten RCTs including 380 patients with severe to critical COVID-19, in which mesenchymal stem-cell transplantation was compared against standard of care. Our results showed:

- Mesenchymal stem-cell transplantation may reduce mortality, RR 0.66 (95%CI 0.47 to 0.92); RD -5.4% (95%CI -8.5% to -1.3%); Low certainty ⊕⊕◯◯ (Figure 32)

Figure 32. Mortality in randomized studies comparing mesenchymal stem-cell transplantation vs standard of care in patients with COVID-19

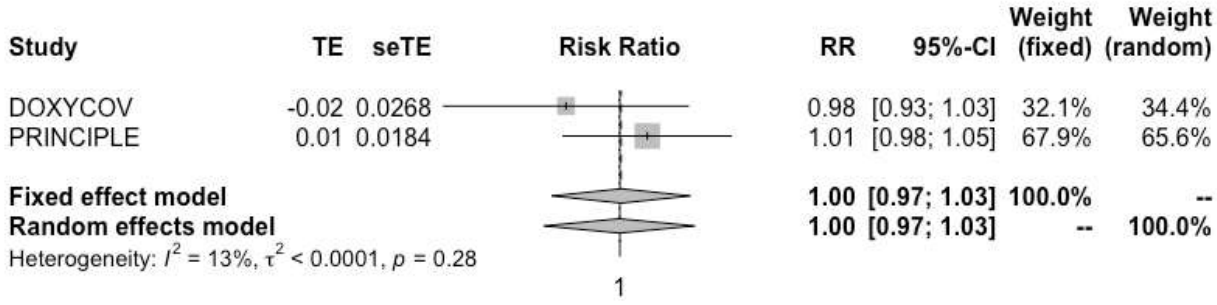


Doxycycline

We identified four RCTs including 2,415 patients with mild COVID-19, in which doxycycline was compared against standard of care. Our results showed:

- It is uncertain if doxycycline reduce or increase mortality, RR 1.10 (95%CI 0.63 to 1.93); RD 1.6% (95%CI -5.9% to 14.9%); Very low certainty ⊕○○○
- Doxycycline does not increase symptom resolution or improvement, RR 1 (95%CI 0.97 to 1.03); RD -0% (95%CI -91.8% to -1.8%); High certainty ⊕⊕⊕⊕ (Figure 33)
- Doxycycline may not reduce hospitalizations, RR 1.16 (95%CI 0.76 to 1.76); RD 0.7% (95%CI -1.1% to 3.6%); Low certainty ⊕⊕○○

Figure 33. Symptom resolution or improvement in randomized studies comparing doxycycline vs standard of care in patients with COVID-19



Inhaled corticosteroids

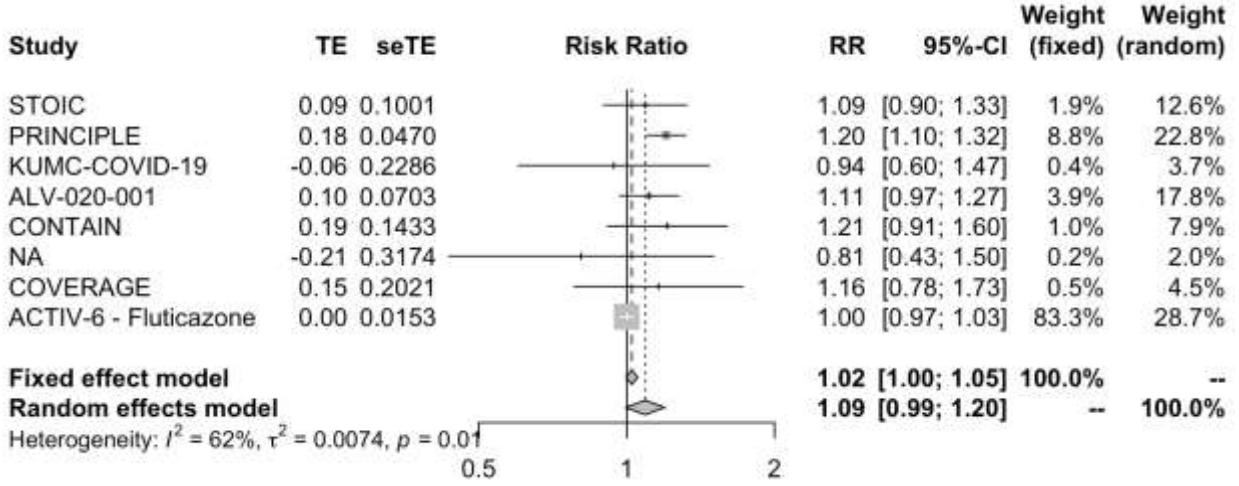
See Summary of findings Table 19, Appendix 1

We identified nine RCTs including 4,309 patients with mild COVID-19, in which inhaled coticosteroids were compared against standard of care. Our results showed:

- It is uncertain if inhaled corticosteroids reduce or increase mortality, RR 0.82 (95%CI 0.44 to 1.53); RD -2.8% (95%CI -9% to 8.5%); Very low certainty ⊕○○○

- It is uncertain if inhaled corticosteroids reduce or increase mechanical ventilation, RR 0.94 (95%CI 0.44 to 1.98); RD -1% (95%CI -9.6% to 17%); Very low certainty ⊕◯◯◯
- Inhaled corticosteroids probably increase symptom resolution or improvement, RR 1.09 (95%CI 0.99 to 1.2); RD 5.5% (95%CI -0.6% to 12.1%); Low certainty ⊕⊕◯◯ (Figure 34)
- Inhaled corticosteroids probably does not have an important effect on hospitalizations, RR 0.9 (95%CI 0.7 to 1.15); RD -0.5% (95%CI -1.4% to 0.7%); Moderate certainty ⊕⊕⊕◯
- It is uncertain if inhaled corticosteroids reduce or increase severe adverse events, RR 0.5 (95%CI 0.23 to 1.12); RD -5.1% (95%CI -7.9% to 1.2%); Very low certainty ⊕◯◯◯

Figure 34. Symptom resolution or improvement in randomized studies comparing inhaled corticosteroids vs standard of care in patients with COVID-19



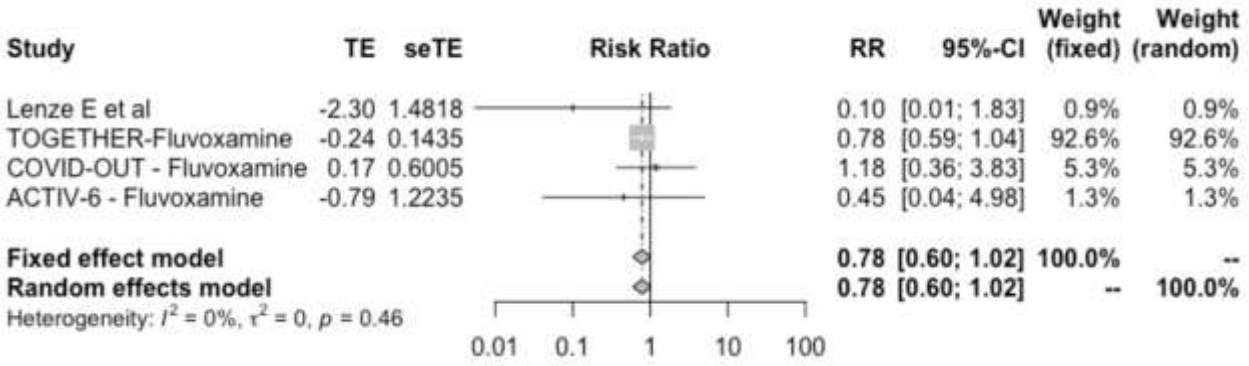
Fluvoxamine

See Summary of findings Table 20, Appendix 1

We identified five RCTs including 3,617 patients with COVID-19, in which fluvoxamine was compared against standard of care. Our results showed:

- It is uncertain if fluvoxamine reduces or increase mortality, RR 0.69 (95%CI 0.36 to 1.27); RD -5% (95%CI -10.2% to 4.3%); Very low certainty ⊕◯◯◯
- It is uncertain if fluvoxamine reduces or increase mechanical ventilation, RR 0.77 (95%CI 0.45 to 1.3); RD -3.7% (95%CI -8.8% to 4.8%); Very low certainty ⊕◯◯◯
- Fluvoxamine does not increase symptom resolution, RR 0.99 (95%CI 0.96 to 1.02); RD -0.7% (95%CI -2.6% to 1.2%); High certainty ⊕⊕⊕⊕
- Fluvoxamine probably does not have an important effect on hospitalizations in patients with recent onset disease, RR 0.78 (95%CI 0.6 to 1.02); RD -1.1% (95%CI -1.9% to 0.1%); Moderate certainty ⊕⊕⊕◯ (Figure 35). The observed effect would probably be considered important in patients with very high hospitalization risk.
- Fluvoxamine may not increase severe adverse events, RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕◯◯

Figure 35. Hospitalizations in randomized studies comparing fluvoxamine vs standard of care in patients with COVID-19



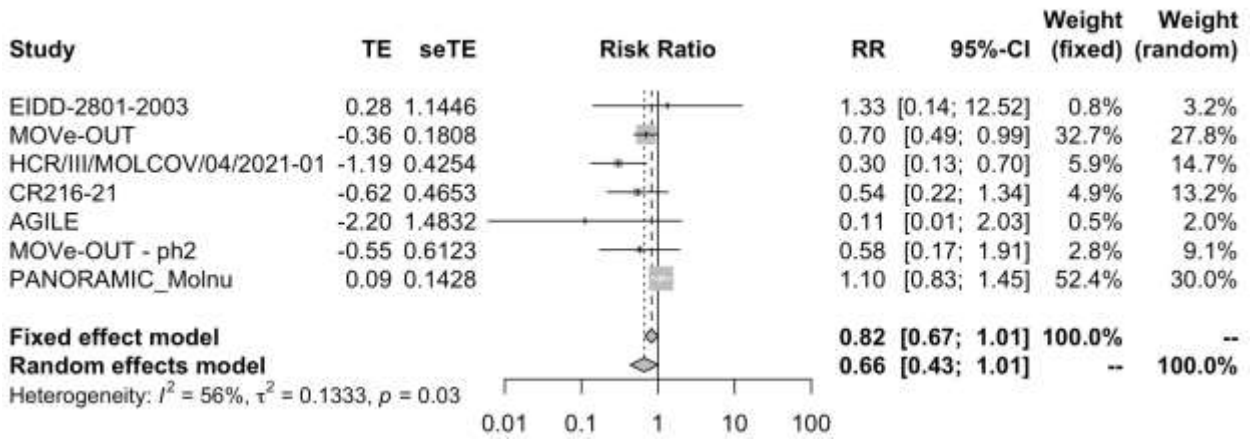
Molnupiravir

See Summary of findings Table 21, Appendix 1

We identified eleven RCTs including 29,532 patients with COVID-19, in which molnupiravir was compared against standard of care. Our results showed:

- It is uncertain if molnupiravir reduces or increase mortality, RR 0.38 (95%CI 0.11 to 1.35); RD -9.9% (95%CI -14.2% to 5.6%); Very low certainty ⊕◯◯◯
- It is uncertain if molnupiravir reduces or mechanical ventilation, RR 0.36 (95%CI 0.11 to 1.12); RD -11.1% (95%CI -15.4% to 2.1%); Very low certainty ⊕◯◯◯
- Molnupiravir probably has no important effect on hospitalizations in patients with recent onset disease, RR 0.66 (95%CI 0.43 to 1.01); RD -1.6% (95%CI -2.7% to 0%); Moderate certainty ⊕⊕⊕◯ (Figure 36)
- Molnupiravir probably increases symptom resolution, RR 1.88 (95%CI 1.2 to 2.9); RD 39.4% (95%CI 12.1% to 39.4%); Low certainty ⊕⊕◯◯
- Molnupiravir may not increase severe adverse events, RR 0.75 (95%CI 0.48 to 1.19); RD -2.6% (95%CI -5.3% to -1.9%); Low certainty ⊕⊕◯◯

Figure 36. Hospitalizations in randomized studies comparing molnupiravir vs standard of care in patients with COVID-19



Nirmatrelvir-ribavirin

See Summary of findings Table 22, Appendix 1

We identified one RCT including 2,085 patients with COVID-19, in which nirmatrelvir-ritonavir was compared against standard of care. Our results showed:

- It is uncertain if nirmatrelvir-ritonavir reduces or increase mortality, RR 0.04 (95%CI 0.002 to 0.68); RD -15.3% (95%CI -15.9% to -5.1%); Very low certainty ⊕◯◯◯
- Nirmatrelvir-ritonavir probably reduces hospitalizations in patients with recent onset disease, RR 0.12 (95%CI 0.06 to 0.25); RD -5.2% (95%CI -7.1% to -2%); Moderate certainty ⊕⊕⊕◯
- Nirmatrelvir-ritonavir probably does not increase severe adverse events, RR 0.49 (95%CI 0.30 to 0.80); RD -5.2% (95%CI -7.8% to 0.5%); Moderate certainty ⊕⊕⊕◯

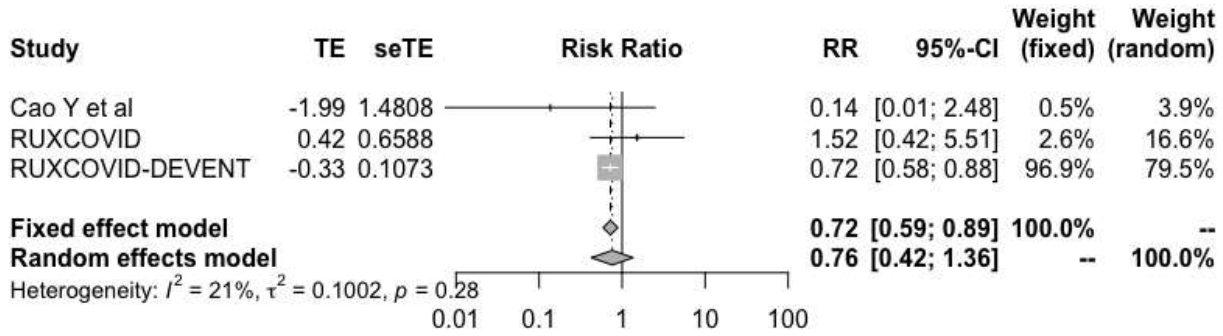
Ruxolitinib

See Summary of findings Table 23, Appendix 1

We identified three RCTs including 686 patients with COVID-19, in which ruxolitinib was compared against standard of care. RUXOCOVID-DEVENT was the biggest trial including 211 patients with critical COVID-19. Our results showed:

- Ruxolitinb may reduce mortality, RR 0.72 (95%CI 0.59 to 0.89); RD -4.5% (95%CI -6.5% to -1.7%); Low certainty ⊕⊕◯◯ (Figure 37)
- It is uncertain if ruxolitinib increases or decreses mechanical ventilation, RR 0.99 (95%CI 0.49 to 1.99); RD -0.1% (95%CI -8.8% to 17.%); Very low certainty ⊕◯◯◯
- Ruxolitinib may not improve time to symptom resolution, RR 1.05 (95%CI 0.89 to 1.24); RD 3% (95%CI -6.7% to 14.5%); Low certainty ⊕⊕◯◯
- It is uncertain if ruxolitinib increses or decreases severe adverse events, RR 1.12 (95%CI 0.69 to 1.82); RD 1.2% (95%CI -3.7% to 8.4%); Very low certainty ⊕◯◯◯

Figure 37. Mortality in randomized studies comparing ruxolitinib vs standard of care in patients with COVID-19



CD24Fc

See Summary of findings Table 24, Appendix 1

We identified one RCT including 234 patients with COVID-19, in which CD24Fc was compared against standard of care. Our results showed:

- It is uncertain if CD24Fc reduces or increases mortality, RR 0.9 (95%CI 0.49 to 1.69); RD -1.5% (95%CI -8.2% to 11%); Very low certainty ⊕◯◯◯
- CD24Fc may decrease mechanical ventilation, RR 0.57 (95%CI 0.34 to 0.96); RD -7.4% (95%CI -11.4% to -0.7%); Low certainty ⊕⊕◯◯
- CD24Fc may increase symptom resolution, RR 1.18 (95%CI 1 to 1.39); RD 10.7% (95%CI -0.2% to 23.4%); Low certainty ⊕⊕◯◯

- It is uncertain if CD24Fc increases or decreases severe adverse events, RR 0.98 (95%CI 0.61 to 1.57); RD -0.2% (95%CI -4% to 5.8%); Very low certainty ⊕◯◯◯

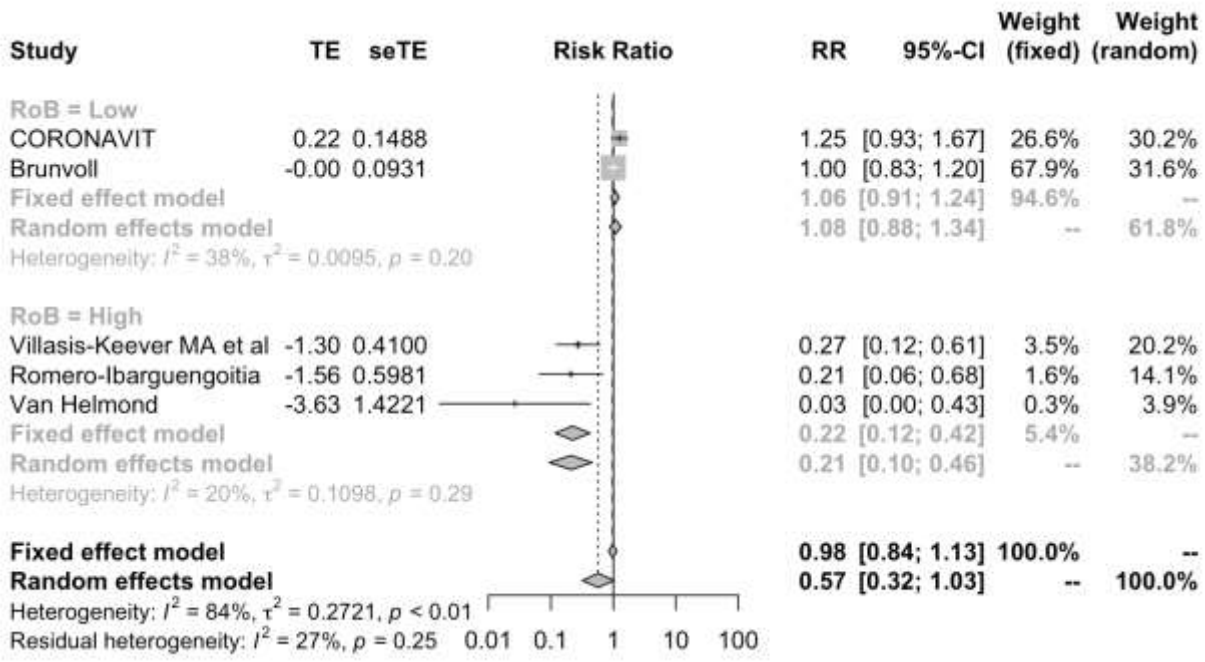
Vitamin D

See Summary of findings Table 25, Appendix 1

We identified 20 RCTs including 44,071 patients with COVID-19, in which Vitamin D was compared against standard of care or other treatments. Our results showed:

- It is uncertain if vitamin D reduces or increases mortality, RR 1.24 (95%CI 0.8 to 1.91); RD 3.8% (95%CI -3.2% to 14.4%); Very low certainty ⊕◯◯◯
- It is uncertain if vitamin D reduces or increases mechanical ventilation, RR 0.5 (95%CI 0.25 to 1); RD -8.6% (95%CI -13% to 0%); Very low certainty ⊕◯◯◯
- It is uncertain if vitamin D reduces or increases symptom resolution or improvement, RR 1.78 (95%CI 1.1 to 2.94); RD 39.4.6% (95%CI 4.6% to 39.4%); Very low certainty ⊕◯◯◯
- Vitamin D does not reduce symptomatic infections in exposed individuals, RR 1.06 (95%CI 0.91 to 1.24); RD 1% (95%CI -1.6% to 4.2%); High certainty ⊕⊕⊕⊕ (excluding high risk of bias studies) (Figure 38)
- Vitamin D probably does not reduce hospitalizations, RR 1.26 (95%CI 0.84 to 1.89); RD 1.2% (95%CI -0.8% to 4.3%); Moderate certainty ⊕⊕⊕◯
- Vitamin D may not increase severe adverse events, RR 1.03 (95%CI 0.84 to 1.26); RD 0.3% (95%CI -1.6% to 2.7%); Low certainty ⊕⊕◯◯

Figure 38. Symptomatic infections in randomized studies comparing vitamin D vs standard of care in persons exposed to COVID-19



In addition one study that compared high dose vitamin D supplementation (cholecalciferol 400,000 IU) versus standard dose (cholecalciferol 50,000 IU) reported no significant differences in mortality at 28 days (HR 0.7 95%CI 0.36 to 1.36) in patients hospitalized for COVID-19.

Tixagevimab–Cilgavimab

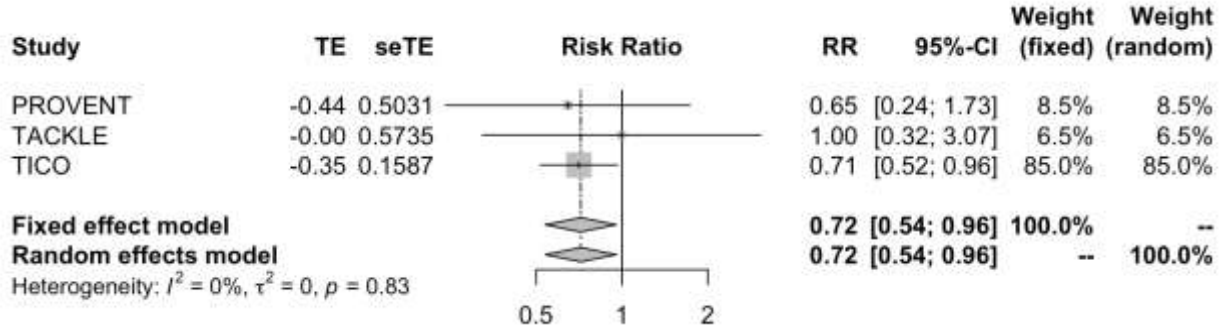
See Summary of findings Table 26, Appendix 1

We identified three RCT including 7,492 individuals with COVID-19 or exposed to SARS-COV-2, in which Tixagevimab–cilgavimab was compared against standard of care. Our results showed:

- Tixagevimab–cilgavimab probably reduces mortality, RR 0.72 (95%CI 0.54 to 0.96); RD -4.5% (95%CI -7.4% to -0.6%); Moderate certainty ⊕⊕⊕◯ (Figure 39)

- Tixagevimab–cilgavimab probably does not increase symptom resolution or improvement, RR 1.03 (95%CI 0.99 to 1.08); RD 2% (95%CI -0.6% to 4.7%); Moderate certainty ⊕⊕⊕◯
- Tixagevimab–cilgavimab probably reduces symptomatic infections in exposed individuals, RR 0.18 (95%CI 0.09 to 0.35); RD -14.2% (95%CI -15.8% to -11.2%); Moderate certainty ⊕⊕⊕◯
- Tixagevimab–cilgavimab may not increase severe adverse events, RR 0.95 (95%CI 0.69 to 1.31); RD -0.5% (95%CI -3.2% to 3.2%); Low certainty ⊕⊕◯◯
- Tixagevimab–cilgavimab probably reduces mortality, RR 0.42 (95%CI 0.24 to 0.74); RD -2.8% (95%CI -3.6% to 1.3%); Moderate certainty ⊕⊕⊕◯

Figure 39. Mortality in randomized studies comparing Tixagevimab–cilgavimab vs standard of care in patients with COVID-19



Vilobelimab

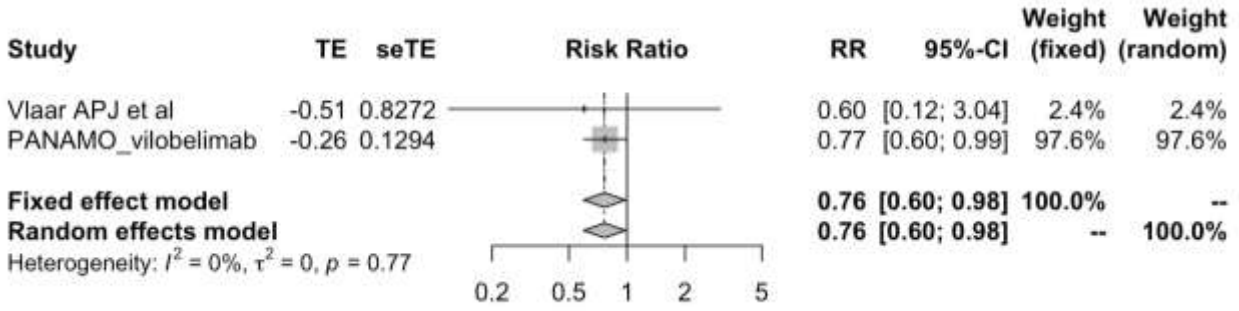
See Summary of findings Table 27, Appendix 1

We identified two RCT including 398 individuals with severe to critical COVID-19 in which vilobelimab was compared against standard of care. Our results showed:

- Vilobelimab probably reduces mortality, RR 0.76 (95%CI 0.6 to 0.98); RD -3.8% (95%CI -6.4% to -0.3%); Moderate certainty ⊕⊕⊕◯ (Figure 40)

- Tixagevimab–cilgavimab may not increase severe adverse events, RR 0.94 (95%CI 0.8 to 1.11); RD -0.6% (95%CI -2% to 1.1%); Moderate certainty ⊕⊕⊕◯

Figure 40. Mortality in randomized studies comparing vilobelimab vs standard of care in patients with COVID-19



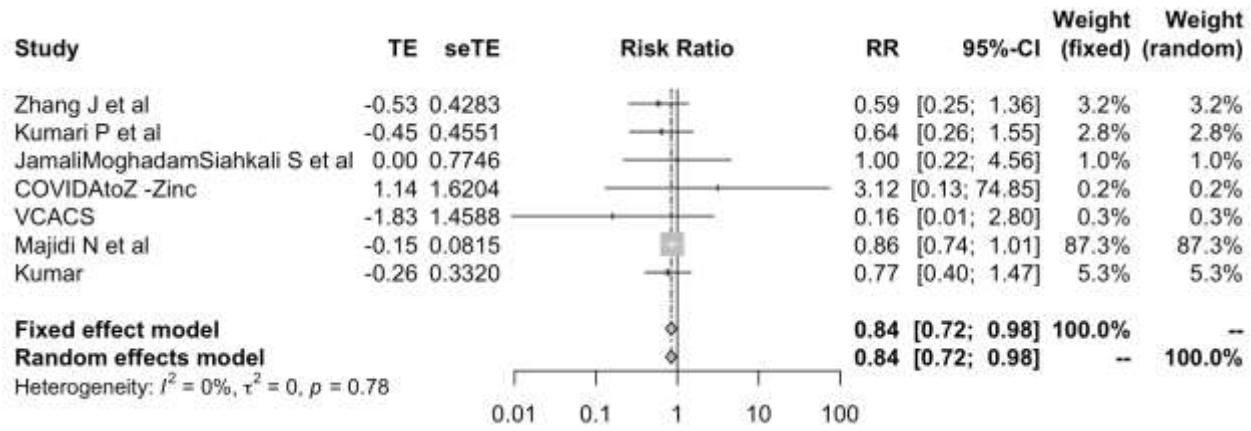
Vitamin C

See Summary of findings Table 28, Appendix 1

We identified ten RCT including 935 individuals with severe to critical COVID-19 in which vitamin C was compared against standard of care. Our results showed:

- Vitamin C may reduce mortality, RR 0.84 (95%CI 0.72 to 0.98); RD -2.6% (95%CI -4.5% to -0.3%); Low certainty ⊕⊕◯◯ (Figure 41)
- It is uncertain if vitamin C increases or decreases mechanical ventilation, RR 0.93 (95%CI 0.59 to 1.45); RD -1.2% (95%CI -7.1% to 7.8%); Very low certainty ⊕◯◯◯
- Vitamin C may increase symptom resolution or improvement, RR 1.16 (95%CI 1.01 to 1.33); RD 9.7% (95%CI 0.6% to 20%); Low certainty ⊕⊕◯◯
- It is uncertain if vitamin C increases severe adverse events, RR 2 (95%CI 0.46 to 8.6); RD 10.2% (95%CI -5.5% to 77.8%); Very low certainty ⊕◯◯◯

Figure 41. Mortality in randomized studies comparing vitamin C vs standard of care in patients with COVID-19



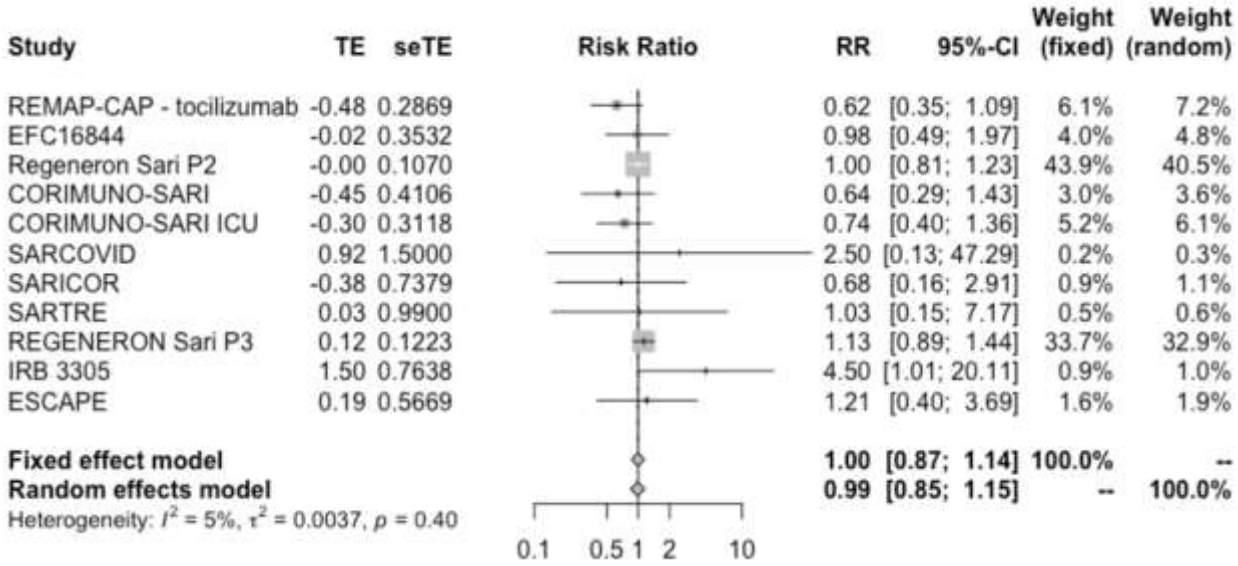
Sarilumab

See Summary of findings Table 29, Appendix 1

We identified eleven RCT including 4663 individuals with severe to critical COVID-19 in which sarilumab was compared against standard of care. Our results showed:

- Sarilumab may not reduce mortality, RR 0.99 (95%CI 0.89 to 1.15); RD -0.2% (95%CI -1.8% to 2.4%); Low certainty ⊕⊕◯◯ (Figure 42)
- Sarilumab may not reduce mechanical ventilation requirements, RR 0.98 (95%CI 0.68 to 1.42); RD -0.3% (95%CI -5.5% to 7.3%); Low certainty ⊕⊕◯◯
- Sarilumab probably does not increase symptom resolution or improvement, RR 1.01 (95%CI 0.97 to 1.06); RD 0.6% (95%CI -1.8% to 3.6%); Moderate certainty ⊕⊕⊕◯
- Sarilumab probably does not increase severe adverse events, RR 1.01 (95%CI 0.9 to 1.13); RD 0.1% (95%CI -1% to 1.3%); Moderate certainty ⊕⊕⊕◯

Figure 42. Mortality in randomized studies comparing sarilumab vs standard of care in patients with COVID-19



Vv116 (oral remdesivir)

See Summary of findings Table 30, Appendix 1

We identified one RCT including 771 individuals with recent onset mild COVID-19 in which vv116 was compared against nirmatrelvir/ritonavir. Our results showed:

- vv116 is as effective as nirmatrelvir/ritonavir in attaining symptom resolution, RR 1.09 (95%CI 0.95 to 1.25); RD 5.6% (95%CI -2.9% to 15.3%); High certainty ⊕⊕⊕⊕
- It is uncertain if vv116 increases or decreases severe adverse events compared to nirmatrelvir/ritonavir, RR 0.67 (95%CI 0.24 to 1.87); RD -3.3% (95%CI -7.7% to 8.9%); Very low certainty ⊕◯◯◯

Full description of included studies

Table 5, below, lists all the identified studies that were included in this systematic review by intervention. The treatments are arranged in alphabetical order. Study or author names, publication status, patient populations, interventions, sources of bias, outcomes, effect sizes and certainty are listed for each study.

Table 5. Description of included studies and interventions effects

99mTc-MDP Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Yuan et al;[15] preprint; 2020	Patients with mild COVID-19 infection. 10 assigned to 99mTc-MDP 5/ml once a day for 7 days and 11 assigned to standard of care.	Median age 61 ± 20, male 42.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Adalimumab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Fakharian A et al trial;[16] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 34 assigned to adalimumab 40 mg once and 34 assigned to SOC	Mean age 54.6 ± 12, male 58.8%, hypertension 29.4%, diabetes 27.9%, COPD 1.5%, CHD 4.4%, CKD 1.5%, cancer 1.5%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Alpha-1 antitrypsin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
McElvaney et al;[17] peer reviewed; 2021	Patients with critical COVID-19 infection. 25 assigned to alpha-1 antitrypsin 120 mg/kg once a week and 11 assigned to SOC	Mean age 58.4 ± , male 61.1%, hypertension 44.4%, diabetes 27.7%, COPD 30.5%, CHD 16.6%, CKD 27.7%, obesity 66.6%	Corticosteroids 72.2%, remdesivir 0%, hydroxychloroquine 0%, tocilizumab 0%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕⊕◯◯ **Hospitalization:** No information

Amiodarone Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ReCOVery-SIRIO trial;[18] Navarese et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 71 assigned to amiodarone 200 to 400 mg a day and 72 assigned to SOC	Median age 61.3 , male 62.3%, diabetes 23.7%, COPD 6.5%, cancer 7%,	Remdesivir 1.9%, hydroxychloroquine 2.3%, azithromycin 6%, convalescent plasma 1.9%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕⊕◯◯ **Hospitalization:** No information

Ammonium chloride Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Siami et al;[19] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 60 assigned to ammonium chloride 125 mg and 60 assigned to SOC	NR	Corticosteroids 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

AMP5A (inhaled) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
AP-014 trial;[20] Roshon et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to AMP5A (inhaled) four nebulization a day for 5 days and 21 assigned to SOC	Mean age 64 ± 15, male 62.5%	Corticosteroids 78%, remdesivir 40%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕⊕◯◯ **Hospitalization:** No information

Anakinra Anakinra may not reduce mortality or increase severe adverse events. However the cerrtainty of the evidence was low because of risk of bias and imprecision. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CORIMUNO-ANA-1 trial;[21] Bureau et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 59 assigned to anakinra 400 mg a day for 3 days followed by 200 mg for 1 day followed by 100 mg for 1 day and 55 assigned to SOC	Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD 31.6%, cancer 9.6%,	Corticosteroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%, tocilizumab 0.8%, azithromycin 24.6%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.96 (95%CI 0.57 to 1.6); RD -0.6% (95%CI -6.9% to 9.6%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.98 (95%CI 0.78 to 1.24); RD -0.2% (95%CI -2.2% to 2.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
SAVE-MORE trial;[22] Kyriazopoulou et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 405 assigned to anakinra 100 mg SC a day for 7 to 10 days and 189 assigned to SOC	Mean age 61.9 ± 12.1, male 57.9%, diabetes 15.8%, COPD 4%, asthma %, CHD 3%, CKD 1.7%	Corticosteroids 86.2%, remdesivir 71.9%, azithromycin 18.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COV-AID-3 trial;[23] Declercq et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 112 assigned to anakinra 100 mg a day for 28 days and 230 assigned to SOC	Mean age 65.5, male 77.4%, hypertension 46.4%, diabetes 27.7%, COPD %, CHD 20.5%, CKD 10.8%	Corticosteroids 62.3%, remdesivir 5%, hydroxychloroquine 11.7%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Kharazmi et al;[24] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 15 assigned to anakinra 100 mg a day for up to 14 days and 15 assigned to SOC	Mean age 54.1, male 63.3%, hypertension 33.3%, diabetes 36.6%, CHD 26.6%	Corticosteroids 63.3%, remdesivir 20%, lopinavir-ritonavir 63.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zeyad et al;[25] preprint; 2022	Patients with severe to critical COVID-19 infection. 40 assigned to Anakinra 200 mg a day for 3 days and 40 assigned to SOC	Mean age 49.9 ± 11.7, male 82.5%, diabetes 43.8%, COPD 1.3%, CHD 8.8%, CKD 1.3%	Corticosteroids 100%, remdesivir 83.8%, azithromycin 78.8%, convalescent plasma 67.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ANACONDA trial;[26] Audemard-Verger et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 36 assigned to anakinra 400 mg a day for 3 days followed by 200 mg a day for 7 days and 34 assigned to SOC	Mean age 70.6 , male 73.2%, hypertension 49.3%, diabetes 21.1%, COPD 9.9%, asthma 4.2%, CHD 12.7%, CKD 9.9%	Corticosteroids 63.4%, hydroxychloroquine 1.5%, azithromycin 12.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) Continuing or initiating ACEIs or ARBs may not reduce mortality. Further research is needed to confirm or discard these findings					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
REPLACE COVID trial;[27] Cohen et al; Peer reviewed; 2020	Patients with mild to severe COVID-19 previously treated with ACEI/ARB. 75 assigned to continuation of ACEI/ARB and 77 assigned to discontinuation of ACEI/ARB	Mean age 62 ± 12, male 55.5%, hypertension 100%, diabetes 37%, COPD 17%, asthma %, CHD 12%,	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.12 (95%CI 0.78 to 1.63); RD 1.9% (95%CI -3.5% to 10.8%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.99 (95%CI 0.75 to 1.29); RD -0.2% (95%CI -4.3% to 5%); Low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⨁◯◯◯
BRACE CORONA trial;[28] Lopes et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB	Median age 55.5 ± 19, male 59.6%, hypertension 100%, diabetes 31.9%, COPD %, asthma 3.9%, CHD 4.6%, CKD 1.4%, cancer 1.5%,	Corticosteroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.	

ACEI-COVID trial;[29] Bauer et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 100 assigned to continuation of ACEI/ARB and 104 assigned to discontinuation of ACEI/ARB	Mean age 72 ± 11, male 63%, hypertension 98%, diabetes 33%, CHD 22%	Remdesivir 6.8%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ATTRACT trial;[30] Tornling et al; peer reviewed; 2020	Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200 mg a day for 7 days and 55 assigned to SOC	Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%	Corticosteroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Nouri-Vaskeh et al;[31] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan 50 mg a day for 14 days and 39 assigned to Amlodipine 5 mg a day for 14 days	Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
SURG-2020-28683 trial;[32] Puskarich et al; Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to losartan 25 mg a day for 10 days and 59 assigned to SOC	Age (35-54) 46%, male 51.4%, hypertension 7.7%, diabetes 6%, COPD %, asthma 10.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

COVID-ARB trial;[33] Geriak et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 16 assigned to losartan 25 mg a day for 10 days and 15 assigned to SOC	Median age 53, male %, hypertension 38.7%, diabetes 25.8%, CHD 3.2%, obesity 41.9%	Corticosteroids 22.6%, remdesivir 29%, hydroxychloroquine 9.7%, , azithromycin 16.1%, convalescent plasma 6.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Duarte et al;[34] peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 71 assigned to telmisartan 80 mg twice daily and 70 assigned to SOC	Mean age 66 ± 17, male 53.2%, hypertension 44.3%, diabetes 19%, chronic lung disease 11.4%, asthma 1.3%, CHD NR%, CKD 3.2%, cerebrovascular disease 6.9%, obesity 15.2%	Corticosteroids 50.6%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. Significant number of exclusions post randomization. Stop early for benefit in the context of multiple interim analysis.	
Najmeddin et al;[35] peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to continuation of ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB	Mean age 66.3 ± 9.9, male 46.9%, diabetes 50%, COPD 1.6%, CHD 25%, CKD 1.6%, cancer 4.7%,	Corticosteroids 42.2%, remdesivir 10.9%, , azithromycin 9.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes: 10.9% lost to follow-up	
ALPS-COVID trial;[36] Puskarich et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 101 assigned to ACEI/ARB losartan 100 mg a day and 104 assigned to SOC	Mean age 55, male 60%, hypertension 42%, diabetes 22.9%, COPD 11.7%, asthma 13.2%, CHD 7.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

COVID MED trial;[37] Freilich et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 9 assigned to losartan 25 mg and 5 assigned to SOC	Mean age 63, male 64.2%, diabetes 7.1%, COPD 42.9%, asthma %, CHD 42.9%, CKD 0%, immunosuppression 35.7%, obesity 14.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
RAAS-COVID-19 trial;[38] Sharma et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 25 assigned to continuation of ACEI/ARB and 21 assigned to discontinuation of ACEI/ARB	Mean age 71.5 ± 12.9, male 56.5%, hypertension 100%, diabetes 43.5%, COPD 4.4%, CKD 19.6%, cerebrovascular disease 6.5%, cancer 6.5%,	Corticosteroids 47.8%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
INTENSE-COV trial;[39] Bonnet et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 100 assigned to Telmisartan 10 mg a day for 10 days and 96 assigned to SOC	Mean age 37, male %, hypertension 5.1%, diabetes 2.6%, COPD %, asthma 3.6%, CHD 0.5%, CKD 0%, cancer 0.5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Gotberg et al;[40] preprint; 2022	Patients with moderate to severe COVID-19 infection. 151 assigned to Losartan 25 to 50 mg a day and 149 assigned to SOC	Mean age 56 ± , male 70.6%, hypertension 12%, diabetes 7.3%	Corticosteroids 83.7%, remdesivir 2.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	

Anticoagulants

There are specific recommendations on the use of antithrombotic agents[8] for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) probably do not decrease mortality in comparison with prophylactic dose (i.e., enoxaparin 40 mg a day). Anticoagulants in intermediate or full dose decrease venous thromboembolic events but probably increase major bleeding in comparison with prophylactic dose.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
HESACOVID trial;[41] Bertoldi Lemos et al; peer reviewed; 2020	Patients with critical COVID-19. Ten assigned to low molecular weight heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and 10 assigned to prophylactic dose (i.e., enoxaparin 40 mg a day)	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, coronary heart disease 10%, immuno-suppression 5%	Corticosteroids 70%, hydroxy-chloroquine 25%, azithromycin 90%	Some concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.99 (95%CI 0.81 to 1.21); RD -0.2% (95%CI -3% to 3.4%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis**
REMAP-CAP, ACTIV-4a, ATTACC trial;[42] Zarychanski et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 534 assigned low molecular weight	Mean age 61 ± 12.5, male 70%, diabetes 32.7%, COPD 24.1%, CHD 6.9%, CKD 9.6%,	Corticosteroids 79.3%, remdesivir 30.8%, tocilizumab 1.8%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution,	

	heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and 564 assigned to prophylactic dose (i.e., enoxaparin 40 mg a day)			infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	**studies):** No information **Venous thromboembolic events (intermediate dose):** RR 0.82 (95%CI 0.46 to 1.46); RD -1.2% (95%CI -3.7% to 3.2%); Low ⊕⊕◯◯ **Venous thromboembolic events (therapeutic dose):** RR 0.56 (95%CI 0.44 to 0.72); RD -3.1% (95%CI -3.9% to -2%); High ⊕⊕⊕⊕ **Major bleeding:** RR 1.63 (95%CI 1.16 to 2.33); RD 1.2% (95%CI 0.3% to 2.5%); High ⊕⊕⊕⊕ **Hospitalization:** No information
INSPIRATION trial;[43] Sadeghipour et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 276 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 286 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 62 ± 21, male 57.8%, hypertension 44.3%, diabetes 27.7%, COPD 6.9%, CHD 13.9%, CKD %, cerebrovascular disease 3%	Corticosteroids 93.2%, remdesivir 60.1%, lopinavir-ritonavir 1%, tocilizumab 13.2%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
Perepu et al;[44] preprint; 2021	Patients with severe to critical COVID-19 infection. 87 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 86 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 64 ± 62, male 56%, hypertension 60%, diabetes 37%, COPD 23%, CHD 31%, cancer 12%, obesity 49%	Corticosteroids 75%, remdesivir 61%, azithromycin 21%, convalescent plasma 27%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP, ACTIV-4a, ATTACC trial;[45] Zarychanski et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 1171 assigned to enoxaparin 1 mg/kg twice a day and 1048 assigned to	Mean age 59 ± 14, male 58.7%, hypertension 51.8%, diabetes 29.7%, COPD 21.7%, CHD 10.6%, CKD 6.9%, immunosuppressive therapy 9.7%	Corticosteroids 61.7%, remdesivir 36.4%, tocilizumab 0.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events	

	low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)			Notes: Open-label study but outcome assessors were blinded.	
ACTION trial;[46] Lopes et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 311 assigned to enoxaparin 1 mg/kg twice a day or rivaroxaban 20 mg a day and 304 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 56.6 ± 14.3, male 60%, hypertension 49.1%, diabetes 24.4%, COPD 3.1%, asthma 4.7%, CHD 4.6%, cancer 2.6%,	Corticosteroids 83%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Although patients and careers were aware of the intervention arm assigned, outcome assessors were blinded.	
RAPID trial;[47] Sholzberg et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 228 assigned to therapeutic anticoagulation (i.e., enoxaparin 1 mg/kg) twice a day and 237 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 60 ± 14.5, male 56.8%, hypertension 43.8%, diabetes 34.4%, COPD 13.5%, asthma %, CHD 7.3%, CKD 7.1%, cerebrovascular disease 4.1%, cancer 6.9%,	Corticosteroids 69.4%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
HEP-COVID trial;[48] Spyropoulos et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 129 assigned to enoxaparin 1 mg/kg	Mean age 66.7 ± 14, male 53.8%, hypertension 59.9%, diabetes 37.3%, COPD 6.7%, CHD 8.7%, CKD 3.6%,	Corticosteroids 81%, remdesivir 70.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution,	

	twice a day and 124 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	cerebrovascular disease 3.2%, cancer 2%		infection, and adverse events	
BEMICOP trial;[49] Marcos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 33 assigned to bemiparin 115 IU/kg once daily and 32 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 62.7 ± 13, male 63.1%, hypertension 33.8%, diabetes 7.7%, COPD 16.9%, asthma %, CHD 6.2%, cancer 3.1%,	Corticosteroids 95.4%, remdesivir 13.8%, tocilizumab 23.1%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Oliynyk et al;[50] peer reviewed; 2021	Patients with severe COVID-19 infection. 84 assigned to enoxaparin 100 anti-Xa IU/kg twice a day or unfractionated heparin 80 U/kg/h intravenously, followed by a maintenance dose of 18 U/kg/h and 42 assigned to enoxaparin enoxaparin 50 anti-Xa IU/kg a day	Mean age 70.6, male 60.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
X-Covid 19 trial;[51] Morici et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91	Mean age 59 ± 21, male 62.8%, hypertension 36.1%, diabetes 13.7%,	Corticosteroids 45.9%, remdesivir 21.8%, tocilizumab 1.1%	Low for mortality and mechanical ventilation; high for symptom resolution,	

	assigned to enoxaparin 40 mg twice a day and 92 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	COPD 5.5%, CKD 1.6%, cerebrovascular disease 2.7%		infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PROTHROMCOVID trial;[52] Muñoz-Rivas et al; preprint; 2021	Patients with severe COVID-19 infection. 103 assigned to tinzaparin 175 IU/kg once daily, 91 assigned to tinzaparin 100 IU/kg once daily and 106 assigned to tinzaparin 4500 IU once daily	Mean age 56.3, male 60.6%, hypertension 33%, diabetes 16.7%, COPD 4%, CHD 3.3%, CKD 2%, cerebrovascular disease 1.3%	Corticosteroids 89.3%, remdesivir 18%, tocilizumab 15%; Vaccinated 23%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVID-HEP trial;[53] Blondon et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 79 assigned to enoxaparin 1 mg/kg twice daily and 80 assigned to enoxaparin 20 to 60 mg once daily. Critically ill patients received enoxaparin 40 mg twice daily.	Mean age 62 ± 12, male 66%, hypertension 36.5%, diabetes 18.9%, COPD 11.9%, CHD 9.4%, cancer 6.3%	Corticosteroids 94.3%, tocilizumab 11.9%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TACOVID trial;[54] Rashidi et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 5 assigned to UFH 80 IU/kg and 5 assigned to UFH 15000 IU a day	Mean age 61.5, male 60%, hypertension 40%, diabetes 30%, CHD 10%, CKD 0%, cancer 0%, obesity 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	

				inappropriate.	
Kumar et al;[55] peer reviewed ; 2021	Patients with moderate COVID-19 infection. 115 assigned to rivaroxaban 10 to 15 mg a day and 113 assigned to LMWH-P	Mean age 53 ± , male 71.3%, hypertension 26.6%, diabetes 30.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ASCOT trial;[56] McQuilten et al; peer reviewed; 2023	Patients with moderate COVID-19 infection. 50 assigned to enoxaparin 1 mg /kg twice a day or similar, 601 assigned to enoxaparin 40 mg twice a day or similar and 596 assigned to enoxaparin 40 mg a day or similar	Mean age 49, male 59%, hypertension 24%, COPD 2%, asthma 3%, CHD 2%, CKD 0.3%, obesity 3%	Corticosteroids 64.4%, remdesivir 48.7%; Vaccinated 30.9%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTIV-4B trial;[57] Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 278 assigned to apixaban 2.5 to 5 mg twice a day and 136 assigned to SOC	Median age 54 ± 13, male 40.9%, hypertension 35.3%, diabetes 18.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.08 (95%CI 0.92 to 1.27); RD 4.8% (95%CI -4.8% to 16.4%); Low ⊕⊕◯◯ **Symptomatic infection**
Gates MRI RESPOND-1 trial;[58] Ananworanich et al; peer reviewed; 2021	Patients with mild covid-19 and risk factors for severity. 222 assigned to rivaroxaban 10 mg a day and 222 assigned to SOC	Median age 49, male 39.3%, hypertension 51.8%, diabetes 27.7%, COPD 6.1%, immunosuppressive therapy 3.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OVID trial;[59] Barco et al; peer reviewed; 2022	Patients with mild to moderate COVID-19	Mean age 56.5 ± , male 54%, hypertension 24.4%,	Corticosteroids 1.7%, remdesivir %, hydroxychloroquine	Low for mortality and mechanical ventilation; High for	

	infection. 234 assigned to LMWH-P enoxaparin 40 mg a day for 14 days and 238 assigned to SOC	diabetes 8%, COPD 2%, asthma %, CHD %, CKD %, cerebrovascular disease %, immunosuppresive therapy %, cancer %, obesity %	%, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 0.6%	symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**(prophylaxis studies):** No information **Venous thromboembolic events (intermediate dose):** No information **Clinically important bleeding:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.94 (95%CI 0.55 to 1.59); RD -0.3% (95%CI -2.2% to 2.8%); Low ⊕⊕◯◯
ETHIC trial;[60] Cools et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 105 assigned to enoxaparin 40 mg a day for 21 days and 114 assigned to SOC	Mean age 59 ± , male 55.7%, hypertension 70.4%, diabetes 30.8%, COPD 12.3%, cerebrovascular disease 1.8%, immunosuppression 2.5%, cancer 1.2%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

APMV2020 (aspirin, promethazine and micronutrients)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Kumar et al;[61] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 99 assigned to APMV2020 (aspirin 150 mg, promethazine 5 mg, vit D 2000 IU, vit C 750 mg, niacinamide 80 mg, zinc 15 mg ,	Mean age 37 ± , male 55.5%	Vaccinated 95%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

	potassium 100 micrograms, sodioum selenate 82.5 micrograms) twice a day for 10 days and 93 assigned to SOC				**improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Aprepitant

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Mehboob et al;[62] preprint; 2020	Patients with mild to critical COVID-19 infection. 10 assigned to aprepitant 80 mg once a day for 3–5 days and 8 assigned to standard of care	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Aprotinin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Redondo-Calvo et al;[63] peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to aprotinin 500 KIU a day for 11 days and 32 assigned to SOC	Mean age 55, male 65%, hypertension 47.4%, diabetes 29.8%, COPD 10.8%, CHD 17%	Corticosteroids 96.5%, remdesivir 12%, tocilizumab 10.5%, Vaccinated 35.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No

					information **Adverse events:** No information **Hospitalization:** No information
Arbidol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Khodashahi et al;[64] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 50 assigned to arbidol 600 mg a day for 7 days and 50 assigned to SOC	Mean age 60.6 ± 19, male 55.6%, hypertension 13%, diabetes 12%	Hydroxychloroquine 100%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

					Hospitalization: No information

ArtemiC (artemisinin, curcumin, frankincense, and vitamin C) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
MGC-006 trial;[65] Hellou et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 33 assigned to ArtemiC (artemisinin, curcumin, frankincense and vitamin C) oral spray twice a day and 17 assigned to SOC	Mean age 52 ± , male 50%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:**

					No information

Artemisinin

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
ARTI-19 trial;[66] Tieu et al; Preprint; 2020	Patients with mild to moderate COVID-19. 39 assigned to artemisinin 500 mg for 5 days and 21 assigned to SOC	Mean age 43.3 ± 11.9, male 63.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Aspirin **Aspirin probably does not reduce mortality or mechanical ventilation and probably does not increase symptom resolution or improvement.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
RESIST trial;[67] Ghati et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 221 assigned to aspirin 75 mg once a day for 10 days and 219 assigned to SOC	Mean age 53.1 ± 9.2, male 73.3%, hypertension 28.6%, diabetes 27.7%, CHD 1.1%, CKD 2.4%	Corticosteroids 27.3%, remdesivir 20.6%, hydroxychloroquine 9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** RR 0.95 (95%CI 0.89 to 1.02); RD -0.8% (95%CI -1.8% to 0.3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.95 (95%CI 0.87 to 1.04); RD -0.9% (95%CI -2.2% to 0.7%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis**
RECOVERY - ASA trial;[68] Horby et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 7351 assigned to aspirin 150 mg a day and 7541 assigned to SOC	Median age 59.2 ± 14.2, male 61.5%, diabetes 22%, COPD 19%, asthma %, CHD 10.5%, CKD 3%,	Corticosteroids 94%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTIV-4B trial;[57] Connors et al;	Patients with mild COVID-19	Median age 54 ± 13, male 40.9%,	NR	Low for mortality and mechanical	

peer reviewed; 2021	infection. 144 assigned to aspirin 81 mg a day and 136 assigned to SOC	hypertension 35.3%, diabetes 18.3%		ventilation; low for symptom resolution, infection and adverse events	**studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
REMAP-CAP - ASA trial;[69] Bradbury et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 565 assigned to aspirin 75 to 100 mg a day for 14 days and 529 assigned to SOC	Median age 57, male 65%, hypertension %, diabetes 22.7%, CHD 4.2%, CKD 3.4%	Corticosteroids 98.1%, remdesivir 22%, tocilizumab 42.9%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ASCOT trial;[56] McQuilten et al; peer reviewed; 2023	Patients with moderate COVID-19 infection. 601 assigned to LMWH-I enoxaparin 40 mg twice a day and 596 assigned to LMWH-P	Mean age 49 ± , male 59%, hypertension 24%, diabetes %, COPD 2%, asthma 3%, CHD 2%, CKD 0.3%, cerebrovascular disease %, immunosuppresive therapy %, cancer %, obesity 3%	Corticosteroids 64.4%, remdesivir 48.7%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 30.9%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Atazanavir/ritonavir **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Nekoukar et al;[70] peer reviewed; 2021	Patients with severe COVID-19 infection. 62 assigned to atazanavir/ritonavir 300/100 mg a day	Mean age 49.9 ± 12.6, male 55.6%, hypertension 16.9%, diabetes 27.4%, COPD 0.8%, asthma 1.6%,	Corticosteroids 42.7%, remdesivir 13.7%, tocilizumab 3.2%, azithromycin 50.8%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical**

	for 5 to 10 days and 62 assigned to lopinavir-ritonavir 200/50 mg a day for 5 to 10 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Atovacuone

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
STU-2020-0707 trial;[71] Jain et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 41 assigned to atovacuone 3000 mg a day for 10 days and 19 assigned to SOC	Mean age 50.9, male 63%, hypertension 63%, diabetes 63%, COPD 20%, asthma %, CHD 12%, CKD 33%, cancer 10%, obesity 38%	Corticosteroids 73.3%, remdesivir 60%, convalescent plasma 8.3%;	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Auxora

Auxora may not increase severe adverse events. The effects of auxora on other importan outcomes are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
CARDEA trial;[72] Bruen et al; Preprint; 2020	Patients with severe COVID-19 infection. 130 assigned to auxora initial dose 2.0 mg/kg (max 250 mg), followed by 1.6 mg/kg (max 200 mg) at 24 and 48 h and 131 assigned to SOC	Mean age 60, male 67.4%, hypertension 62.8%, diabetes 41.8%	Steroids 100%, remdesivir 77.6%, tocilizumab 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 0.68 (95%CI 0.39 to 1.17); RD -5.1% (95%CI -9.8% to 2.7%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.07 (95%CI 0.94

					to 1.22); RD 4.2% (95%CI -3.6% to 13.3%); Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.69 (95%CI 0.48 to 1); RD -3.2% (95%CI -5.3% to 0%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Avdoralimab **Uncertainty in potential benefits and harms. Further research is needed**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
FORCE trial ;[73] Carvelli et al ; preprint ; 2021	Patients with severe to critical COVID-19 infection. 103 assigned to avdoralimab 500 mg once followed by 200 mg every 48 hours and 104 assigned to SOC	Mean age 63.6, male 71%, hypertension 51%, diabetes 36%, obesity 45%	Corticosteroids 85%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.68 (95%CI 0.87 to 3.26); RD 10.9% (95%CI -2.1% to 36.2%); Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** RR 1.15 (95%CI 0.85 to 1.55); RD 1.5% (95%CI -1.5% to 5.6%); Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Aviptadil **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
COVID-AIV trial;[74] Jihad et al; preprint (now retracted); 2021	Patients with severe to critical COVID-19 infection. 136 assigned to aviptadil three infusions of 50, 100 and 150 pmol/kg/hr and 67 assigned to SOC	Mean age 61 ± NR, male 69%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Ayush-64 **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Singh et al;[75] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 37 assigned to Ayush-64 1500 mg a day for 30 days and 37 assigned to SOC	Mean age 35.89, male 62.1%, comorbidities 0%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
AZD1656 **AZD1656 may improve time to symptom resolution. The effects of AZD 1656 on other important outcomes are uncertain. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ARCADIA trial;[76] Chorlton et al; peer reviewed; 2022	Diabetic patients with moderate to severe COVID-19 infection. 80 assigned to AZD1656 200 mg a day for 21 days and 73 assigned to SOC	Mean age 64, male 63.4%, hypertension %, diabetes 100%,	Corticosteroids 73.2%, tocilizumab 3.9%, anakinra 0.7%, sarilumab 0.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.18 (95%CI 0.9 to 1.62); RD 11% (95%CI -8.4% to

					37.5%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Azelastine (inhaled) **Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CARVIN trial;[77] Klussmann et al; preprint; 2021	Patients with mild COVID-19 infection. 56 assigned to azelastine (inhaled) 0.02 to 0.1% twice a day for 11 days and 28 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Azithromycin

Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Sekhavati et al[78] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to azithromycin 500 mg twice daily and 55 assigned to standard of care	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.92 (95%CI 0.77 to 1.1); RD -1.4% (95%CI -4% to 1.7%); Moderate
Guvenmez et	Patients with	Mean age 58.7 ± 16,	NR	High for mortality and	

al;[79] peer-reviewed; 2020	moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	male 70.8%,		invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -2.3% to 4.1%); Low certainty ⊕⊕◯◯
COALITION II trial;[80] Furtado et al; peer-reviewed; 2020	Patients with severe COVID-19. 214 assigned to azithromycin 500 mg once a day for 10 days and 183 assigned to standard of care	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, coronary heart disease 5.8%, chronic kidney disease 11%, cerebrovascular disease 3.8%, immunosuppression %, cancer 3.5%, obesity %	Corticosteroids 18.1%, lopinavir-ritonavir 1%, oseltamivir 46%, ATB 85%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY trial[81] Horby et al; preprint; 2020	Patients with moderate to critical COVID-19. 2582 assigned to azithromycin 500 mg a day for 10 days and 5182 assigned to standard of care	Mean age 65.3 ± 15.6, male 62%, diabetes 27.5%, COPD 24.5%, asthma %, coronary heart disease 26.5%, chronic kidney disease 6%	Corticosteroids 61%,	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Rashad et al;[82] preprint ; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to Clarithromycin 1000 mg a day for	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded	

	7 days and 99 assigned to SOC			study. Concealment of allocation is probably inappropriate.	
PRINCIPLE trial;[83] Butler et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 500 assigned to azithromycin 500 mg a day for 3 days and 629 assigned to SOC	Mean age 60.7 ± 7.8, male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,	NR	Some concerns for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	
ATOMIC2 trial;[84] Hinks et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 145 assigned to azithromycin 500 mg a day for 14 days and 147 assigned to SOC	Mean age 45.9 ± 14.8, male 51.5%, hypertension 17.6%, diabetes 8.5%, COPD 4.1%, asthma 18%, CHD 4.1%, cancer 0.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTION trial;[85] Oldenburg et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 131 assigned to azithromycin 1.2 g once and 70 assigned to SOC	Median age 43, male 44%, hypertension 12.2%, diabetes 3.8%, COPD 1.5%, asthma 12%, CKD 1%, cerebrovascular disease 1%, cancer 0.4%,	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	
Ghanei et al;[86] peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution,	

	lopinavir-ritonavir 200/50 mg twice a day for 7 days and 110 assigned to azithromycin 500 mg once followed by 250 mg a day for 5 days	asthma 4.5%, CHD 8.9%, CKD 1.2%,		infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
DAWn-AZITHRO trial;[87] Gyselinck et al; peer reviewed; 2021	Patients with sevre to critical COVID-19 infection. 119 assigned to AZT 500 mg a day for 5 days and 64 assigned to SOC	Mean age 62 ± 15, male 61.8%, hypertension 44.8%, diabetes 16.9%, COPD 8.2%, asthma 8.2%, CHD 9.8%, CKD 8.7%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Azvudine

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Ren et al;[88] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 10 assigned to azvudine 5 mg once a day and 10 assigned to standard of care	Median age 52 ± 59, male 60%, hypertension 5%, diabetes 5%, coronary heart disease 5%	Antivirals 100%, antibiotics 40%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis**

					studies): No information **Adverse events:** No information **Hospitalization:** No information
Baloxavir **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Lou et al;[89] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%	Antivirals 100%, interferon 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information

Bamlanivimab +/- etesevimab (monoclonal antibody)

Bamlanivimab may reduce hospitalizations and infections in exposed individuals. It is uncertain if it affects mortality or mechanical ventilation requirements. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
BLAZE-1 trial;[90] Chen et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700 mg, 2800 mg, or 7000 mg once and 143 assigned to standard of care	Mean age 45 ± 68, male 55%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.06); RD 1.2% (95%CI 3.6% to 5.4%); Moderate certainty ⊕⊕⊕◯
ACTIV-3/TICO trial;[91] Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000 mg once and 151 assigned to SOC	Median age 71 ± 22, male 66%, hypertension 49%, diabetes 29%, COPD %, asthma 9%, CHD 4%, CKD 11%, obesity 52%	Corticosteroids 49%, remdesivir 95%,	Low for mortality and adverse events; high for symptom resolution. Notes: Significant loss to follow-up for symptom	

				improvement/resolution outcome.	**Symptomatic infection (prophylaxis studies):** RR 0.56 (95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Moderate certainty ⊕⊕⊕◯ **Adverse events:** RR 1.12 (95%CI 0.75 to 1.66); RD 1.2% (95%CI -2.5% to -6.7%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.37 (95%CI 0.21 to 0.65); RD -3% (95%CI -3.8% to -1.7%); Moderate certainty ⊕⊕⊕◯
Gottlieb et al;[92] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700-7000 mg once, 112 assigned to bamlanivimab + etesevimab and 156 assigned to SOC	Mean age 44.7 ± 15.7, male 45.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
BLAZE-2 trial;[93] Cohen et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 484 assigned to bamlanivimab 4200 mg once and 482 assigned to SOC	Median age 53	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
BLAZE-1 trial;[94] Dougan et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 518 assigned to bamlanivimab + etesevimab 2800/2800 mg and 517 assigned to SOC	Mean age 53.8 ± 16.8, hypertension 33.9%, diabetes 27.5%, COPD %, CHD 7.4%, CKD 3.5%, immunosuppressive therapy 4.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
J2W-MC-PYAA trial;[95] Chen et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 18 assigned to bamlanivimab 700 to 7000 mg once and 6 assigned to SOC	Mean age 53.9, male 54.2%, hypertension 33.3%, diabetes 25%, asthma 25%, CHD 12.5%, CKD 4%, obesity 8.3%	Corticosteroids 29.1%, remdesivir 50%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OPTIMISE-C19 trial;[96] McCreary et al; peer reviewed; 2022	Patients with mild COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2	Mean age 56 ± 16, male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	(Regeneron) and 1013 assigned to bamlanivimab +/- etesevimab	6.5%, immunosuppresive therapy 27%, obesity 48%			
ACTIV-2 trial;[97] Chew et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 159 assigned to bamlanivimab 700 to 7000 mg and 158 assigned to SOC	Mean age 46.2 ± , male 48.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OPTIMISE-C19 trial;[98] Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD 16%, CKD 4.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
MANTICO trial;[99] Mazzaferri et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 107 assigned to sotrovomab 500 mg once and 106 assigned to bamlanivimab + etesevimab 700/1400 mg once and 106 assigned to REGEN-COV2 600/600 mg once	Mean age 65 ± 15, male 57.2%, diabetes 2.9%, COPD 16.7%, asthma %, CHD 37.9%, CKD 5.1%, immunosuppression 19.6%, obesity 25.4%	Vaccinated 28.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BLAZE-4 trial;[100] Dougan et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 225 assigned to bebtelovimab 175 mg once and 175 assigned to bebtelovimab 175 mg + bamlanivimab 700 mg +	Median age 35 ± , male 44.5%	Vaccinated 20.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	etesevimab 1400 mg mg once				

Baricitinib

Baricitinib reduces mortality and probably reduces mechanical ventilation requirements and improves time to symptom resolution, without increasing severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
ACTT-2 trial;[101] Kalil et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 515 assigned to baricitinib + remdesivir 4 mg a day for 14 days + 200 mg once followed by 100 mg a day for 10 days and 518 assigned to remdesivir	Mean age 55.4 ± 15.7, male 63.1%, comorbidities 84.4%	Corticosteroids 11.9%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	**Mortality:** RR 0.73 (95%CI 0.57 to 0.92); RD -4.3% (95%CI -6.9% to -1.3%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 0.83 (95%CI 0.66 to 1.04); RD -2.9% (95%CI -5.9% to 0.7%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.27 (95%CI 1.13
COV-BARRIER trial;[102] Marconi et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 764 assigned to baricitinib 4 mg for 14 days and 761 assigned to SOC	Mean age 57.6 ± 14.1, male 63.1%, hypertension 47.9%, diabetes 30%, COPD 4.6%, obesity 33%	Corticosteroids 79.3%, remdesivir 18.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

COV-BARRIER-IMV trial;[103] Wesley et al; preprint; 2021	Patients with critical COVID-19 infection. 51 assigned to baricitinib 4 mg a day for 14 days and 50 assigned to SOC	Mean age 58.6 ± 13.8, male 54.5%, hypertension 54.5%, diabetes 35.6%, COPD 3%, obesity 56.4%	Corticosteroids 86.1%, remdesivir 2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	to 1.42); RD 16.4% (95%CI 7.9% to 25.5%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
RECOVERY trial;[104] Horby et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 4148 assigned to baricitinib 4 mg a day for 10 days and 4008 assigned to SOC	Mean age 58.1± 15.5, male 66%, hypertension %, diabetes 23%, COPD 20.4%, asthma %, CHD 18.2%, CKD 2%,	Corticosteroids 95.2%, remdesivir 20.4%, tocilizumab 23%, Regeneron 11%; Vaccinated42%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTT-4 trial;[105] Wolfe et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 516 assigned to baricitinib 4 mg a day for 14 days and 494 assigned to dexamethasone 6 mg a day for 10 days	Mean age 58.3 ± 14, male 58%, hypertension 59.2%, diabetes 39.6%, COPD 9%, asthma 11%, CHD 9.6%, CKD 9.3%, immunosuppression 3.4%, cancer 5.6%, obesity 61.9%	Remdesivir 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Karampitsakos et al;[106] preprint; 2022	Patients with severe COVID-19 infection. 125 assigned to baricitinib 4 mg a day for 14 days and 126 assigned to TCZ 8 mg/kg once	Mean age 72.5, male 59.4%, hypertension 53.8%, cancer 9.2%, obesity 8%	Corticosteroids 100%, remdesivir 100%; Vaccinated 20.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PanCOVID19 trial;[107] Montejano et al; peer reviewed;	Patients with severe COVID-19 infection. 145 assigned to	Median age 67, male 65.5%, hypertension 57.5%, diabetes 29.6%, obesity	Corticosteroids 100%, remdesivir 15.3%, Vaccinated 91%	Low for mortality and mechanical ventilation; high for symptom resolution,	

2022	baricitinib 2 to 4 mg a day for 14 days and 142 assigned to SOC	18.8%		infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BCG **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Padmanabhan et al;[108] preprint; 2020	Patients with severe COVID-19. 30 assigned to BCG 0.1 ml once and 30 assigned to standard of care	Mean age 45.2 ± 36.5, male 60%, obesity 23%	Remdesivir 6.6%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No

					information
Bebtelovimab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
BLAZE-4 trial;[100] Dougan et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 252 assigned to bebtelovimab 175 +/- bamlanivimab/etesevimab mg once and 128 assigned to SOC	Median age 35 ± , male 44.5%	Vaccinated 20.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: Very low certainty ⊕◯◯◯

Beta glucans

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Raghavan et al;[109] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 16 assigned to beta glucans 3 to 13 gr a day and 8 assigned to SOC	Mean age 41.2	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No
Pushkala et al;[110] preprint; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to beta glucans 19 gr a day and assigned to SOC	Mean age 44 ± , male 65%, hypertension 10%, diabetes 37.5%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

					information

Bicarbonate (inhaled)

Inhaled bicarbonate may reduce mortality and may not reduce hospitalizations. However, certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Delic et al;[111] peer reviewed; 2022	Patients with critical COVID-19 infection. 42 assigned to bicarbonate (inhaled) twice a day and 52 assigned to SOC	Mean age 66, male 79.8%, hypertension 57.4%, diabetes 33%, CHD 5.3%, cerebrovascular disease 5.3%	Corticosteroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
El-Badrawy et al;[112] preprint; 2022	Patients with moderate to critical COVID-19 infection. 272 assigned to nebulization with bicarbonate every 4 hours for 30 days and 274 assigned to SOC	Mean age 50.7 ± 16.8, male 39.4%, hypertension 13.2%, diabetes 20.1%, COPD 7.7%, asthma 6.2%, immunosuppression 11%, cancer 0.7%, obesity 19.8%	Vaccinated 20.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Bioven **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Rybakov et al;[113] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 32 assigned to bioven 0.8-1 g/kg once a day for 2 days and 34 assigned to SOC	NA	NA	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No

					information
Boswellia extract **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Barzin Tond et al;[114] peer reviewed; 2021	Patients with severe COVID-19 infection. 24 assigned to Boswellia extract 300 ml a day and 23 assigned to SOC	Mean age 53.8, male 52%, hypertension 22%, diabetes 28%, COPD 2%, asthma 2%, CHD 2%, obesity 24%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Bromhexine hydrochloride **Bromhexine may reduce symptomatic infections in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Li T et al;[115] peer-reviewed; 2020	Patients with severe to critical COVID-19. 12 assigned to bromhexine hydrochloride 32 mf three times a day for 14 days and 6 assigned to standard of care	Median age 52 ± 15.5, male 77.8%, hypertension 33.3%, diabetes 11.1%	Corticosteroids 22.2%, interferon 77.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** RR 0.38 (95%CI 0.13 to 1.09); RD -10.8%
Ansarin et al;[116] peer-reviewed; 2020	Patients with mild to critical COVID-19. 39 assigned to bromhexine 8 mg three time a day for 14 days and 39 assigned to standard of care	Mean age 59.7 ± 14.9, male 55.1%, hypertension 50%, diabetes 33.3%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

				probably inappropriate.	(95%CI -15.1% to 1.6%); Low certainty ⊕⊕◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Mikhaylov et al;[117] Peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 25 assigned to bromhexine 12 mg a day and 25 assigned to SOC	Mean age 40.6 ± 7.6, male 42%, comorbidity 6%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tolouian et al;[118] Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 48 assigned to bromhexine 32 mg a day for 14 days and 52 assigned to SOC	Mean age 52 ± 16, male 46%, hypertension 39%, diabetes 33%, COPD 7%, asthma 6%, CHD 9%, CKD 5%, cerebrovascular disease 2%, cancer 6%	Lopinavir-ritonavir 100%, interferon 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tolouian et al;[119] preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 187 assigned to bromhexine 24 mg a day for 14 days and 185 assigned to SOC	Median age 40 , male 53.2%, hypertension 6.2%, diabetes 9.1%, COPD 0.5%, asthma 1.1%, CHD 8.3%, CKD 1.6%, immunocompromised 0.8%, cancer 0.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Vila Mendez et al;[120] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 98 assigned to bromhexine 48 mg a day for 7 days and 93 assigned to SOC	Mean age 48.8, male 33.5%	Vaccinated 95.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Calcitriol

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Elamir et al;[121] peer reviewed; 2022	Patients with moderate COVID-19 infection. 25 assigned to calcitriol 0.5 µg daily for 14 days and 25 assigned to SOC	Mean age 66.5, male 30%, hypertension 60%, diabetes 40%, COPD 16%, cancer 4%, obesity 20%	Corticosteroids 50%, remdesivir 52%, convalescent plasma 12%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom**

				inappropriate.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Camostat mesilate

Camostat mesilate may not increase symptom resolution. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
CamoCO-19 trial;[122] Gunst et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 137 assigned to camostat mesilate 200 mg a day for 5 days and 68 assigned to SOC	Median age 61 ± 23, male 60%, hypertension 34%, diabetes 17%, COPD 10%, asthma 13%, CHD 19%, cancer 14%, obesity 33%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty

Chupp et al;[123] preprint; 2021	Patients with mild COVID-19 infection. 35 assigned to camostat mesilate 800 mg a day for 7 days and 35 assigned to SOC	Mean age 44.1 ± 13.3, male 60%, hypertension 20%, diabetes 5.7%, CKD 2.9%, obesity 68.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	⊕◯◯◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.94 to 1.11); RD 1.2% (95%CI -3.6% to 6.6%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
CANDLE trial;[124] Kinoshita et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 78 assigned to camostat mesilate 2400 mg a day for 14 days and 77 assigned to SOC	Mean age 55.9 ± 18.4, male 50.3%, hypertension 28.4%, diabetes 17.4%, COPD 16.1%, asthma %, CHD 5.2%, CKD 5.8%, obesity 9.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Terada et al;[125] peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 56 assigned to camostat 600 mg + ciclesonide (inhaled) 1200 µg a day and 61 assigned to SOC	Mean age 58.3, male 64.9%, diabetes 24.8%, COPD 9.4%, CHD 2.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Tobback et al;[126] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 61 assigned to camostat mesilate 300 mg a day for 5 days and 29 assigned to SOC	Median age 40, male 45.6%, diabetes 1.1%, cancer 6.7%, obesity 6.7%	Vaccinated 7.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Canakinumab

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence

RCT					
CAN-COVID trial;[127] Caricchio et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 223 assigned to canakinumab 450–750 mg/kg once and 223 assigned to SOC	Median age 59, male 58.8%, hypertension 55.7%, diabetes 36.1%, COPD 7.3%, asthma 7.7%, CHD 20.3%, CKD 8.8%, cerebrovascular disease 5.9%	Corticosteroids 36.3%, remdesivir 20.7%, hydroxychloroquine 13.2%, azithromycin 37.4%, convalescent plasma 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯
Three C trial;[128] Cremer et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 29 assigned to canakinumab 300 to 600 mg once and 16 assigned to SOC	Mean age 68.8 ± 13.2, male 73.3%, hypertension 71.1%, diabetes 46.7%, COPD 17.8% CHD 22.2%, CKD 33.3%, cerebrovascular disease 4.4%	Steroids 46.7%, remdesivir 46.7%, convalescent plasma 9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Cannabidiol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CANDIDATE trial;[129] Crippa et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 49 assigned to cannabidiol 300 mg a day for 14 days and 42 assigned to	Mean age 39.7, male 32.7%, hypertension 4.4%, diabetes 2.2%, COPD %, asthma 3.3%, cancer 1.1%, obesity 6.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty

	SOC				⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

CD24Fc (soluble CD24 appended to heavy chains 2 and 3 of human immunoglobulin G1)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
SAC-COVID trial;[130] Welker et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 116 assigned to CD24Fc 480 mg once and 118 assigned to SOC	Mean age 57.8 ± 14, male 74.8%, hypertension 54.7%, diabetes 21.4%, COPD 1.7%, asthma 9.4%, obesity 15.4%	Corticosteroids 83.3%, remdesivir 68.4%, hydroxychloroquine 1.3%, convalescent plasma 54.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** RR 0.57 (95%CI 0.34 to 0.96); RD -7.4%

					(95%CI -11.4% to -0.7%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.18 (95%CI 1 to 1.39); RD 10.7% (95%CI -0.2% to 23.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
CERC-002 (monoclonal antibody) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Perlin et al;[131] preprint; 2021	Patients with mild to moderate COVID-19 infection. 31 assigned to CERC-002 16 mg/kg once and 31 assigned to SOC	Mean age 58.5 ± 14, male 69.5%	Corticosteroids 91.5%, remdesivir 68.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

				follow-up.	**improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Chloroquine nasal drops

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Thakar et al;[132] Peer reviewed; 2020	Patients with mild COVID-19. 30 assigned to chloroquine nasal drops 0.03% six times a day for 10 days and 30 assigned to SOC	Mean age 34.9 ± 10.35, male 78.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Chlorpheniramine (nasal) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ACCROS trial;[133] Valerio-Pascua et al; preprint; 2022	Patients with mild COVID-19 infection. 61 assigned to Chlorpheniramine (nasal) 600 100 µL a day and 40 assigned to SOC	Mean age 46.2 ± 15.3, male 51.5%, hypertension 29.7%, diabetes 10.9%, asthma 2%	Vaccinated 99%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information

CIGB-325

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
ATENEA-Co-300 trial;[134] Cruz et al; preprint; 2020	Patients with mild to moderate COVID-19. 10 assigned to CIGB-325 2.5 mg/kg/day during 5-consecutive days) and 10 assigned to standard of care	Mean age 45.3 ± 12, male 70%, hypertension 25%, diabetes 0%, cancer 5%, obesity 25%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Clarithromycin

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Rashad et al;[82] preprint; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to clarithromycin 1000 mg a day for 7 days and 99 assigned to SOC	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Clazakizumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Lonze et al;[135] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 78 assigned to clazakizumab 12.5 to 25 mg a day and 74 assigned to SOC	Mean age 61.8 ± 12.2, male 70.4%, hypertension 63.2%, diabetes 42.4%, COPD 16.4%, asthma %, CHD 34.2%, immunosuppresive therapy 7.2%, cancer 8.6%, obesity 11.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** RR 0.66 (95%CI 0.43 to 1.01); RD -7.6% (95%CI -9.8% to 1.7%); Low certainty ⊕⊕◯◯ **Symptom**

					resolution or improvement: RR 1.23 (95%CI 0.87 to 1.76); RD 13.9% (95%CI -7.9% to 46%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Clevudine

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
BK-CLV-201 trial;[136] Song et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 41 assigned to clevudine 120 mg a day for 14 days and 20 assigned to SOC	Mean age 59.9 ± 12.8, male 49.2%, hypertension 45.9%, diabetes 26.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
COVID-19-MCS trial;[137] Altay et al; preprint; 2020	Patients with mild to moderate COVID-19. 71 assigned to cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 22 assigned to standard of care	Mean age 35.6 ± 47, male 60%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Outcome assessors not blinded. Possible reporting bias.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty
COVID-19-MCS	Patients with mild	Mean age 36.3 ,	Hydroxychloroquine	High for mortality and	

trial;[138] Altay et al; peer reviewed; 2021	to moderate COVID-19 infection. 229 assigned to cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 75 assigned to SOC	male 57.6%, hypertension 9.2%, diabetes 6.2%	81.9%	mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Hu et al;[139] peer reviewed; 2021	Patients with moderate to severe with diabetes COVID-19 infection. 12 assigned to nicotinamide 500 mg a day and 12 assigned to SOC	Mean age 69.5, male 45.8%, hypertension 33.3%, diabetes 16.6%, COPD 0%, CHD 8.3%, CKD 4.2%, cerebrovascular disease 8.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Colchicine

Colchicine probably does not reduce mortality and mechanical ventilation requirements or improve time to symptom resolution. In mild ambulatory patients it may not have an important effect on hospitalizations but the certainty of the evidence is low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
GRECCO-19 trial;[140] Deftereos et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 50 assigned to colchicine 1.5 mg once followed by 0.5 mg twice daily until hospital discharge or 21 days and 55 assigned to	Median age 64 ± 11, male 58.1%, hypertension 45%, diabetes 20%, chronic lung disease 4.8%, coronary heart disease 13.3%, immunosuppression 3.75%	Hydroxychloroquine 98%, lopinavir-ritonavir 31.4%, tocilizumab 3.8%, azithromycin 92%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and	**Mortality:** RR 0.99 (95%CI 0.92 to 1.06); RD -0.2% (95%CI -1.3% to 1%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR

	standard of care			adverse events outcomes results.	0.98 (95%CI 0.89 to 1.02); RD -0.3% (95%CI -1.9% to 1.4%); Moderate certainty ⊕⊕⊕◯
Lopes et al;[141] preprint; 2020	Patients with moderate to severe COVID-19 infection. 19 assigned to colchicine 0.5 mg three times a day, for 5 days followed by 0.5 mg twice daily for 5 days and 19 assigned to standard of care	Median age 50.75 ± 26.2, male 40%, diabetes 31.4%, chronic lung disease 14.2%, coronary heart disease 40%	Corticosteroids 40%, hydroxychloroquine 100%, azithromycin 100%, heparin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptom resolution or improvement:** RR 1 (95%CI 0.98 to 1.02); RD 0% (95%CI -1.2% to 1.2%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕ **Pulmonary embolism:** RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.81 (95%CI 0.63 to 1.04); RD -0.9% (95%CI -1.8% to 0.2%); Low certainty ⊕⊕◯◯
Salehzadeh et al;[142] preprint; 2020	Patients with moderate to critical COVID-19. 50 assigned to colchicine 1 mg a day for 6 days and 50 assigned to standard of care	Mean age 56, male 41%, hypertension 11%, diabetes 11%, chronic lung disease 4%, coronary heart disease 15%, chronic kidney disease 5%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Tardif et al;[143] peer-reviewed; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe disease. 2235 assigned to colchicine 1 mg a day for 3 days followed by 0.5 mg for a total of 27 days and 2253 assigned to SOC	Mean age 54.3, male 46%, hypertension 36.3%, diabetes 19.9%, COPD 26.5%, CHD 5.4%, obesity 45.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
RECOVERY - Colchicine trial;[144] Horby et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 5610 assigned to colchicine 500 mg twice a day for 10 days and 5730 assigned to SOC	Mean age 63.4 ± 13.8, male 69.5%, diabetes 25.5%, COPD 21.5%, asthma %, CHD 21%, CKD 3%	Corticosteroids 94%	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study which might have introduced bias to symptoms and adverse events outcomes results.	
COL-COVID trial;[145] Figal et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 52 assigned to colchicine 1.5 gr once followed by 1 gr a day for 7 days and 51 assigned to SOC	Mean age 51 ± 12, male 52.4%, hypertension 27.2%, diabetes 14.6%, COPD 1%, CHD 2.9%, CKD 6.8%, cerebrovascular disease 1.9%, immunosuppresive therapy %, cancer %, obesity 21.4%	Corticosteroids 74.8%, remdesivir 32%, lopinavir-ritonavir 1%, tocilizumab 9.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PRINCIPLE - Colchicine trial;[146] Dorward et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 156 assigned to colchicine 500 µg a day for 14 days and 133 assigned to SOC	Mean age 61, male 50%, hypertension 19.5%, diabetes 10.9%, COPD or asthma 32.2%, CHD 8%, cerebrovascular disease, or other neurological diseases 5.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, hospitalization, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COLCOVID trial;[147] Diaz et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 640 assigned to colchicine 1.5 mg once followed by 1 mg a day for 14 days and 639 assigned to SOC	Mean age 62 ± 14, male 64.9%, hypertension 47.7%, diabetes 22.7%, COPD 9.6%, CHD 7.1%, CKD 2.3%, cerebrovascular disease 2%, cancer 2.3%	Corticosteroids 91.5%, hydroxychloroquine 0.3%, lopinavir-ritonavir 0.2%, convalescent plasma 7.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Alsultan et al;[148] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to colchicine 1.5 mg once followed by 1 mg a day for 5 days	Age 60 to 80 65.3, male 38.8%, diabetes 53.1%, CKD 8.2%, cerebrovascular disease 4.1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	

	and 21 assigned to SOC			study. Concealment of allocation probably inappropriate.	
Pourdowlat et al;[149] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 89 assigned to colchicine 0.5 mg for 3 days and then continued 1 mg/day for 12 days and 63 assigned to SOC	Mean age 55, male 56.4%, hypertension 12.7%, diabetes 14.5%, COPD %, asthma 3.6%, CHD 5.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Gorial et al;[150] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 80 assigned to colchicine 1 mg a day for 7 days followed by 0.5 mg a day for 14 days and 80 assigned to SOC	Median age 49, male 53.1%, hypertension 41.2%, diabetes 20.6%, COPD %, asthma 1.2%, cancer 2.5%, obesity 35%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mostafaie et al; NCT04392141, other; 2021	Patients with moderate to severe COVID-19 infection. 60 assigned to colchicine and 60 assigned to SOC	Mean age 53.5 ± 15.1, male 54.2%, hypertension 26.7%, diabetes 7.5%, cancer 5.8%,	NR	NA	
STRUCK trial;[151] Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to colchicine 1 mg a day for 4 weeks and 16 assigned to SOC	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD 5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Cecconi et al;[152] peer reviewed; 2022	Patients with moderate to severe COVID-19	Mean age 65.1 ± 16, male 59%, hypertension 40%,	Corticosteroids 98%, remdesivir 15.5%,	Low for mortality and mechanical ventilation; high for	

	infection. 119 assigned to colchicine 1 mg once followed by 0.5 mg a day for 5 days and 120 assigned to SOC	diabetes 16%, COPD 4%, asthma 5%, CHD 7%	hydroxychloroquine 0%, lopinavir-ritonavir 0.8%,	symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Rabbani et al;[153] peer reviewed; 2022	Patients with moderate to severe with cardiac injury COVID-19 infection. 48 assigned to colchicine 1.2 mg a day for 30 days and 45 assigned to SOC	Mean age 71, male 67.7%, hypertension 78.5%, diabetes 26.9%, COPD 10.8%, CKD 28%,	Corticosteroids 62.4%, remdesivir 69.9%, hydroxychloroquine 1.1%, convalescent plasma 14%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COLVID trial;[154] Perricone et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 77 assigned to Colchicine 1.5 mg a day and 75 assigned to SOC	Mean age 68, male 63.8%, hypertension 53%, COPD 21.3%, CKD 4.6%,	Corticosteroids 100%, hydroxychloroquine 18.4%, I	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	

Colchicine + rosuvastatin

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence

RCT					
Gaitan-Duarte et al;[155] preprint; 2021	Patients with moderate to severe COVID-19 infection. 153 assigned to colchicine + rosuvastatin 1 mg + 40 mg a day for 14 days and 161 assigned to SOC	Mean age 55.4 ± 12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%	Corticosteroids 98%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Convalescent plasma

Convalescent plasma does not reduce mortality or mechanical ventilation requirements or improve time to symptom resolution. Convalescent plasma probably has no important effect on hospitalizations and may not increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence

RCT					
Li et al;[156] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 52 assigned to convalescent plasma 4 to 13 mL/kg of recipient body weight and 51 assigned to standard of care	Median age 70 ± 8, male 58.3%, hypertension 54.3%, diabetes 10.6%, coronary heart disease 25%, chronic kidney disease 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%	Corticosteroids 39.2%, antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.98 (95%CI 0.93 to 1.03); RD -0.3% (95%CI -1.1% to 0.5%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 1.03 (95% CI 0.94 to 1.11); RD 0.5% (95%CI -1% to 1.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 0.99 (95% CI 0.95 to 1.02); RD -0.6% (95%CI -3% to 1.2%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** RR 1.05 (95% CI 0.9 to 1.22); RD 0.5% (95%CI -1% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.77 (95% CI 0.57 to 1.03); RD -1.1% (95%CI -2.1% to 0.1%); Moderate certainty ⊕⊕⊕◯
CONCOVID trial; Gharbharan et al;[157] preprint; 2020	Patients with moderate to critical COVID-19 infection. 43 assigned to convalescent plasma 300 ml once or twice and 43 assigned to standard of care	Median age 62 ± 18, male 72%, hypertension 26%, diabetes 24.4%, chronic lung disease 26.7%, coronary heart disease 23.2%, chronic kidney disease 8.1%, immunosuppression 12.8%, cancer 9.3%	NR	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Avendaño-Solá et al;[158] preprint; 2020	Patients with severe COVID-19. 38 assigned to convalescent plasma 250-300 ml once and 43 assigned to standard of care	Mean age 60.8 ± 15.5, male 54.3%, hypertension 39.5%, diabetes 20.9%, chronic lung disease 12.3%, asthma NR%, coronary heart disease 18.5%, chronic kidney disease 4.9%	Corticosteroids 56.8%, remdesivir 4.94%, hydroxychloroquine 86.4%, lopinavir-ritonavir 41.9%, tocilizumab 28.4%, azithromycin 61.7%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLACID trial;[159] Agarwal et al; preprint; 2020	Patients with severe COVID-19. 235 assigned to convalescent plasma 200 ml twice in 24 h and 229 assigned to	Median age 52 ± 18, male 76.3%, hypertension 37.3%, diabetes 43.1%, chronic lung disease 3.2%, coronary heart disease 6.9%,	Corticosteroids 64.4%, remdesivir 4.3%, hydroxychloroquine 67.7%, lopinavir-ritonavir 14.2%, tocilizumab 9%,	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	

	standard of care	chronic kidney disease 3.7%, cerebrovascular disease 0.9%, cancer 0.2%, obesity 7.1%	azithromycin 63.8%	Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLASM-AR trial;[160] Simonovich et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 228 assigned to convalescent plasma and 105 assigned to standard of care	Mean age 62 ± 20, male 67.6%, hypertension 47.7%, diabetes 18.3%, COPD 7.5%, asthma 4.2%, coronary heart disease 3.3%, chronic kidney disease 4.2%	Corticosteroids 93.3%, hydroxychloroquine 0.3%, lopinavir-ritonavir 3%, tocilizumab 4.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
ILBS-COVID-02 trial;[161] Bajpai et al; preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to convalescent plasma 500 ml twice and 15 assigned to standard of care	Mean age 48.2 ± 9.8, male 75.9%,	Hydroxychloroquine 100%, azithromycin 100%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
AlQahtani et al;[162] preprint; 2020	Patients with severe to critical COVID-19. 20 assigned to convalescent plasma 200 ml twice and 20 assigned to standard of care	Mean age 51.6 ± 13.7, male 80%, hypertension 25%, diabetes 30%, COPD 7.5%, asthma %, coronary heart disease 10%, chronic kidney disease 5%	Corticosteroids 12.5%, hydroxychloroquine 92.5%, lopinavir-ritonavir 85%, tocilizumab 30%, azithromycin 87.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Fundacion INFANT-Plasma trial;[163] Libster et al; preprint; 2020	Patients with mild to moderate COVID-19. 80 assigned to convalescent plasma 250 ml and 80 assigned to standard of care	Mean age 77.1 ± 8.6, male 47.5%, hypertension 71.2%, diabetes 22.5%, COPD 4.4%, asthma 3.8%, coronary heart disease 13.1%, chronic kidney disease 2.5%, cancer 3.8%, obesity 7.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
PICP19 trial;[164] Ray et al; peer reviewed; 2020	Patients with severe COVID-19. 40 assigned to convalescent plasma 200 ml and 40 assigned to standard of care	Mean age 61 ± 11.5, male 71.2%, hypertension 43.7%, diabetes 58.7%, COPD 6.2%, CHD 10%, cerebrovascular disease 2.5%	Steroids 50%, remdesivir 31.2%, hydroxychloroquine 37.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RECOVERY-Plasma trial;[165] Horby et al; Other; 2020	Patients with severe to critical COVID-19 infection. 5795 assigned to CP 275 ml a day for two days and 5763 assigned to SOC	Median age 63.5 ± 14.7, male 64.2%, diabetes 26%, COPD 24%, CHD 22%	Corticosteroids <1%, lopinavir-ritonavir <1%, azithromycin 10%, colchicine 14%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Baklaushev et al;[166] peer reviewed; 2020	Patients with moderate to severe COVID-19. 46 assigned to CP 640 ml divided in two infusions and 20 assigned to SOC	Age 56.3 ± 11, male 60.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

				probably inappropriate.	
O'Donnell et al;[167] Peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 150 assigned to CP one infusion and 73 assigned to SOC	Median age 61 ± 23, male 65.9%, hypertension 33.6%, diabetes 36.8%, COPD 9%, CHD 37.7%, CKD 9.4%, obesity 48.8%	Corticosteroids 81%, remdesivir 6%, hydroxychloroquine 6%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Sensitivity analysis including loss to follow-up patients significantly modified results. At the time mortality was measured the number of patients on IMV was significantly higher in the intervention arm.	
Beltran Gonzalez et al;[168] preprint; 2021	Patients with severe to critical COVID-19 infection. 130 assigned to CP 200 ml a day for 2 days and 60 assigned to IVIG	Mean age 58 ± 25, male 62.6%, hypertension 35.2%, diabetes 34.7%, COPD 4.7%, CHD 3.1%, CKD 3.1%, cerebrovascular disease 1.05%, cancer 0.53%, obesity 41.5%	Corticosteroids 82.6%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Pouladzadeh et al;[169] peer reviewed; 2021	Patients with severe COVID-19 infection. 30 assigned to CP 500 ml once or twice and 30 assigned to SOC	Mean age 55.3 ± 13.6, male 55%, comorbidities 50%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

SBU-COVID19 - Convalescent Plasma trial;[170] Bennett-Guerrero et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 59 assigned to CP 480 ml once and 15 assigned to SOC	Mean age 65.5 ± 16.6, male 59.5%, hypertension 68.9%, diabetes 33.7%, COPD 12.1%, CHD 17.6%, CKD 9.5%, cerebrovascular disease 14.8%, immunosuppressive therapy 8.1%	Corticosteroids 60.8%, remdesivir 24.3%, hydroxychloroquine 31%, tocilizumab 21.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Salman et al;[171] peer reviewed; 2021	Patients with severe COVID-19 infection. 15 assigned to CP 250 ml once and 15 assigned to SOC	Median age 57 ± 10, male 70%, diabetes 30%, asthma 16.6%, cerebrovascular disease 43.3%	Corticosteroids 76.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CAPSID trial;[172] Koerper et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to CP 850 ml in three infusions and 52 assigned to SOC	Mean age 60 ± 13, male 73.3%, hypertension 56.2%, diabetes 31.4%, COPD 16.2%, CHD 21.9%, cancer 4.7%, obesity 54.2%	Corticosteroids 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP trial;[173] Green et al; 2021	Patients with moderate to critical COVID-19 infection. 1075 assigned to CP 550-700 ml and 904 assigned to SOC	Mean age 62 ± 12.9, male 67.6%, diabetes 30.9%, COPD 23.2%, asthma 19.4%, CHD 8.1%, CKD 10.4%, immunosuppressive therapy 6.4%, cancer 1.4%	Corticosteroids 93.4%, remdesivir 45.1%, tocilizumab 2%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CONCOR-1 trial;[174] Bégin et al; preprint; 2021	Patients with severe COVID-19 infection. 614 assigned to CP	Mean age 67.5 ± 15.6, male 59.1%, diabetes 35%, COPD 24.1%, CHD	Corticosteroids 80.4%, azithromycin 44.3%	Low for mortality and mechanical ventilation; high for symptom resolution,	

	500 ml and 307 assigned to SOC	62%		infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLACOVID trial;[175] Sekine et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 80 assigned to CP 300 ml twice and 80 assigned to SOC	Median age 60.5 ± 20, male 58.1%, hypertension 61.3%, diabetes 39.4%, COPD 13.8%, CHD 21.9%, obesity 56.9%	Corticosteroids 98.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVIDIT trial;[176] Kirenga et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 69 assigned to CP 150 -300 ml twice and 67 assigned to SOC	Mean age 50 ± 23.5, male 71.3%, hypertension 36%, diabetes 32%, asthma 3.7%, obesity 33.3%	Corticosteroids 58.8%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
C3PO trial;[177] Korley et al; peer reviewed; 2021	Patients with early mild to moderate COVID-19 infection with risk factors for severe disease. 257 assigned to CP 250 ml and 254 assigned to SOC	Median age 54 ± 21, male 46%, hypertension 42.3%, diabetes 27.8%, COPD 6.1%, CHD 10%, CKD 5.3%, cancer 0.8%, obesity %	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
DAWn-Plasma trial;[178] Devos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 320	Mean age 62 ± 14, male 68.7%, hypertension %, diabetes 29.6%,	Corticosteroids 66.4%, remdesivir 14.8%, hydroxychloroquine	Low for mortality and mechanical ventilation; high for symptom resolution,	

	assigned to CP 200 to 250 ml once or twice and 163 assigned to SOC	COPD 9.4%, asthma 10.1%, CHD 14.1%, CKD 13.4%,	1.4%, lopinavir-ritonavir 0.4%, tocilizumab 0.6%,	infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PennCCP2 trial;[179] Bar et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 40 assigned to CP two units and 39 assigned to SOC	Mean age 63 , male 45.6%, hypertension 67.1%, diabetes 40.5%, COPD 29.1%, CHD 29.1%, CKD 32.9%, immunosuppression 13.9%, cancer 26.6%, obesity 45.6%	Corticosteroids 83.5%, remdesivir 81%, hydroxychloroquine 2.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
TSUNAMI trial;[180] Manichetti et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 231 assigned to CP 200 ml a day for 1 to 3 days and 239 assigned to SOC	Median age 64 ± 20, male 64.3%, hypertension 37.8%, diabetes 19.2%, COPD 5.7%, CKD 4.7%, cancer 3.6%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COnV-ert & CoV-Early trial;[181] Millat-Martinez et al; other; 2021	Patients with mild to moderate COVID-19 infection. 390 assigned to CP 200 to 300 ml once and 392 assigned to SOC	Median age 58 ± 11, male 66.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
CSSC-004 trial;[182] Sullivan et al; peer reviewed; 2022	Patients with mild COVID-19 infection. 592 assigned to CP 250 ml and 589 assigned to SOC	Median age 44, male 43%, hypertension 23.3%, diabetes 8.4%, asthma 11.2%, CHD 2%, CKD 0.9%,	Vaccinated 17.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

		cerebrovascular disease 0.2%, cancer 0.5%, obesity 17.3%			
COP20 trial;[183] Holm et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 17 assigned to CP 200 to 250 ml on three consecutive days and 14 assigned to SOC	Mean age 73.2 ± , male 61.3%, hypertension 41.9%	Corticosteroids 71%, remdesivir 10%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CONTAIN COVID-19 trial;[184] Ortigoza et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 463 assigned to CP 250 ml once and 463 assigned to SOC	Median age 63, male 59.1%, hypertension 60.7%, diabetes 35.3%, COPD %, asthma 11.7%, CHD 42.9%, CKD 10.5%, cancer 11.3%,	Corticosteroids 76.6%, remdesivir 57.1%, hydroxychloroquine 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
IMPACT trial;[185] Baldeón et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 63 assigned to CP 5 ml/kg and 95 assigned to SOC	Mean age 55.5, male 67.7%, hypertension 22.2%, diabetes 19.6%, obesity 24.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
De Santis et al;[186] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 36 assigned to CP 600 ml a day for 3 days and 71 assigned to SOC	Mean age 59.8, male 62.6%, hypertension 56%, diabetes 38.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events	

				outcomes results.	
PROTECT-Patient trial;[187] van den Berg et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 52 assigned to CP 200-250 ml once and 51 assigned to SOC	Median age 56, male 40.8%, hypertension 54.4%, diabetes 38.8%, COPD 3.9%, CHD 2.9%, CKD 2.9%, cancer 1.9%, obesity 47.6%	Corticosteroids 94.2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
LIFESAVER trial;[188] et al; other; 2021	Patients with severe to critical COVID-19 infection. 4 assigned to CP and 8 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
RECOVER trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 43 assigned to CP and 47 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
LACCPT trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 11 assigned to CP and 11 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CPC-SARS trial;[189] Fernández-Sánchez	Patients with severe to critical COVID-19 infection. 29	Mean age 55.9 ± 9.6, male 76.9%, hypertension 51.3%, diabetes 35.9%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution,	

et al; preprint; 2021	assigned to CP 300 ml twice and 10 assigned to SOC	COPD 2.6%		infection and adverse events	
Herrick J et al;[188] other; 2021	Patients with severe to critical COVID-19 infection. 8 assigned to CP and 6 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Tatem G et al;[188] other; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to CP and 10 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Chowdhury FR et al;[188] other; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to CP and 10 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
PLACO-COVID trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 60 assigned to CP and 60 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	

ASCOT trial;[188] other; 2021	Patients with moderate to severe COVID-19 infection. 15 assigned to CP and 18 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Co-CLARITY trial; [188] other; 2021	Patients with moderate to severe COVID-19 infection. 13 assigned to CP and 12 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Rego EM et al;[188] other; 2021	Patients with moderate to severe COVID-19 infection. 9 assigned to CP and 8 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
PERUCONPLASMA trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 12 assigned to CP and 13 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CP-COVID-19 trial;[188] other; 2021	Patients with severe to critical COVID-19	NR	NR	Low for mortality and mechanical ventilation; low for	

	infection. 49 assigned to CP and 51 assigned to SOC			symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CONFIDENT trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 150 assigned to CP and 151 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
PC/COVID-19 trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 38 assigned to CP and 36 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
COP-COVID-19 trial;[188] other; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to CP and 11 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CCAP-2 trial;[190] peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 98 assigned to CP 600 ml once and 46	Mean age 65.3, male 72.2%, hypertension 28.5%, diabetes 22.2%, COPD 11.1%, cancer 6.9%,	Corticosteroids 88.9%, remdesivir 86.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	assigned to SOC				
COOPCOVID trial;[191] Song et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 87 assigned to CP 200 to 400 ml once and 42 assigned to SOC	Median age 61 ± , male 68%, one or more comorbidities 92%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COPLA-II trial;[192] Bajpai et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 200 assigned to CP 250 ml twice and 200 assigned to SOC	Mean age 55.5 ± 1.17, male 67.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CAPRI trial; NCT 04421404; other; 2021	Patients with moderate to severe COVID-19 infection. 16 assigned to CP 250 ml once and 18 assigned to SOC	Median age 57, male 44.1%	NR	NA	
CoVIP trial;[193] Bartelt et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 14 assigned to CP (high titer) 200 to 300 ml twice and 41 assigned to CP (normal titer) 200 to 300 ml twice	Median age 61, male 64%, hypertension 20%, diabetes 43.6%, COPD 16.3%, CHD 12.7%, immunosuppressive therapy 29.1%, cancer 5.5%, obesity 58.2%	Corticosteroids 90.9%, remdesivir 92.7%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Significant cross-over which affected blinding. No intention to treat analysis estimates	

				provided.	
CSSC-001 trial;[194] Shoham et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 81 assigned to CP one unit once and 87 assigned to SOC	Median age 47, male 55%, diabetes 6.1%, asthma 5%, CHD 2.2%, immunosuppresive therapy 0.5%, cancer 1.1%	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Rojas et al;[195] peer reviewed; 2022	Patients with severe COVID-19 infection. 46 assigned to CP 250 ml twice and 45 assigned to SOC	Mean age 55, male 70.3%, hypertension 25.3%, diabetes 16.5%, COPD %, asthma 4.4%, CKD 5.5%	Corticosteroids 96.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Bargay-Lleonart et al;[196] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 37 assigned to CP 300 ml twice and 17 assigned to SOC	Mean age 58.2, male 61.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Self et al;[197] peer reviewed; 2022	Patients with moderate to critical COVID-19 infection. 487 assigned to CP 200 to 400 ml once and 473 assigned to SOC	Median age 60, male 57.3%, hypertension 60.5%, diabetes 34.1%, COPD 27%, CKD 17.7%, cancer 8.1%,	Corticosteroids 86.7%, remdesivir 70.8%, Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Balcells et al;[198] peer reviewed; 2020	Patients with moderate to severe COVID-19. 28 assigned to convalescent plasma at	Mean age 65.8 ± 65, male 50%, hypertension 67.2%, diabetes 36.2%, chronic lung disease %, asthma 5.1%,	Corticosteroids 51.7%, hydroxychloroquine 12%, lopinavir-ritonavir 1.7%, tocilizumab 3.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical**

	enrolment, 200 mg twice and 30 assigned to convalescent plasma when clinical deterioration was observed (43.3% received CP in this arm)	coronary heart disease %, chronic kidney disease 8.6%, cerebrovascular disease 5.1%, immunosuppression 12%, cancer 7%, obesity 12%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Non-RCT					
Joyner et al;[199] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 20000 received CP	Median age 62.3 ± 79.3, male 60.8%	NR	Low for specific transfusion related adverse events	**Adverse events:** Transfusion related circulatory overload 0.18%; Transfusion related lung injury 0.10%; Severe allergic transfusion reaction 0.10%

Crizanlizumab

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE

					certainty of the evidence
RCT					
CRITICAL trial;[200] Leucker et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to crizanlizumab 5 mg/kg once and 20 assigned to SOC	Mean age 56.6, male 54.5%, hypertension 70.4%, diabetes 43.1%, COPD 9.1%, asthma 6.8%, CHD 11.3%, CKD 11.3%, cerebrovascular disease 2.2%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Curcumin + Piperine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE**

					certainty of the evidence
RCT					
Askari et al;[201] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 23 assigned to curcumin + piperine 1000/10 mg a day for 14 days and 23 assigned to SOC	Mean age 47.6 ± 13.9, male 58.7%, hypertension 23.9%, diabetes 26.1%, CHD 15.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Curcumin + Quercetin + Vitamin D **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication	**Patients and interventions**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard**

status	analyzed				of care and GRADE certainty of the evidence
RCT					
Khan et al;[202] peer reviewed; 2022	Patients with moderate COVID-19 infection. 25 assigned to curcumin + quercetin + Vit D 168 mg + 260 mg + 360 IU and 25 assigned to SOC	Mean age 43.9, male 50%, hypertension 28%, diabetes 34%	Vaccinated 52%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Dapagliflozin

Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.

Study; publication	Patients and interventions	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard

status	analyzed				of care and GRADE certainty of the evidence
RCT					
DARE-19 trial;[203] Kosiborod et al; peer reviewed; 2021	Patients with moderate COVID-19 infection and cardiometabolic risk factors. 625 assigned to dapagliflozin 10 mg for 30 days and 625 assigned to SOC	Mean age 61.4 ± 13.5, male 57.4%, hypertension 84.8%, diabetes 50.9%, COPD 4.6%, CHD 7.2%, CKD 6.6%, obesity 48.1%	Corticosteroids 28.4%, remdesivir 18%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.76 (95%CI 0.51 to 1.12); RD -3.8% (95%CI -7.8% to 1.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.02 (95%CI 0.98 to 1.06); RD 1.2% (95%CI -1.2% to 3.6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Darunavir-cobicistat **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
DC-COVID-19 trial;[204] Chen et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 15 assigned to darunavir-cobicistat 800 mg/150 mg once a day for 5 days and 15 assigned to standard of care	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, coronary heart disease 26.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Degarelix

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
HITCH trial;[205] Nickols et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 62 assigned to degarelix 240 mg once and 34 assigned to SOC	Mean age 68.5 ± 8.4, male 100%, hypertension 78.1%, diabetes 51%, COPD 15.6%, asthma 12.5%, CHD 28.1%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
DFV890 **DFV890 may improve time to symptom resolution. The effects of AZD 1656 on other important outcomes are uncertain. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Madurka et al;[206] peer reviewed; 2022	Patients with severe COVID-19 infection. 70 assigned to DFV890 100 mg a day for 14 days and 72 assigned to SOC	Mean age 61, male 67.6%, hypertension 60.6%, diabetes 26.1%, COPD 9.9%, CHD 12%, CKD 2.1%, cerebrovascular disease 4.9%, cancer 6.4%,	Corticosteroids 71.1%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.15 (95%CI 0.96 to 1.36); RD 9.1% (95%CI 2.4% to 21.8%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Dimethyl sulfoxide (DSMO) (nasal spray) **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hosseinzadeh et al;[207] preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 116 assigned to DSMO three applications a day for one month and 116 assigned to SOC	Mean age 37.2 ± 8.7	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information
Dornase alfa (inhaled) **Doxycycline does not improve time to symptom resolution. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COVASE trial;[208] Porter et al; preprint; 2021	Patients with severe COVID-19 infection. 30 assigned to inhaled dornase alfa 5 mg a day for 7 days and 9 assigned to SOC	Mean age 56, male 76.9%, any commorbiditie 51.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Doubase C

Doxycycline does not improve time to symptom resolution. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Madioko et al;[209] preprint; 2022	Patients with moderate COVID-19 infection. 138 assigned to doubase C 6 to 12 tablets a day for 7 days and 123 assigned to HCQ + AZT	Mean age 41 ± 15, male 54.4%, hypertension 14%, diabetes 4%, asthma 3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Doxycycline

Doxycycline does not improve time to symptom resolution. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
DOXYCOV trial;[210] Sobngwi et al; preprint; 2021	Patients with mild COVID-19 infection. 92 assigned to doxycycline 200 mg a day for 7 days and 95 assigned to	Mean age 39 ± 13, male 52.4%, hypertension 1.1%, asthma 1.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical**

	SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**ventilation:** No information **Symptom resolution or improvement:** RR 1 (95%CI 0.97 to 1.03); RD 0% (95%CI -1.8% to 1.8%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR 1.16 (95%CI 0.76 to 1.76); RD 0.7% (95%CI -1.1% to 3.6%); Low certainty ⊕⊕◯◯
PRINCIPLE trial;[211] Butler et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 780 assigned to doxycycline 200 mg once followed by 100 mg a day for 7 days and 948 assigned to SOC	Mean age 61.1 ± 7.9, male 44.1%, hypertension 41.5%, diabetes 18%, COPD 37.3%, CHD 14.2%, cerebrovascular disease 6.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
DOXPREVENT ICU trial;[212] Dhar et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 192 assigned to doxycycline 200 mg a day and 195 assigned to SOC	Mean age 58.6, male 63.8%, hypertension 53.2%, diabetes 35.7%, COPD 9%, asthma 7.5%, CHD 13.4%, cancer 1.3%,	Corticosteroids 81.4%, tocilizumab 1.3%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Stambouli et al;[213] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 56 assigned to doxycycline 100 mg a day for 6 weeks and 57 assigned to SOC	Mean age 38.4 ± 10.7, male 61%, hypertension 4.1%, diabetes 2.3%, COPD 0.6%, asthma 1.2%,	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Dupilumab

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

SafeDrop trial;[214] Sasson et al; preprint; 2021	Patients with severe COVID-19 infection. 19 assigned to dupilumab 600 mg once followed by 300 mg on days 14 and 28 and 21 assigned to SOC	Mean age 61, male 57.5%, hypertension 45%, diabetes 37.5%, COPD 12.5%, asthma 20%, CHD 22.5%, CKD 25%, cancer 17.5%, obesity 72.5%	Corticosteroids 97.5%, remdesivir 85%, tocilizumab 0%; Vaccinated 65%	Some Concerns for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Dutasteride

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
AB-DRUG-SARS-004 trial;[215] Cadegiani et al; preprint; 2020	Patients with mild COVID-19. 64 assigned to dutasteride (dosage not reported) and 66 assigned to standard of care	Mean age 42 ± 12, male 100 %, diabetes 11%, COPD 0%, asthma 1%, coronary heart disease 1%, cancer 0%, obesity 15.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment	**Mortality:** No information **Invasive mechanical ventilation:** No information

				of allocation probably inappropriate.	**Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
EAT-DUTA AndroCoV trial;[216] Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 43 assigned to dutasteride 0.5 mg a day for 30 days and 44 assigned to SOC	Mean age 41.9 ± 12.4, male 100%, hypertension 21.8%, diabetes 9.2%, COPD 0%, asthma 1.1%, CHD 1.1%, cancer 0%, obesity 10.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Significant lost to follow-up.	

Edaravone

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Moslemi et al;[217] peer reviewed; 2022	Patients with severe COVID-19 infection. 19 assigned to edaravone 30 mg a day for 3 days and 19 assigned to SOC	Mean age 60.5, male 47.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty

				study. Concealment of allocation probably inappropriate.	⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Electrolyzed saline **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
TX-COVID19 trial;[218] Delgado-Enciso et al; preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to electrolyzed saline nebulizations 4 times a day for 10 days and 39	Mean age 47 ± 14.6, male 53.5%, hypertension 18.9%, diabetes 11.9%	Corticosteroids 3.65%, hydroxychloroquine 7.5%, ivermectin 9.4%, ATB 30.6%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

	assigned to standard of care			study. Concealment of allocation is probably inappropriate.	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
ICU-VR trial; Gutiérrez-García et al;[219] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 79 assigned to electrolyzed saline nasal sprays and gargles three times a day and 84 assigned to SOC	Mean age 42 ± , male 26.4%, hypertension 6.7%, diabetes 4.9%, obesity 13.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Endothelial dysfunction protocol

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
MEDIC-LAUMC trial;[220] Matli et al; peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 17 assigned to nicorandil 20 mg a day, L-arginine 3 gr a day, folate 5 mg a	Mean age 56.6, male 81.8%, hypertension 27%, diabetes 21.6%, asthma 10.8%, CHD 5.4%, CKD 2.7%, cancer 2.7%,	Corticosteroids 91.9%, remdesivir 59.5%, tocilizumab 8.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very

	day, nebivolol 2.5 to 5 mg a day, and atorvastatin 40 mg a day for 14 days, and 20 assigned to SOC			Notes: Concealment of allocation probably inappropriate.	low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Enisamium

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Holubovska et al;[221] Preprint; 2020	Patients with moderate to severe COVID-19. assigned to enisamium 500 mg 4 times a day for 7	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No

	days or SOC. Number of patients in each arm not reported.			Notes: Concealment of allocation probably inappropriate.	information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ensitrelvir

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Mukae et al;[222] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 30 assigned to ensitrelvir 125 to 250 mg a day for 5 days and 17 assigned to SOC	Mean age 38.9, male 61.7%,	Vaccinated 80.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ensovibep

Ensovibep may not improve time to symptom resolution. The effectos of ensovibep on other importan outcomes are uncertain. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

ACTIV-3/TICO trial;[223] Barkauskas et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 247 assigned to ensovibep 600 mg once and 238 assigned to SOC	Median age 57 ± , male 56.7%, hypertension 39.4%, diabetes 23.5%, COPD 6.2%, asthma 9.3%, CHD %, CKD 9.5%, cerebrovascular disease %, immunosuppresive therapy 6.2%, cancer %, obesity 13.4%	Corticosteroids 72.9%, remdesivir 68.7%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 31.6%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 0.95 (95%CI 0.8 to 1.16); RD -2.8% (95%CI -13.1% to 9.7%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Enzalutamide **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					

COVIDENZA trial;[224] Welen et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 30 assigned to enzalutamide 160 mg a day for 5 days and 12 assigned to SOC	Median age 64.9, hypertension 45.2%, diabetes 19%, asthma 14.3%, CHD 9.5%, cancer 11.9%,	Corticosteroids 85.7%, remdesivir 28.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ethanol (inhaled)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
Non-RCT					

Amoushahi et al;[225] preprint; 2022	Patients with moderate to severe COVID-19 infection. 44 assigned to ethanol (inhaled) 3 sprays, four times a day for 7 days and 55 assigned to SOC	Mean age 46.4 ± 12.8, male 43.7%,	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Famotidine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
Non-RCT					

Samimagham et al;[226] preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to famotidine 160 mg for up to 14 days and 10 assigned to SOC	Mean age 47.5 ± 13, male 60%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Brennan et al;[227] peer reviewed; 2021	Patients with mild recent onset COVID-19 infection. 27 assigned to famotidine 60 mg a day for 14 days and 28 assigned to SOC	Mean age 35 ± 20, male 36.4%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	
Pahwani et al;[228] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 89 assigned to famotidine 40 mg a day and 89 assigned to SOC	Mean age 51.5 ± 11.5, male 68.5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Favipiravir

Favipiravir may increase mortality and mechanical ventilation requirements; it may not reduce hospitalizations and it does not improve symptom resolution. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Chen et al; preprint;[229] 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days	Mean age not reported male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.08 (95%CI 0.77 to 1.52); RD 1.3% (95%CI -3.7% to 8.3%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.27 (95%CI 0.91 to 1.76); RD 4.7% (95%CI -1.6% to 13.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.97 to 1.05); RD 0.6% (95%CI -1.8% to 3%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.92 (95%CI 0.56 to 1.52); RD -0.8% (95%CI -4.5% to 5.3%); Very low certainty ⊕◯◯◯ **Hospitalization:** RR 1.33 (95%CI 0.64 to 1.78); RD 1.6% (95%CI -1.7% to 3.7%); Low certainty ⊕⊕◯◯
Ivashchenko et al;[230] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 20 assigned to favipiravir 1600 mg once followed by 600 mg twice a day for 12 days, 20 assigned to favipiravir and 20 assigned to standard of care	Mean age not reported	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Lou et al;[89] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%,	Antivirals 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Doi et al;[232] peer-reviewed; 2020	Patients with mild COVID-19. 44 assigned to favipiravir (early) 1800 mg on day 1 followed by 800 mg twice daily for 10 days and 45 assigned to favipiravir (late)	Median age 50 ± 26.5, male 61.4%, comorbidities 39%	Corticosteroids 2.3%, ATB 12.5%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

	1800 mg on day 6 followed by 800 mg twice daily for 10 days			probably inappropriate.	
Dabbous et al;[232] preprint (now retracted); 2020	Patients with mild to moderate COVID-19. 50 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 10 days and 50 assigned to hydroxychloroquine + oseltamivir 800 mg once followed by 400 mg a day for 10 days + 75 mg a day for 10 days	Mean age 36.3 ± 12, male 50%, any comorbidities 15%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Zhao et al;[233] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to TCZ 400 mg once or twice and 5 assigned to favipiravir + TCZ	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khamis et al;[234] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 44 assigned to favipiravir + inhaled interferon beta-1B 1600 mg once followed by 600 mg twice a day for 10 days + 8 million UI for 5 days and 45 assigned to standard of care	Mean age 55 ± 14, male 58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart disease 15%, chronic kidney disease 20%	Corticosteroids 67%, tocilizumab 35%, convalescent plasma 58%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Ruzhentsova et al;[235] preprint; 2020	Patients with mild to moderate COVID-19. 112 assigned to favipiravir 1800 mg once followed by 800 mg twice a day for 10 days and 56 assigned to standard of care	Mean age 42 ± 10.5, male 47%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Promomed; NCT04542694; Other; 2020	Patients with moderate COVID-19. 100 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 14 days and 100 assigned to standard of care	Mean age 49.68 ± 13.09, male 48.5%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Udwadia et al;[236] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 72 assigned to favipiravir 3600 mg once followed by 800 mg twice a day for 14 days and 75 assigned to standard of care	Mean age 43.4 ± 11.7, male 73.5%, comorbidities 25.9%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Balykova et al;[237] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 100 assigned to favipiravir 3200 mf once followed by 1200 mg a day for 14 days and 100 assigned to SOC	Mean age 49.7 ± 13, male 50%, hypertension 28.5%, diabetes 9%, COPD 5%, asthma %, CHD 6%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

				probably inappropriate.	
Solaymani-Dodaran et al;[238] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 190 assigned to favipiravir 1800 mg a day for 7 days and 183 assigned to lopinavir-ritonavir	Mean age 57.6 ± 17.3, male 55%, hypertension 34.9%, diabetes 25.7%, COPD 3.5%, asthma 3.8%, CHD 10.7%, CKD 1.6%	Corticosteroids 27.6%, remdesivir 1.1%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Zhao et al;[239] peer reviewed; 2021	Patients with COVID-19 infection who were discharged from hospital. 36 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 19 assigned to SOC	Mean age 55.7 ± 13.6, male 45.5%, hypertension 30.9%, diabetes 14.5%, CHD 7.3%, cancer 7.3%	Corticosteroids 3.6%, remdesivir 0%, hydroxychloroquine 5.5%, lopinavir-ritonavir 16.4%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
FACCT trial;[240] Bosaeed et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 125 assigned to favipiravir + HCQ 3600 mg + 800 mg once followed by 2400 mg + 400 mg a day for 5 days and 129 assigned to SOC	Mean age 52 ± 13, male 59%, hypertension 40.9%, diabetes 42.1%, asthma 11.8%, CKD 2.4%	Corticosteroids 88.6%, tocilizumab 9%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Shinkai et al;[241] peer reviewed; 2021	Patients with moderate COVID-19 infection. 107 assigned to favipiravir 3200 mg once followed by 1600 mg a day for 14 days and 49 assigned to SOC	Mean age 46.2, any comorbidities 75.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and	

				adverse events outcomes results.	
FIGHT-COVID-19 trial;[242] Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800 mg a day or darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day or favipiravir 6000 mg followed by 2400 mg + darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day for 7 to 14 days.	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
CVD-04-CD-001 trial;[243] Shenoy et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 175 assigned to favipiravir 3600 mg on day 1 followed by 1600 mg a day for 10 days and 178 assigned to SOC	Mean age 51.9 ± 12.5, male 67.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Holubar et al;[244] preprint; 2021	Patients with mild to moderate COVID-19 infection. 59 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 10 days and 57 assigned to SOC	Mean age 43 ± 12, male 51.9%, hypertension 8.6%, diabetes 8.6%, COPD 4.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Malaysian Favipiravir Study trial;[245] Chuah et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 250 assigned to favipiravir 3601 mg once followed by 1600 mg a day for 5 days and 250 assigned to SOC	Mean age 62.5 ± 8, male 48.4%, hypertension 80.2%, diabetes 49.8%, COPD 1.4%, asthma 7.4%, CHD 15%, CKD 1.4%, immunocompromised therapy 0.4%, cancer 1.4%, obesity 20.6%	Corticosteroids 24.6%, tocilizumab 2%, vaccinated 0.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
FAVI-COV-US201 trial;[246] Finberg et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 25 assigned to favipiravir 3600 mg once folowed by 2000 mg a day for 14 days and 25 assigned to SOC	Mean age 57.2 ± 13.14, male 60%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Avi-Mild trial;[247] Bosaeed et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 112 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 5 to 7 days and 119 assigned to SOC	Median age 37, male 67%, hypertension 6%, diabetes 10.8%, COPD %, asthma 3.4%, CHD 0.4%, obesity 16.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Hassaniazad et al;[248] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg for 5 days and 31 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Mean age 53.7 ± 13.5, male 57.1%, hypertension 27%, diabetes 20.6%, COPD 1.6%, CHD 14.2%, obesity 7.9%	Interferon beta 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

FLARE trial;[249] Lowe et al; preprint; 2021	Patients with recent onset mild COVID-19 infection. 59 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 7 days and 60 assigned to SOC	Mean age 40 ± 12, male 51.2%, obesity 16.7%, any comorbidity 15%	Vaccinated 51.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Tabarsi et al;[250] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 30 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Median age 57, male 58.1%, hypertension 12.9%, diabetes 21%, COPD %, asthma 3.2%, CHD 14.5%, CKD 3.2%, therapy %, cancer 4.8%, obesity 3.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
AlQahtani et al;[251] peer reviewed; 2021	Patients with moderate COVID-19 infection. 54 assigned to favipiravir 1600 mg once followed by 1200 mg a day for 10 days and 52 assigned to SOC	Mean age 44, male 47.1%, diabetes 26.1%, COPD 7.6%, asthma %, CHD 1.3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Rahman et al;[252] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 25 assigned to favipiravir 1200 mg a day for 5 days and 25 assigned to SOC	Mean age 37.8 ± 10.7, male 66%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
McMahon et al;[253] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 95 assigned to	Mean age 36, male 54.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse	

	favipiravir 1800 mg once followed by 1600 mg a day for 14 days and 95 assigned to SOC			events	
Golan et al;[254] peer reviewed; 2022	Patients with mild COVID-19 infection. 599 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 10 days and 588 assigned to SOC	Age >60 14.7%, male 45.7%, any comorbidities 17.9%	Vaccinated 11%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Sirijatuphat et al;[255] preprint; 2022	Patients with mild to moderate COVID-19 infection. 62 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 5 to 14 days and 31 assigned to SOC	Median age 30, male 35.5%, obesity 28%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Febuxostat

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Davoodi et al;[256] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to HCQ	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Fenofibrate

Fenofibrate may not increase severe adverse events. The effects of fenofibrate on other importan outcomes are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

FERMIN trial;[257] Chirinos et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 350 assigned to fenofibrate 145 mg a day for 10 days and 351 assigned to SOC	Mean age 49 ± 16, male 53%, hypertension 27%, diabetes 15%, COPD 12%, CHD 7%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.76 (95%CI 0.53 to 1.08); RD -2.5% (95%CI -4.8% to 0.8%); Low certainty ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Finasteride

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Zarehoseinzade et al;[258] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to finasteride 5 mg a day for 7 days and 40 assigned to SOC	Mean age 72 ± 14, male 100%, hypertension 66.3%, diabetes 25%, COPD 12.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Fluvoxamine

Fluvoxamine probably does not have an important effect on hospitalizations, does not increase symptom resolution and may not increase adverse events. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Lenze et al;[259]	Patients with mild	Median age 45.5 ±	NR	Low for mortality and	**Mortality:** Very

peer-reviewed; 2020	to moderate COVID-19. 80 assigned to fluvoxamine incremental dose to 100 mg three times a day for 15 days and 72 assigned to standard of care	20.5, male 28.2%, hypertension 19.7%, diabetes 11%, asthma 17.1%, obesity 56.6%		mechanical ventilation; low for symptom resolution, infection, and adverse events	low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.99 (95%CI 0.96 to 1.02); RD -0.7% (95%CI -2.6% to 1.2%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.78 (95%CI 0.6 to 1.02); RD -1.1% (95%CI -1.9% to 0.1%); Moderate certainty ⊕⊕⊕◯
TOGETHER-Fluvoxamine trial;[260] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 741 assigned to fluvoxamine 100 mg a day for 10 days and 756 assigned to SOC	Median age 50 ± 18, male 42.5%, hypertension 13.2%, diabetes 16.5%, COPD 0.6%, asthma 1.9%, CHD 1.1%, CKD 0.3%, obesity 0.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes:	
Seo et al;[261] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 26 assigned to fluvoxamine 200 mg a day for 10 days and 26 assigned to SOC	Mean age 53, male 59.6%, hypertension 26.9%, diabetes 7.7%, COPD 3.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-OUT trial;[262] Bramante et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 334 assigned to fluvoxamine 100 mg a day for 14 days and 327 assigned to SOC	Median age 44.5, male 45.8%, hypertension 26.9%, diabetes 1.1%, obesity 47.2%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 56.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
ACTIV-6 trial;[263] McCarthy et al; peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 674 assigned to fluvoxamine 100 mg a day for 7 days and 614 assigned to SOC	Mean age 47.5, male 42.8%, hypertension 24.4%, diabetes 9.2%, asthma 13.2%, CHD 4.3%, CKD 0.6%, cancer 3.4%	Remdesivir 0.1%, nirmatrelvir-ritonavir 1%, monoclonal antibodies 2.9%; Vaccinated 68%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Fostamatinib Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Strich et al;[264] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to fostamatinib 300 mg a day for 14 days and 29 assigned to SOC	Mean age 55.6 ± 13.7, male 79.7%, hypertension 54.2%, diabetes 37.3%, asthma 11.9%, CHD 13.6%, obesity 57.6%	Corticosteroids 100%, remdesivir 100%, convalescent plasma 42.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Gabapentin +/- Montelukast Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Soltani et al;[265] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 127 assigned to gabapentin +/- montelukast 900 mg a day +/- 10 mg a day for 5 days and 53 assigned to dextromethorphan	Mean age 56.7, male 56.1%, hypertension 22.2%, diabetes 16.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

GB0139 (inhaled) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DEFINE trial;[266] Gaughan et al; preprint; 2021	Patients with severe COVID-19 infection. 20 assigned to GB0139 (inhaled) and 21 assigned to SOC	Mean age 65, male 56%, hypertension 39%, diabetes 17%, asthma 14.6%, CHD 24.4%, CKD 7.3%, cancer 9.7%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Gimsilumab (Anti-GM-CSF Monoclonal Antibody) Gimsilumab may not reduce mortality nor increase symptom resolution. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BREATHE trial;[267] Criner et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 113 assigned to gimsilumab 400 mg on day 1 and 200 mg on day 8 and 112 assigned to SOC	Mean age 60 ± 14, male 68.4%, hypertension 46.2%, diabetes 20.9%, COPD 7.6%, asthma %, CHD 8%, CKD %, cerebrovascular disease %, immunosuppresive therapy %, cancer %, obesity 26.7%	Corticosteroids 87.5%, remdesivir 50.6%, hydroxychloroquine 4%, Itocilizumab 7.6%, azithromycin 32.4%, convalescent plasma 0.4%;	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.02 (95%CI 0.67 to 1.56); RD 0.3% (95%CI -5.3% to 6%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 0.98 (95%CI 0.82 to 1.16); RD -1.2% (95%CI -10.9% to 9.7%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Helium (inhaled) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Shogenova et al;[268] peer reviewed; 2020	Patients with severe to critical COVID-19. 38 assigned to helium 50% to 79% mixed with oxygen and 32 assigned to SOC	Mean age 53.5 ± 16, male 51.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Hesperidin Hesperidin may not improve symptom resolution; however, the certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
HESPERIDIN trial;[269] Dupuis et al; preprint; 2021	Patients with mild COVID-19 infection. 104 assigned to hesperidin 1000 mg once a day and 107 assigned to SOC	Mean age 41 ± 12.1, male 44.9%, hypertension 10.6%, diabetes 3.2%, COPD 0.9%, asthma 13.5%, CHD 0%, cerebrovascular disease 0%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.87 (95%CI 0.57 to 1.34); RD -7.9% (95%CI -26.1% to 20.6%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Hemadsorption Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
CYTOCOV-19 trial;[270] Jarczak et al; preprint; 2021	Patients with critical COVID-19 infection. 12 assigned to hemadsorption and 12 assigned to SOC	Mean age 64.5 , male 75%, hypertension 66.6%, diabetes 33.3%, CHD 4%, CKD 25%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Hydroxychloroquine and chloroquine

Hydroxychloroquine or chloroquine probably increases mortality, and probably does not reduce invasive mechanical ventilation or significantly improve time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19, it probably has no important effect on the risk of infection; and in patients with mild, recent onset disease, it may not have an important effect on hospitalizations. However, certainty of the evidence is low because of risk of bias and imprecision.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CloroCOVID19 trial;[271] Borba et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 41 assigned to chloroquine 600 mg twice a day for 10 days and 40 assigned to chloroquine 450 mg twice on day 1 followed by 450 mg once a day for 5 days	Mean age 51.1 ± 13.9, male 75.3%, hypertension 45.5%, diabetes 25.5%, chronic lung disease NR%, asthma 7.4%, coronary heart disease 17.9%, chronic kidney disease 7.4%, alcohol use disorder 27.5%, HIV 1.8%, tuberculosis 3.6%,	Azithromycin 100%, oseltamivir 89.7%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 1.09 (95%CI 1 to 1.19); RD 1.4% (95%CI 0% to 3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.08 (95%CI 0.93 to 1.25); RD 1.4% (95%CI -1.2% to 4.3%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% to 6.1%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.85 (95%CI 0.73 to 0.98); RD -2.6% (95%CI -4.6% to -0.4%); Moderate certainty ⊕⊕⊕◯ **Severe Adverse events:** RR 0.90
Huang et al;[272] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to chloroquine 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RECOVERY - Hydroxychloroquine trial;[273] Horby et al; preprint; 2020	Patients with Mild to critical COVID-19 infection. 1561 assigned to hydroxychloroquine 800 mg once followed by 400 mg twice a day for 9 days and 3155 assigned to standard of care	Mean age 65.3 ± 15.3, male %, diabetes 26.9%, chronic lung disease 21.9%, asthma NR%, coronary heart disease 25.4%, chronic kidney disease 7.8%, HIV 0.4%	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias	

				to symptoms and adverse events outcomes results.	(95%CI 0.66 to 1.22); RD -1% (95%CI -3.5% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.82 (95%CI 0.61 to 1.1); RD -0.9% (95%CI -1.9% to 0.5%); Low certainty ⊕⊕◯◯
BCN PEP CoV-2 trial;[274] Mitja et al; preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 1116 assigned to hydroxychloroquine 800 mg once followed by 400 mg x once a day for 6 days and 1198 assigned to standard of care	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, coronary heart disease 13.3%, Nervous system disease 4.1%	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant number of patients excluded from analysis.	
COVID-19 PEP trial;[275] Boulware et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 414 assigned to hydroxychloroquine 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	Median age 40 ± 6.5, male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma 7.6%, comorbidities 27.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Significant loss of information that might have affected the study's results.	
Cavalcanti et al trial;[276] Cavalcanti et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 159 assigned to hydroxychloroquine 400 mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to standard of care	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%, diabetes 19.1%, chronic lung disease 1.8%, asthma 16%, coronary heart disease 0.8%, chronic kidney disease 1.8%, cancer 2.9%, obesity 15.5%	Corticosteroids 1.5%, ACE inhibitors 1.2%, ARBs 17.4%, NSAID 4.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Kamran SM et al trial;[277] Kamran et al; preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to hydroxychloroquine 400 mg twice a day once then 200 mg twice a day for 4 days and 151 assigned to standard of care	Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%	NR	High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PET trial;[278] Skipper et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 212 assigned to hydroxychloroquine 1400 mg once followed by 600 mg once a day for 5 days and 211 assigned to standard of care	Median age 40 ± 9, male 44%, hypertension 11%, diabetes 4%, chronic lung disease %, asthma 11%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
BCN PEP CoV-2 trial;[279] Mitja et al; preprint; 2020	Patients with mild COVID-19 infection. 136 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 6 days and 157 assigned to standard of care	Mean age 41.6 ± 12.6, male 49%, comorbidities 53.2%	NR	High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tang et al; peer-reviewed;[280] 2020	Patients with mild to moderate COVID-19 infection. 75 assigned to hydroxychloroquine 1200 mg daily for three days followed by 800 mg daily to complete 7 days and 75 assigned to standard of care	Mean age 46.1 ± 14.7, male 54.7%, hypertension 6%, diabetes 14%, other comorbidities 31%	Corticosteroids 7%, lopinavir-ritonavir 17%, umifenovir 47%, oseltamivir 11%, entecavir 1%, ATB 39%, ribavirin 47%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcome results.	
Chen et al;[281] preprint; 2020	Patients with moderate COVID-	Mean age 44 ± 15.3, male 46.8%,	ATB 100%, IVIG 100%, antivirals	High for mortality and invasive mechanical	

	19 infection. 31 assigned to hydroxychloroquine 200 mg twice a day for 5 days and 31 assigned to standard of care		100%	ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Chen et al;[282] preprint; 2020	Patients with moderate COVID-19 infection. 18 assigned to hydroxychloroquine 200 mg twice a day for 10 days, 18 assigned to chloroquine and 12 assigned to standard of care	Mean age 47.4 ± 14.46, male 45.8%, hypertension 16.7%, diabetes 18.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Chen et al;[283] preprint; 2020	Patients with mild to severe COVID-19 infection. 21 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg twice a day for 6 days and 12 assigned to standard of care	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HC-nCoV trial;[284] Jun et al; peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 15 assigned to hydroxychloroquine 400 mg once a day for 5 days and 15 assigned to standard of care	Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%, chronic lung disease 3.3%	Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Abd-Elsalam et al;[285] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg tablets twice daily for 15 days and 97 assigned to standard of care	Mean age 40.7 ± 19.3, male 58.8%, chronic kidney disease 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PREP trial;[286] Rajasingham et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 989 assigned to hydroxychloroquine 400 mg twice in one day followed by 400 mg once weekly for 12 weeks or 400 mg twice weekly for 12 weeks and 494 assigned to standard of care	Median age 41 ± 15, male 49%, hypertension 14%, asthma 10%	NR	Low for infection, and adverse events	
TEACH trial;[287] Ulrich et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 67 assigned to hydroxychloroquine 800 mg on day 1 followed by 200 mg twice a day for 2 to 5 days and 61 assigned to standard of care	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart disease 26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%	Corticosteroids 10.2%, remdesivir 0.8%, lopinavir-ritonavir 0.8%, azithromycin 23.4%, convalescent plasma 13.3%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
PrEP_COVID trial;[288] Grau-Pujol et al; preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 142 assigned to hydroxychloroquine 400 mg daily for four days followed by 400 mg weekly for 6 months and 127 assigned to	Median age 39 ± 20, male 26.8%, hypertension 1.8%, diabetes 0.4%, chronic lung disease 2.6%	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	

	standard of care				
PATCH trial;[289] Abella et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 64 assigned to hydroxychloroquine 600 mg a day for 8 weeks and 61 assigned to standard of care	Median age 33 ± 46, male 31%, hypertension 21%, diabetes 3%, asthma 17%	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
WHO SOLIDARITY;[290] Pan et al; Preprint; 2020	Patients with moderate to critical COVID-19 infection. 948 assigned to HCQ 800 mg once followed by 200 mg twice a day for 10 days and 900 assigned to SOC	Age range 50 – 69 43.5% years old, male 59.8%, diabetes 21.9%, COPD 6.9%, asthma 4.9%, CHD 14.1%	Steroids 20.9%, convalescent plasma 1.4%, Anti IL6 2.1%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.	
Davoodi et al;[256] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PEP (University of Washington) trial; Barnabas et al;[291] Abstract; 2020	Individuals exposed to SARS-CoV-2 infection. 381 assigned to hydroxychloroquine 400 mg for three days followed by 200 mg for 11 days and 400 assigned to standard of care	Median age 39 ± 24, male 40%	NR	Low for symptom resolution, infection, and adverse events	

PETAL trial;[292] Self et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 242 assigned to hydroxychloroquine 800 mg on day 1 followed for 200 mg twice a day for 5 days and 237 assigned to standard of care	Median age 58.5 ± 24.5, male 56%, hypertension 52.8%, diabetes 34.6%, COPD 8.1%, asthma %, coronary heart disease %, chronic kidney disease 8.8%,	Corticosteroids 18.4%, remdesivir 21.7%, azithromycin 19%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
HAHPS trial;[293] Brown et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19. 42 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 5 days and 43 assigned to azithromycin	Median age 55 ± 23, male 61%, diabetes 26%, coronary heart disease 11%, chronic kidney disease 9%, cerebrovascular disease 8%, cancer 2%	Corticosteroids 15%, remdesivir 11%, lopinavir-ritonavir 1%, tocilizumab 24%, convalescent plasma 24%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Co-interventions were not balanced between study arms	
HYCOVID trial;[294] Dubee et al; peer reviewed; 2020	Patients with mild to moderate COVID-19. 124 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 8 days and 123 assigned to standard of care	Median age 77 ± 28, male 48.4%, hypertension 53.4%, diabetes 17.3%, COPD 11.2%, cerebrovascular disease 17.3%, obesity 27.7%	Corticosteroids 9.6%, lopinavir-ritonavir 1.2%, azithromycin 8.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Q-PROTECT trial;[295] Omrani et al; peer-reviewed; 2020	Patients with mild COVID-19. 152 assigned to hydroxychloroquine 600 mg daily for 7 days and 152 assigned to hydroxychloroquine + azithromycin	Mean age 41 ± 16, male 98.4%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Dabbous et al;[296] peer reviewed; 2020	Patients with mild to moderate COVID-19. 44 assigned to favipiravir 3200 mg	Mean age 35.5 ± 16.8, male 48.9%, comorbidities 18.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and	

	once followed by 600 mg twice a day for 10 days and 48 assigned to CQ			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HYDRA trial;[297] Hernandez-Cardenas et al; Preprint; 2020	Patients with severe to critical COVID-19. 106 assigned to hydroxychloroquine 400 mg a day for 10 days and 108 assigned to SOC	Mean age 49.6 ± 12, male 75%, hypertension 16%, diabetes 47%, CHD 11%, CKD 0%, obesity 66%	Corticosteroids 52.4%, lopinavir-ritonavir 30.4%, tocilizumab 2.5%, azithromycin 24.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COVID-19 Early Treatment trial;[298] Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 10 days, 65 assigned to HCQ + AZT 500 mg once followed by 250 mg a day for 5 days and 65 assigned to SOC	Median age 37 ±, male 43.3%, hypertension 20.9%, diabetes 11.6%, COPD 9.3%, asthma 1.6%, immunosuppressive therapy 0.8%, obesity 76%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Purwati et al;[299] peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to hydroxychloroquine 200 mg a day and 119 to SOC	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Beltran et al;[300] peer reviewed; 2020	Patients with moderate to severe COVID-19. 33 assigned to hydroxychloroquine 800 mg once	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%,	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	followed by 400 mg a day for 5 days and 37 assigned to SOC	cerebrovascular disease 5.3%		Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
PATCH 1 trial;[301] Amaravadi et al; preprint; 2020	Patients with mild COVID-19 infection. 17 assigned to hydroxychloroquine 400 mg a day and 17 assigned to SOC	Median age 53 ± 37, male 26%, hypertension 18%, diabetes 9%, , asthma 12%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Bermejo Galan et al;[302] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to ivermectin 42 mg and 115 assigned to hydroxychloroquine or CQ	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer 3%, obesity 37.5%	Corticosteroids 98%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Seet et al;[303] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 432 assigned to hydroxychloroquine 400 mg once followed by 200 mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOGETHER trial;[304] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to	Mean age 53, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and	

	hydroxychloroquine 800 mg once followed by 400 mg a day for 9 days and 227 assigned to SOC	3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%		adverse events	
CLOROTRIAL trial;[305] Réa-Neto et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 5 days and 52 assigned to SOC	Median age 53 ±, male 66.7%, hypertension 38.1%, diabetes 25.7%, COPD 8.6%, immunosuppressive therapy 5.7%	Corticosteroids 72.4%, azithromycin 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
CHEER trial;[306] Syed et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 154 assigned to hydroxychloroquine 200-400 mg once a week to three weeks and 46 assigned to SOC	Mean age 30.6 ± 8, male 54.5%, hypertension 4.5%, diabetes 3.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
ProPAC-COVID trial;[307] Sivapalan et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 61 assigned to hydroxychloroquine + AZT 400 mg plus 500 to 250 mg a day and 56 assigned to SOC	Median age 65 ± 25, male 56%, hypertension 38%, diabetes 24%, COPD 9%, asthma 22%, CHD 7%, CKD 7%	Corticosteroids 32%, remdesivir 25%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
HONEST trial;[308] Byakika-Kibwika et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 55 assigned to hydroxychloroquine 800 mg once followed by 400 mg	Median age 32 ± 27, male 72%, hypertension 2.8%, diabetes 2.8%, COPD %, CHD 0.9%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	a day for 5 days and 50 assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ALBERTA HOPE-Covid19 trial;[309] Schwartz et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 111 assigned to hydroxychloroquine 800 mg once followed by 400 mg for 5 days and 37 assigned to SOC	Mean age 46.8 ± 11.2, male 55.4%, hypertension 27.8%, diabetes 19.6%, asthma 13.5%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
HERO-HCQ trial ;[310] Naggie et al ; preprint ; 2021	Individuals exposed to SARS-CoV-2 infection. 683 assigned to hydroxychloroquine 1200 mg once followed by 400 mg daily for 29 days and 676 assigned to SOC	Mean age 43.6 ± , male 44.7%, hypertension 14.6%, diabetes 4%, COPD 0.2%, asthma 9.9%, CHD 0.8%, obesity 33.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Rodrigues et al;[311] peer reviewed; 2021	Patients with mild COVID-19 infection. 42 assigned to hydroxychloroquine + azithromycin 400/500 mg a day for 7 days and 42 assigned to SOC	Mean age 36.5 ± 9.6, male 40.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Babalola et al;[312] preprint; 2021	Patients with mild to severe COVID-19 infection. 31 assigned to hydroxychloroquine + AZT 200/500 mg a day for 3 days and 30 assigned to SOC	Mean age 40.4 ± 1.9, male 63%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

FIGHT-COVID-19 trial;[242] Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or hydroxychloroquine 800 mg a day or Darunavir ritonavir 1200/200 mg a day + hydroxychloroquine 400 mg a day or favipiravil 6000 mg followed by 2400 mg + darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day for 7 to 14 days.	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
SEV-COVID trial;[313] Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 37 assigned to hydroxychloroquine 400 mg twice on first day followed by 400 mg per oral daily for 10 days + ribavirin (1.2 g orally as a loading dose followed by 600 mg orally every 12 hours) for 10 days and 40 assigned to SOC	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ahmad et al;[314] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to	Mean age 37.6, male 95.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse	

	hydroxychloroquine 800 once followed by 400 mg a day for 5 days or chloroquine 500 mg a day for 7 days and 50 assigned to SOC			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
WHIP COVID-19 trial;[315] McKinnon et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 398 assigned to hydroxychloroquine 400 mg a week or 400 mg once followed by 200 mg a day and 200 assigned to SOC	Mean age 44.9 ± 11.9, male 42%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
PHYDRA trial;[316] Rojas-Serrano et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 62 assigned to hydroxychloroquine 200 mg a day for 60 days and 65 assigned to SOC	Mean age 31.1, male 42.5%, obesity 18.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
EPICOS trial;[317] Polo et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 231 assigned to hydroxychloroquine 200 mg a day and 223 assigned to SOC	Mean age 38, male 38.5%, hypertension 5%, diabetes 0.8%, COPD 0%, asthma 6.4%, CHD 0.7%, cancer 0.6%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	
COPE – Coalition V trial;[318] Avezum et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 689 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 7 days and 683 assigned to SOC	Median age 45 ± 20, male 46.9%, hypertension 53.4%, diabetes 16.2%, asthma 13%, CHD 3.4%, obesity 54.8%	Azithromycin 19%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
AlQahtani et al;[251] peer	Patients with moderate COVID-	Mean age 44, male 47.1%, diabetes	NR	High for mortality and mechanical	

reviewed; 2021	19 infection. 51 assigned to HCQ 800 mg once followed by 400 mg a day for 10 days and 52 assigned to SOC	26.1%, COPD 7.6%, asthma %, CHD 1.3%,		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Omehecatl trial;[319] Roy-García et al; preprint; 2021	Patients with moderate COVID-19 infection. 61 assigned to HCQ 400 mg +/- AZT 500 mg a day for 5 days and 31 assigned to SOC	Mean age 37 ± , male 48.9%, commorbidities 27.2%	NR; Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
HOPE trial, Tirupakuzhi et al;[320] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 213 assigned to HCQ 800 mg once followed by 400 mg a week for 12 weeks and 203 assigned to SOC	Mean age 32.1 ± 9.2, male 52.6%, hypertension 1.2%, diabetes 2.4%, COPD 0%, asthma %, CHD 0%	Vaccinated 76.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
IRICT trial;[321] Elshafie et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 97 assigned to HCQ 400 mg once followed by 200 mg a day for 5 days and 102 assigned to SOC	Mean age 60, male 54.3%, hypertension 40.7%, diabetes 30.1%, CKD 10.6%, obesity 20.6%	Corticosteroids 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Choudhary et al;[322] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 99 assigned to HCQ	Mean age 43, male 48%, hypertension 24%, diabetes 3.5%, asthma 7.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse	

	1400 mg once followed by 600 mg a day for 5 days and 99 assigned to SOC			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Dhibar et al;[323] peer reviewed; 2022	Patients with exposed to COVID-19 infection. 574 assigned to HCQ 800 mg once followed by 400 mg per week for 3 weeks and 594 assigned to SOC	Mean age 35 ± 10.4, male 74%, hypertension 3.5%, diabetes 3.7%, asthma 0.1%, CHD 0.3%	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Hyperbaric oxygen

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hadanny et al;[324] preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric oxygen two sessions a day for 4 days and 9 assigned to SOC	Median age 65.4 ± 7.8, male 60%, hypertension 72%, diabetes 60%, COPD %, asthma 8%, CHD 24%, cancer 4%, obesity 8%	Corticosteroids 92%, tocilizumab 24%, convalescent plasma 80%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment are probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information
Cannellotto et al;[325] peer reviewed; 2021	Patients with severe COVID-19 infection. 20 assigned to hyperbaric oxygen 5 sesions (90 minutes duration each) and 20 assigned to SOC	Mean age 55.2 ± 9.2, male 65%, hypertension 32.5%, diabetes 17.5%, COPD 5%, asthma 5%, CHD %, CKD 5%, cancer 5%, obesity 35%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	

				inappropriate. The study was stopped early for benefit.	**Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
COVID-19-HBO trial;[326] Kjellberg et al; preprint; 2021	Patients with severe COVID-19 infection. 15 assigned to hyperbaric oxygen 60 minutes at 2.4 ATA for up tp 5 sesions and 15 assigned to SOC	Mean age 64, male 56.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Siewiera et al;[327] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 14 assigned to Hyperbaric Oxygen 5 sessions and 14 assigned to SOC	Mean age 55 ± 13.4, male 80%	Remdesivir 17.8%, tocilizumab 3.6%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Hyperimmune anti-COVID-19 intravenous immunoglobulin (C-IVIG)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Ali et al;[328] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to C-IVIG 0.15-0.3 g/kg once and 10 assigned to SOC	Mean age 56.5 ± 13.1, male 70%, hypertension 52%, diabetes 36%, COPD 10%, CHD 8%	Corticosteroids 100%, remdesivir 94%, tocilizumab 6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information

				have introduced bias to symptoms and adverse events outcomes results.	**Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Parikh et al;[329] preprint; 2021	Patients with moderate to severe COVID-19 infection. 30 assigned to C-IVIG 30 ml twice and 30 assigned to SOC	Mean age 52 ± 10.1, male 73.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ITAC trial; Polizzotto et al;[330] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 295 assigned to C-IVIG 400 mg/kg and 284 assigned to SOC	Mean age 59 ± 21, male 57%, hypertension 43%, diabetes 28%, COPD 7%, asthma 10%, CHD 5%, CKD 7%, immunosuppression 5%	Corticosteroids 56%; Vaccinated 2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
COVID-Compromise trial;[331] Huygens et al; preprint; 2021	Immunocompromised patients with moderate to severe COVID-19 infection. 10 assigned to C-IVIG 15 gr once and 8 assigned to IVIG	Median age 58, male 55.5%, immunocompromised 100%	Corticosteroids 77.7%; Vaccinated 72.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Hypertonic saline (inhaled) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Delic et al;[111] peer reviewed; 2022	Patients with critical COVID-19 infection. 42	Mean age 65.7 , male 68%, hypertension 60.6%,	Corticosteroids 100%	High for mortality and mechanical ventilation; high for	**Mortality:** Very low certainty ⊕◯◯◯

	assigned to hypertonic saline (inhaled) twice a day and 52 assigned to SOC	diabetes 30.9%, CHD 7.4%, cerebrovascular disease 2.1%		symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
hzVSF-v13 **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Prasenohadi et al;[332] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 43 assigned to hzVSF-v13 200 to 400 mg once followed by two infusions of 100 to 200 mg and 19 assigned to SOC	Mean age 50.8 ± , male 61.3%, obesity 22.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ibrutinib

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
iNSPIRE trial;[333] Coutre et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 22 assigned to ibrutinib 420 mg a day for 14 to 28 days and 24 assigned to SOC	Median age 51.5, male 70%, hypertension 39%, diabetes 43%, COPD 2%, asthma 9%, CHD 2%, CKD 4%, obesity 24%	Corticosteroids 63%, remdesivir 72%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Icatibant

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mansour et al;[334] preprint; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to icatibant 30 mg every 8 hours for 4 days, and 10 assigned to SOC	Mean age 51.6 ± 11.5, male 53.3%, hypertension 50%, diabetes 46.7%, asthma 3.3%, obesity 43.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯
ICAT-COVID	Patients with	Mean age 53, male	Vaccinated 32.9%	High for mortality and	

trial;[335] Malchair et al; peer reviewed; 2022	severe COVID-19 infection. 37 assigned to icatibant 90 mg a day for 3 days and 36 assigned to SOC	67.1%		mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Icosapent ethyl

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
VASCEPA COVID-19 CARDIOLINK-9 trial;[336] kosmopoulos et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 46 assigned to icosapent ethyl 8 g a day for three days followed 4 g a day for 11 days and 49 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:**

					Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Imatinib

Imatinib may not increase severe adverse events. The effects of imatinib on other importan outcomes are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COUNTER-COVID trial;[337] Aman et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 197 assigned to imatinib 800 mg once followed by 400 mg a day for 10 days and 188 assigned to SOC	Median age 64 ± 17, male 69%, hypertension 37.6%, diabetes 25%, COPD 18.4%, asthma 18%, CHD 22%, obesity 38%	Corticosteroids 72%, remdesivir 21%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom**

					resolution or improvement: No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.05 (95%CI 0.84 to 1.32); RD 0.5% (95%CI -1.6% to 3.3%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Indomethacin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Ravichandran et al;[338] preprint; 2021	Patients with moderate COVID-19 infection. 102 assigned to indomethacin 75 mg a day and 108 assigned to SOC	Mean age 47 ± 16, male 56.2%, hypertension 19%, diabetes 29%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom**

				inappropriate.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Infliximab

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CATALYST trial;[339] Fisher et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 29 assigned to infliximab and 34 assigned to SOC	Median age 64.5 ± 20, male 61.8%	Corticosteroids 94.3%, remdesivir 61.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

				inappropriate.	**improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

INM005 (polyclonal fragments of equine antibodies)

INM005 may not improve symptom resolution and may not increase severe adverse events. Its effects on other important outcomes are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Lopardo et al;[340] peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005 4 mg/kg in two doses on days 1 and 3 and 123 assigned to SOC	Mean age 53.8 ± 12.5, male 65.1%, comorbidities 80%	Corticosteroids 57.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯

					Symptom resolution or improvement: RR 1.06 (95%CI 0.96 to 1.66); RD 3.6% (95%CI -2.4% to 10.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information

Interferon alpha-2b and interferon gamma

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ESPERANZA trial;[341] Esquivel-Moynelo et al; preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to interferon alpha-2b plus interferon gamma twice a week for two weeks (standard care) and 33 assigned to	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%, coronary heart disease 6.3%, any comorbidities 50.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, antibiotics 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No

	interferon alpha-2b three times a week (IM)			inappropriate.	information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Interferon beta-1a

IFN beta-1a probably does not reduce mortality or invasive mechanical ventilation requirements. Inhaled interferon beta-1a may improve time to symptom resolution.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Davoudi-Monfared et al;[342] preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three times a week and 39 assigned to standard of care	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	Corticosteroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.99 (95%CI 0.75 to 1.31); RD -0.2% (95%CI -4% to 5%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.01 (95%CI 0.87 to 1.18); RD 0.2% (95%CI -2.2% to 3.1%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 0.96 (95%CI 0.92 to 0.99); RD -2.6% (95%CI -4.8% to -3.2%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** Very low certainty ⊕◯◯◯
WHO SOLIDARITY trial;[290] Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 2144 assigned to interferon beta-1a three doses over six days of 44µg and 2147 assigned to SOC	Age range 50-69 years old 46.3%, male 62.3%, diabetes 25.2%, COPD 5.4%, asthma 4.3%, CHD 22%	Steroids 58.7%, convalescent plasma 2.4%, Anti IL6 3.6%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.	
COVIFERON trial;[343] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6, 20 assigned to interferon beta-1b 0.25 mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Darazam et al;[344] Preprint; 2020	Patients with severe to critical COVID-19. 85 assigned to interferon beta-1a 88 micrograms on	Mean age 59.8 ± 16.5, male 61.9%, hypertension 37.3%, diabetes 26.8%, COPD 1.2%, asthma 1.8%, CHD 18.7%,	Corticosteroids 1.1%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	

	days 1, 3 and 6 and 83 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6	CKD 8.3%, cerebrovascular disease 5.4%, cancer 0.6%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTT-3 trial;[345] Kalil et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 487 assigned to interferon beta-1a 44 µg a day for up to four days and 482 assigned to SOC	Mean age 58.7 ± 15.9, male 58%, hypertension 58%, diabetes 37%, COPD 11%, asthma 13%, CKD 12%, obesity 58%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
INTEREST trial;[346] Ranieri et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 144 assigned to interferon beta-1a 10 µg a day for 6 days and 152 assigned to SOC	Mean age 58, male 65.8%	Corticosteroids 35.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Castro-Rodriguez et al;[347] preprint; 2022	Individuals exposed to SARS-CoV-2 infection. 607 assigned to interferon beta-1a 125µg three time and 565 assigned to SOC	Mean age 34 ± , male 47.3%, diabetes 3.9%, COPD 0.1%, asthma 5.6%, CHD 5.1%, CKD 0.3%, cancer 1.2%	Corticosteroids %, Vaccinated 23.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. Significant loss to follow-up.	

Monk P et al;[348] et al; peer-reviewed; 2020	Patients with mild to severe COVID-19. 48 assigned to interferon beta-1a nebulized once a day for 15 days and 50 assigned to standard of care	Mean age 57.1 ± 13.2, male 59.2%, hypertension 54.7%, diabetes 22.6%, COPD 44.2%, asthma %, coronary heart disease 24.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Interferon beta-1b **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Rahmani et al;[349] peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to standard of care	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%	Corticosteroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
COVIFERON trial;[343] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6, 20 assigned to interferon beta-1b 0.25 mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
UW 20-535 trial;[350] Tam et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 51 assigned to interferon beta-1b 16 million IU a day for 5 days and 49 assigned to SOC	Mean age 65, male 52.8%, hypertension 42.3%, diabetes 22.6%, COPD %, asthma 3.8%, CHD 9.4%, CKD 4.2%, cerebrovascular disease 2.4%, cancer 8.5%, obesity 4.7%	Corticosteroids 29.2%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Interferon gamma **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Myasnikov et al;[351] Peer reviewed; 2021	Patients with moderate COVID-19 infection. 18 assigned to interferon gamma 500000 IU a day for 5 days and 18 assigned to SOC	Mean age 63 ± 12, male 44%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Interferon kappa plus TFF2 **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Fu et al;[352] peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2 mg once a day for six days and 40 assigned to standard of care	Mean age 35.2 ± 11.2, male 63.7%, hypertension 5%, diabetes 3.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Interleukin-2

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
STRUCK trial;[151] Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to IL-2 1.5 million IU per day for seven days and 16 assigned to SOC	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD 5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Iota-carrageenan **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
IVERCAR-TUC trial;[353] Chahla et al; Preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 117 assigned to ivermectin + iota-carrageenan 12 mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC	Median age 38 ± 12.5, male 42.7%, hypertension 9%, diabetes, 7.3%, CKD 2.1%, obesity 11.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
CARR-COV-02 trial;[354] Figueroa et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 196 assigned to Iota-carrageenan 1 puff four times a day for 21 days and 198 assigned to SOC	Mean age 38.6 ± 9.6, male 24.8%, hypertension 4.8%, diabetes 0.2%, COPD 3.3%, cancer 0%, obesity 5%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Isothymol **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Ojeda et al;[355] preprint; 2022	Patients with moderate to critical COVID-19 infection. 300 assigned to isothymol 6 mg until discharge and 300 assigned to SOC	Mean age 54, male 48.8%, hypertension 60.6%, diabetes 13.2%, asthma 24%, CHD 10.8%, CKD 5%, obesity 16.8%	Corticosteroids 12.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Unbalanced baseline risk (16% of included patients in intervention on mechanical ventilation vs. 9% in placebo).	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Itolizumab **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ITOLI-C19-02-I-00 trial;[356] Kumar et al; preprint; 2020	Patients with severe COVID-19. 20 assigned to itolizumab 1.6 mg/kg once followed by 0.8 mg/kg weekly and 10 assigned to standard of care	Mean age 49 ± 13, male 86.6%, hypertension 20%,	Nr	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ivermectin

Ivermectin probably does not reduce mortality or improve time to symptom resolution. In patients with recent onset disease, ivermectin probably does not have an important effect on hospitalizations and may not increase severe adverse events. It is uncertain if it reduces symptomatic infections when used as prophylaxis.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zagazig University trial;[357] Shouman et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 203 assigned to ivermectin 15 to 24 mg and 101 assigned to standard of care	Mean age 38.72 ± 15.94, male 51.3%, hypertension 10.2%, diabetes 8.1%, CKD 1%, asthma 2.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1 (95%CI 0.8 to 1.24); RD -0% (95%CI -3.2% to 3.8%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.82 (95%CI 0.58 to 1.17); RD -3.1% (95%CI -7.3% to 2.9%); Very Low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 1.04 (95%CI 0.98 to 1.1); RD 2.4% (95%CI -1.2% to 6%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** RR 1.01 (95%CI 0.54 to 1.89); RD 0.2% (95%CI -8% to 15.5%); Very low certainty ⨁◯◯◯ **Adverse events:** RR 1.05 (95%CI 0.69 to 1.62); RD 0.5% (95%CI -3.2% to 6.3%);
Chowdhury et al;[358] preprint; 2020	Patients with mild to moderate COVID-19. 60 assigned to ivermectin plus doxycycline 200 µgm/kg single dose + 100 mg BID for 10days and 56 assigned to hydroxychloroquine plus azithromycin	Mean age 33.9 ± 14.1, male 72.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Podder et al;[359] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 µgm/kg once and 30 assigned to standard of care	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Hashim et al;[360] preprint; 2020	Patients with mild to critical COVID-	Mean age 48.7 ± 8.6, male %	Corticosteroids 100%, azithromycin	High for mortality and mechanical	

	19. 70 assigned to ivermectin plus doxycycline 200 µgm/kg two or three doses + 100 mg twice a day for 5 to 10 days and 70 assigned to standard of care		100%,	ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.90 (95%CI 0.74 to 1.1); RD -0.5% (95%CI -1.2% to 0.5%); Moderate certainty ⊕⊕⊕◯
Mahmud et al;[361] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 183 assigned to ivermectin plus doxycycline 12 mg once + 100 mg twice a day for 5 days and 180 assigned to standard of care	Mean age 39.6 ± 13.2, male 58.8%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events. Notes: 8% of patients were lost to follow-up.	
Elgazzar et al (mild);[362] preprint (now retracted); 2020	Patients with mild to moderate COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 55.2 ± 19.8, male 69.5%, hypertension 11.5%, diabetes 14.5%, COPD %, asthma 5.5%, coronary heart disease 4%, chronic kidney disease %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elgazzar et al (severe);[362] preprint (now retracted); 2020	Patients with severe COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 58.9 ± 19.5, male 71%, hypertension 16%, diabetes 20%, COPD %, asthma 13%, coronary heart disease 7.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elgazzar et al (prophylaxis);[362]	Individuals exposed to SARS-CoV-2	NR	NR	High for mortality and mechanical	

preprint (now retracted); 2020	infection. 100 assigned to ivermectin 400 µgm/kg twice (second dose after one week) and 100 assigned to standard of care			ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Krolewiecki et al;[363] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 20 assigned to ivermectin 0.6 mg/kg for 5 days and 12 assigned to standard of care	Mean age 40.2 ± 12, male 55.5%, hypertension 13.3%, diabetes 15.5%, COPD 11.1%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Niaee et al;[364] preprint; 2020	Patients with mild to severe COVID-19. 120 assigned to ivermectin 200-800 microg/kg and 60 assigned to standard of care	Median age 67 ± 22, male 50%	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Concealment of allocation possibly inappropriate.	
Ahmed et al;[365] peer-reviewed; 2020	Patients with mild COVID-19. 55 assigned to ivermectin 12 mg a day for 5 days +/- doxycycline and 23 assigned to standard of care	Mean age 42, male 46%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
SAINT trial;[366] Chaccour et al;	Patients mild (early within 3 days of	Median age 26 ± 36, male 50%,	NR	Low for mortality and mechanical	

peer-reviewed; 2020	onset) COVID-19. 12 assigned to ivermectin 400 microg/kg and 12 assigned to SOC			ventilation; low for symptom resolution, infection, and adverse events	
Cachar et al;[367] peer-reviewed; 2020	Patients with mild COVID-19. 25 assigned to ivermectin 36 mg once and 25 assigned to SOC	Mean age 40.6 ± 17, male 62%, hypertension 26%, diabetes 40%, obesity 12%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Babalola et al;[368] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 42 assigned to ivermectin 12 to 24 mg a week for 2 weeks and 20 assigned to lopinavir-ritonavir	Mean age 44.1 ± 14.7, male 69.4%, hypertension 14.5%, diabetes 3.2%,	Corticosteroids 3.2%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Kirti et al;[369] Preprint; 2020	Patients with mild to moderate COVID-19. 55 assigned to ivermectin 24 mg divided in two doses and 57 assigned to SOC	Mean age 52.5 ± 14.7, male 72.3%, hypertension 34.8%, diabetes 35.7%, COPD 0.9%, asthma 0.9%, CHD 8.9%, CKD 2.7%, cerebrovascular disease 0%, cancer 5.4%, obesity %	Corticosteroids 100%, remdesivir 20.5%, hydroxychloroquine 100%, tocilizumab 6.3%, convalescent plasma 13.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
IVERCAR-TUC trial;[353] Chahla et al; Preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 117 assigned to ivermectin + iota-carrageenan 12 mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC	Median age 38 ± 12.5, male 42.7%, hypertension 9%, diabetes, 7.3%, CKD 2.1%, obesity 11.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

				probably inappropriate.	
Mohan et al;[370] preprint; 2020	Patients with mild to moderate COVID-19 infection. 80 assigned to ivermectin 12 to 24 mg once and 45 assigned to SOC	Mean age 35.3 ± 10.4, male 88.8%, hypertension 11.2%, diabetes 8.8%, CHD 0.8%,	Corticosteroids 14.4%, remdesivir 1.6%, hydroxychloroquine 4%, azithromycin 11.2%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Shahbaznejad et al;[371] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 35 assigned to ivermectin 0.2 mg/kg once and 34 assigned to SOC	Mean age 46.4 ± 22.5, male 50.7%	Chloroquine 75.4%, lopinavir-ritonavir 79.7%, azithromycin 57.9%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Spoorthi et al;[372] Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to ivermectin 0.2 mg/kg once or SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. RoB assessment from secondary sources as publication not available.	
Samaha et al;[373] peer-reviewed (now retracted); 2020	Patients with mild (asymptomatic) COVID-19 infection. 50 assigned to ivermectin 9 to 12 mg or 150 µg/kg once and 50 assigned to SOC	Mean age 31.6 ± 7.7, male 50%, hypertension 8%, diabetes 6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Randomization process and concealment of allocation is probably	

				inappropriate.	
Bukhari et al;[374] Preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to ivermectin 12 mg once and 41 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Okumus et al;[375] peer-reviewed; 2021	Patients with severe COVID-19. 30 assigned to ivermectin 0.2 mg/kg for 5 days and 30 assigned to SOC	Mean age 62 ± 12, male 66%, hypertension 21.6%, diabetes 45%, COPD 1.6%, CHD 1.6%, cancer 1.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Beltran et al;[300] peer reviewed; 2021	Patients with moderate to severe COVID-19. 36 assigned to ivermectin 12–18 mg once and 37 assigned to SOC	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
Lopez-Medina et al;[376] peer-reviewed; 2021	Patients with mild to moderate COVID-19 infection. 200 assigned to ivermectin 300 µg/kg a day for 5 days and 198 assigned to SOC	Median age 37 ± 19, male 42%, hypertension 13.4%, diabetes 5.5%, COPD 3%, CHD 1.7%, cancer %, obesity 18.9%	Corticosteroids 4.5%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

Bermejo Galan et al;[302] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to ivermectin 42 mg and 115 assigned to HCQ or CQ	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer 3%, obesity 37.5%	Corticosteroids 98%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Pott-Junior et al;[377] peer-reviewed (now retracted); 2021	Patients with moderate to critical COVID-19 infection. 27 assigned to ivermectin 100 to 400 mcg/kg and 4 assigned to SOC	Mean age 49.4 ± 14.6, male 45.2%	Corticosteroids 32.3%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Kishoria et al;[378] peer-reviewed; 2021	Patients with moderate to severe COVID-19 infection. 19 assigned to ivermectin 12 mg and 16 assigned to SOC	Mean age 38, male 66%	Hydroxychloroquine 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Seet et al;[303] peer-reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 617 assigned to ivermectin 12 mg once and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Abd-Elsalam et al;[379] peer-reviewed; 2021	Patients with moderate COVID-19 infection. 82 assigned to ivermectin 12 mg a day for 3 days and 82 assigned to SOC	Mean age 40.8 ± 16.5, male 50%, hypertension 19.5%, diabetes 16.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Biber et al;[380] peer-reviewed; 2021	Patients with mild recent onset COVID-19 infection. 47 assigned to ivermectin 48 to 55 mg administered for three days and 42 assigned to SOC	Mean age 35 ± 19, male 78.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: 5.2% of patients lost to follow-up.	
Faisal et al;[381] peer-reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to ivermectin 12 mg a day for 5 days and 50 assigned to SOC	Mean age 46 ± 3, male 80%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Vallejos et al;[382] peer reviewed; 2021	Patients with mild COVID-19 infection. 250 assigned to ivermectin 24-36 mg and 251 assigned to SOC	Mean age 42.5 ± 15.5, male 52.7%, hypertension 23.8%, diabetes 9.6%, COPD 2.8%, asthma 7.2%, CHD 1.8%, cancer 1.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COVER trial;[383] Buonfrate et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 61 assigned to	Median age 47 ± 27, male 58.1%, diabetes 9.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and	

	ivermectin 600 to 1200 µg/kg once a day for 5 days and 32 assigned to SOC			adverse events	
Manomaipiboon et al;[384] preprint; 2021	Patients with mild COVID-19 infection. 36 assigned to ivermectin 12 mg a day for 5 days and 36 assigned to SOC	Mean age 48.6 ± 14.8, male 37.5%, hypertension 40.3%, diabetes 23.6%, CHD 2.8%, CKD 6.9%, cerebrovascular disease 2.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
I-TECH trial;[385] Chee Loon Lim et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 241 assigned to ivermectin 6 to 12 mg a day for 5 days and 249 assigned to SOC	Mean age 62.5, male 49.5%, hypertension 82%, diabetes 58.2%, COPD 8.4%, CHD 12.6%, CKD 15.7%, cerebrovascular disease 4.2%, immunosuppressive therapy 0.2%, cancer 3.1%, obesity 26%	Corticosteroids 28.9%, tocilizumab 0.9%, Baricitinib 2.4%; Vaccinated 56.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOGHETER trial;[386] Reis et al; peer reviewed; 2021	Patients with recent onset mild COVID-19 infection. 679 assigned to ivermectin 400 µg/kg once a day for 3 days and 679 assigned to SOC	Median age 49, male 41.8%, hypertension 8.4%, diabetes 12.9%, COPD 3%, asthma 8.4%, CHD 1.8%, CKD 0.5%, obesity 49.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
SILVERBULLET trial;[387] De la Rocha et al; preprint; 2021	Patients with mild COVID-19 infection. 33 assigned to ivermectin and 33 assigned to soc	Mean age 38.5 ± 14.6, male 27.3%, hypertension 8.9%, diabetes 5.3%, CHD 7.1%, CKD 1.8%, obesity 19.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Cruz Arteaga et al;	Patients with mild COVID-19	Age (18 – 65 years old) 96.4% , male	NR	NA	

NCT04673214; other; 2021	infection. 65 assigned to ivermectin adjusted to body weight and 46 assigned to SOC	47.7%,			
ACTIV-6 trial;[388] Naggie et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 817 assigned to ivermectin 400 µg/kg for three days and 774 assigned to SOC	Median age 47, male 46.6%, diabetes 11.8%, COPD 3.65%, asthma 15.5%, CHD 4.5%, CKD 0.77%, cancer 3.02%, obesity 40.8%	Remdesivir 0.3%, Vaccinated 48.8%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Rezai_Mild trial;[389] Rezai et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 268 assigned to ivermectin 0.4 mg/kg a day for 3 days and 281 assigned to SOC	Mean age 35.4 ± 17.4, male 53.4%, hypertension 7.8%, diabetes 7.3%, asthma 2.4%, CHD 2.7%, cancer 0.6%, obesity 21.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Rezai_Severe trial;[389] Rezai et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 311 assigned to ivermectin 0.4 mg/kg a day for 3 days and 298 assigned to SOC	Mean age 53.8, male 47.8%, hypertension 28.4%, diabetes 31.7%, COPD %, asthma 3%, CHD 12.2%, obesity 73.3%	Corticosteroids 90.7%, remdesivir 98.2%, hydroxychloroquine 35%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	
Angkasekwinai treatement trial;[390] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 233 assigned to ivermectin 400–600 µg/kg/d and 214 assigned to SOC	Mean age 39.5 ± 12.1, male 43.2%, hypertension 11.2%, diabetes 6.9%, COPD 0.2%, CHD 1.8%, CKD 0.4%, cerebrovascular disease 0.2%, cancer 0.2%,	Vaccinated 74.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Angkasekwinai prevention trial;[390] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 259 assigned to	Mean age 37.6 ± 12, male 42.2%, hypertension 8.8%, diabetes 4.7%,	Vaccinated 84.1%	Low for mortality and mechanical ventilation; low for symptom resolution,	

	ivermectin 400–600 µg/kg/d and 277 assigned to SOC	COPD 0.2%, CHD 1.1%, cerebrovascular disease 0.4%, cancer 1.3%		infection and adverse events Notes:	
Mirahmadizadeh et al;[391] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 261 assigned to ivermectin 12 to 24 mg once and 130 assigned to SOC	Mean age 39.3, male 53.9%, hypertension 6.1%, diabetes 3.8%, COPD 0.8%, CHD 0.8%, CKD 0.5%, cancer 0.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
George et al;[392] peer reviewed; 2022	Patients with hematological disorders and mild to moderate COVID-19 infection. 73 assigned to ivermectin 12 to 24 mg once and 39 assigned to SOC	Mean age 41.2 ± , male 70.5%, cancer 75.9%	Corticosteroids 62.5%, remdesivir 18.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLATCOV - Iver trial;[393] Schilling et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 45 assigned to ivermectin 600µg/kg daily for seven days and 41 assigned to SOC	Mean age 28, male 45.5%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
IRICT trial;[321] Elshafie et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 104 assigned to ivermectin 36 mg on days 1, 3 and 6 and 102 assigned to SOC	Mean age 59.4 ± , male 53.4%, hypertension 38.3%, diabetes 27.7%, CKD 9.2%, obesity 19.9%	Corticosteroids 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Nimitvilai et al;[394] peer reviewed; 2022	Patients with mild COVID-19 infection. 57 assigned to ivermectin 0.6 mg/kg for 3 days and 56 assigned to HCQ 200 mg a day + darunavir/ritonavir 400/100 mg a day for 5 days	Mean age 40, male 45.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-OUT trial;[262] Bramante et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 410 assigned to Ivermectin 390 to 470 µg/kg a day for 3 days and 398 assigned to SOC	Median age 45.5, male 45.3%, hypertension 22.8%, diabetes 1.6%, obesity 47.4%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; vaccinated 55.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Ivermectin (inhaled) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Aref et al;[395] peer reviewed; 2021	Patients with mild COVID-19 infection. 57 assigned to inhaled (inh) ivermectin and 57 assigned to SOC	Mean age 45 ± 19, male 71.9%, hypertension 17.5%, diabetes 12.3%, COPD 0.9%, cerebrovascular disease 3.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Randomization and concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Intravenous immunoglobulin (IVIG) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Sakoulas et al;[396] preprint; 2020	Patients with severe COVID-19 infection. 16 assigned to IVIG 0.5 g/kg/day for 3 days and 17 assigned to standard of care	Mean age 54 ± NR, male 60.6%, hypertension 33.3%, diabetes 36.3%, chronic lung disease 12%, coronary heart disease 3%, chronic kidney disease 3%, immunosuppression 3%	Corticosteroids 78.7%, remdesivir 51.5%, convalescent plasma 15.2%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Gharebaghi et al;[397] preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to IVIG 5 g a day for 3 days and 29 assigned to standard of care	Mean age 56 ± 16, male 69.5%, hypertension 22%, diabetes 27.1%, chronic lung disease 3.3%,	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
Tabarsi et al;[398] peer-reviewed; 2020	Patients with severe COVID-19. 52 assigned to IVIG 400 mg/kg daily for three doses and 32 assigned to standard of care	Mean age 53 ± 13, male 77.4%, hypertension 20.2%, diabetes 21.4%, COPD 1.2%, asthma %, coronary heart disease %, chronic kidney disease 4.7%, cancer 1.2%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Raman et al;[399] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to IVIG 0.4 g/kg for 5 days and 50 assigned to SOC	Mean age 48.7 ± 12, male 33%, hypertension 31%, obesity 16%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Ixekizumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
STRUCK trial;[151] Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 16 assigned to ixekizumab 80 mg once and 16 assigned to SOC	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD 5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

KB109 (microbiome modificator) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Haran et al;[400] preprint; 2021	Patients with mild to moderate COVID-19 infection. 169 assigned to KB109 9-36 g twice a day for 14 days and 172 assigned to SOC	Median age 36 ± 56, male 40.8%, hypertension 18%, diabetes 2.5%, COPD 8.8%, cerebrovascular disease 2.3%, cancer 0.8%, obesity 3.7%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

L-arginine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Coppola et al;[401] peer reviewed; 2021	Patients with severe COVID-19 infection. 45 assigned to L-arginine 1.66 g twice a day during hospitalization and 45 assigned to SOC	Mean age 61.6, male 81.2%, hypertension 36.7%, diabetes 10%, CHD 14.5%, obesity 10%	Corticosteroids 100%, remdesivir 27.8%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Muralidharan et al;[402] peer reviewed; 2023	Patients with severe COVID-19 infection. 38 assigned to L-arginine 3 gr a day for 10 days and 36 assigned to SOC	Mean age 64, male 59%, hypertension 55.7%, diabetes 57.1%, COPD 28.5%, CHD 16.2%, CKD 13.5%	Corticosteroids 83.9%, remdesivir 17.6%; Vaccinated 87.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

***Lactococcus lactis* (intranasal)** **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
PROBCO trial;[403] Endam et al; preprint; 2021	Patients with mild recently diagnosed COVID-19 infection. 12 assigned to *Lactococcus lactis* (intranasal) two nasal irrigations a day and 11 assigned to SOC	Mean age 30.4 ± 9.1, male 30%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Lactoferrin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Algahtani et al;[404] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 36 assigned to lactoferrin 200 to 400 mg a day and 18 assigned to SOC	Mean age 48.6, male 60.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information
LF-COVID trial;[405] Navarro et al; peer reviewed; 2022	Patients with exposed to COVID-19 infection. 104 assigned to lactoferrin 600 mg a day for 90 days and 105 assigned to SOC	Mean age 36.5, male 24.4%, hypertension 3.3%, diabetes 1.4%, asthma 5.3%, obesity 17.7%	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Leflunomide Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hu et al;[406] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50 mg every 12 h (three doses) followed by 20 mg a day for 10 days and 5 assigned to standard of care	Mean age 52.5 ± 11.5, male 30%, hypertension 60%, chronic lung disease 10%	Umifenovir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Wang et al;[407] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day followed by 20 mg a day for 8 days and 24 assigned to standard of care	Median age 55.7 ± 21.5, male 50%, hypertension 27.2%, diabetes 4.5%, chronic lung disease 4.5%, coronary heart disease 2.3%, cancer 2.3%	Corticosteroids 34.1%, hydroxychloroquine 56.8%, lopinavir-ritonavir 11.4%, umifenovir 75%, IVIG 20.4%, ATB 63.6%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Lenzilumab Lenzilumab may reduce mechanical ventilation requirements and may not increase severe adverse events. The effects of lenzilumab on other importan outcomes are uncertain. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
LIVE-AIR trial;[408] Temesgen et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 236 assigned to lenzilumab 1800 mg once and 243 assigned to SOC	Mean age 60.5 ± 13.9, male 64.7%, hypertension 66%, diabetes 53.4%, COPD 7.3%, asthma 10.6%, CHD 13.6%, CKD 14%,	Corticosteroids 93.7%, remdesivir 72.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.72 (95%CI 0.44 to 1.19); RD -4.5% (95%CI -9% to 3%); Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.71 (95%CI 0.48 to 1.04); RD -5% (95%CI -9% to 0.7%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.82 (95%CI 0.62 to 1.07); RD -1.8% (95%CI -3.9% to 0.7%); Low certainty ⊕⊕⊕◯ **Hospitalization:** No information

Levamisole Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Roostaei et al;[409] Preprint; 2020	Patients with mild to moderate COVID-19. 25 assigned to levamisole 150 mg a day for 3 days and 25 assigned to SOC	Mean age 36.6 ± 13.7, male 60%,	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** **Mortality:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Asgardoon et al;[410] preprint; 2021	Patients with mild to moderate COVID-19 infection. 185 assigned to levamisole 50 mg a day for 10 days and 180 assigned to SOC	Median age 40 ± 18.75, male 56.1%, hypertension 8.8%, diabetes 9.4%, CHD 1.6%	Hydroxychloroquine 11.2%,	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Levilimab Levilimab may improve time to symptom resolution; however, the certainty of the evidence was low. The effects of levilimab on other important outcomes are uncertain. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
CORONA trial;[411] Lomakin et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 103 assigned to levilimab 364 mg once (subcutaneous) and 103 assigned to SOC	Mean age 58.3 ± 11.8, male 52.9%, CHD 15.5%,	Corticosteroids 7.3%, hydroxychloroquine 67.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement: Mortality:** RR 1.48 (95%CI 1.13 to 1.93); RD 29.1% (95%CI -7.9% to 56.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Linagliptin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Abuhasira et al;[412] peer reviewed; 2021	Patients with moderate to severe with diabetes COVID-19 infection. 32 assigned to linagliptin 5 mg a day and 32 assigned to SOC	Mean age 66.9 ± 13.9, male 59.4%, diabetes 100%,	Corticosteroids 82.8%, remdesivir 50%, convalescent plasma 10.9%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Covid19DPP4i trial;[413] Guardado-Mendoza et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 34 assigned to linagliptin 5 mg a day and 35 assigned to SOC	Mean age 58.5, male 63.7%, hypertension %, diabetes 66.6%, CHD 5.8%, CKD 14.5%, cerebrovascular disease 2.9%,	Corticosteroids 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Lincomycin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Guvenmez et al;[79] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Lithium Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Spuch et al;[414] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 15 assigned to lithium 400 mg a day and 15 assigned to SOC	Mean age 58.6, male 56.7%, hypertension 30%, diabetes 3.3%, COPD %, CHD 6.7%, obesity 16.7%	Corticosteroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Lopinavir-ritonavir Lopinavir-ritonavir probably does not reduce mortality with moderate certainty. Lopinavir-ritonavir may not be associated with a significant increase in severe adverse events. However, the certainty is low because of risk of bias and imprecision.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
LOTUS China trial;[415] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to lopinavir-ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Corticosteroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -1.3% to 1.8%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Severe Adverse events:** RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -6.5% to -0.2%); Low
ELACOI trial;[416] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, intravenous immunoglobulin 6.3%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY - Lopinavir-ritonavir trial;[417] Horby et al; other; 2020	Patients with mild to critical COVID-19 infection. 1616 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days and 3424 assigned to standard of care	Mean age 66.2 ± 15.9, male 60.5%, diabetes 27.5%, chronic lung disease 23.5%, coronary heart disease 26%	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might	

				have introduced bias to symptoms and adverse events outcomes results.	certainty ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Huang et al; peer-reviewed;[272] 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Zheng et al; preprint;[418] 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-ritonavir 40 mg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Chen et al; preprint;[419] 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 g IV loading dose followed by orally 400-600 mg every 8 hours for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

WHO SOLIDARITY trial;[290] Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 1404 assigned to lopinavir-ritonavir 200/50MG twice a day for 14 days and 1368 assigned to SOC	Age range 50-69 years old 43.1%, male 59.6%, diabetes 24.2%, COPD 6.5%, asthma 4.9%, CHD 21%	Steroids 27.2%, convalescent plasma 1.4%, anti IL6 3%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.	
Sali et al;[420] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to sofosbuvir 400 mg a day and 32 assigned to lopinavir-ritonavir 400/100 mg every 12 hours	Mean age 56.5 ± 14, male 53.7%, diabetes 33%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Purwati et al;[421] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to HCQ 200 mg a day and 119 to SOC	Median age 36.5 ± NR, male 95.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Kasgari et al;[422] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

	ritonavir			probably inappropriate.	
Yadollahzadeh et al;[423] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/ daclatasvir 400/60 mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100 mg twice a day for 7 days	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%, immunosuppression 3.6%, cancer 10.7%	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
TOGETHER trial;[304] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 244 assigned to lopinavir-ritonavir 1600 mg/400 mg once followed by 800 mg/200 mg a day for 9 days and 227 assigned to SOC	Mean age 53 ± 76, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COPEP trial;[424] Labhardt et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 209 assigned to lopinavir-ritonavir 400/10 mg a day for 5 days and 109 assigned to SOC	Median age 39 ± 22, male 50.6%, hypertension 8.2%, diabetes 3.1%, COPD 7.8%, CHD 2.5%, cancer 0.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Ghanei et al;[86] peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to lopinavir-ritonavir 200/50 mg twice a day for 7 days and	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	110 assigned to azithromycin 500 mg once followed by 250 mg a day for 5 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
FIGHT-COVID-19 trial;[243] Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800 mg a day or darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day or favipiravil 6000 mg followed by 2400 mg + darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day for 7 to 14 days.	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
SEV-COVID trial;[313] Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 24 assigned to lopinavir ritonavir + ribavirin lopinavir (200 mg) + ritonavir (50 mg) two tablets twice daily + ribavirin (1.2 g orally as a loading dose followed by 600 mg orally every 12 hours) for 10 days and 24 assigned to SOC	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Nekoukar et al;[70] peer reviewed;	Patients with severe COVID-19	Mean age 49.9 ± 12.6, male 55.6%,	Corticosteroids 42.7%, remdesivir	High for mortality and mechanical	

2021	infection. 62 assigned to atazanavir/ritonavir 300/100 mg a day for 5 to 10 days and 62 assigned to lopinavir-ritonavir 200/50 mg a day for 5 to 10 days	hypertension 16.9%, diabetes 27.4%, COPD 0.8%, asthma 1.6%	13.7%, tocilizumab 3.2%, azithromycin 50.8%	ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hassaniazad et al;[248] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg for 5 days and 31 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Mean age 53.7 ± 13.5, male 57.1%, hypertension 27%, diabetes 20.6%, COPD 1.6%, CHD 14.2%, obesity 7.9%	Interferon beta 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
FLARE trial;[249] Lowe et al; preprint; 2021	Patients with mild recento onset COVID-19 infection. 60 assigned to lopinavir-ritonavir 800/200 mg a day for 7 days and 60 assigned to SOC	Mean age 40 ± 12, male 51.2%, obesity 16.7%, any comorbidity 15%	Vaccinated 51.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Tabarsi et al;[250] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 30 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Median age 57, male 58.1%, hypertension 12.9%, diabetes 21%, COPD %, asthma 3.2%, CHD 14.5%, CKD 3.2%, therapy %, cancer 4.8%, obesity 3.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Low-dose radiation therapy Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COVID-RT-01 trial;[425] Papachristofilou et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 11 assigned to low-dose radiation therapy 0.5 to 1.0 Gy and 11 assigned to SOC	Mean age 75, male 77.3%, diabetes 54.6%, COPD 22.7%, asthma %, CHD 40.9%, cancer 18.2%,	Corticosteroids 100%, remdesivir 50%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
WINCOVID trial;[426] Ganesan et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 34 assigned to low-dose radiation therapy 0.5 Gy single session and 17 assigned to SOC	Age (>56) 58.8% , male 66.6%, hypertension 35.3%, diabetes 68.6%, asthma 2%	Corticosteroids 100%, remdesivir 50.9%, tocilizumab 21.6%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
IMpaCt-RT trial;[427] Singh et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 7 assigned to low-dose radiation therapy 0.7 Gy and 6 assigned to SOC	Median age 56 ± , male 53.8%	Corticosteroids 100%, remdesivir 46.1%, azithromycin 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Mavrilimumab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
MASH-COVID trial;[428] Cremer et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 21 assigned to mavrilimumab 6 mg/kg once and 19 assigned to SOC	Mean age 56.7 ± 23.8, male 65%, hypertension 55%, diabetes 43%, COPD 8%, CKD 8%, cerebrovascular disease 3%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Melatonin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Farnoosh et al;[429] peer reviewed; 2020	Patients with mild to moderate COVID-19. 24 assigned to melatonin 9 mg a day for 14 days and 20 assigned to SOC	Mean age 51.85 ± 14.25, male 59.1%, hypertension 25%, diabetes 22.7%, CHD 6.8%, cancer 6.8%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation is probably inappropriate. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information
Davoodian et al;[430] preprint; 2021	Patients with severe COVID-19 infection. 41 assigned to melatonin 6 mg a day for 14 days and 39 assigned to SOC	Median age 56 ± 40, male 56.8%, hypertension 18.5%, diabetes 14.8%, CHD 19.8%, CKD 3.7%	Corticosteroids 12.3%, hydroxychloroquine 69%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Alizadeh et al;[431] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 14 assigned to melatonin 6 mg a day for 14 days and 17 assigned to SOC	Mean age 36 ± 8.2, male 64.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mousavi et al;[432] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 48 assigned to melatonin 3 mg a day for 10 days and	Mean age 52.9, male 44.8%, hypertension 30.2%, diabetes 28.1%, COPD 3.1%, asthma 5.2%, CHD 15.6%, CKD 5.2%,	Corticosteroids 82.3%, hydroxychloroquine 97.9%, lopinavir-ritonavir 2.1%, azithromycin 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	48 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hasan et al;[433] peer reviewed; 2021	Patients with severe COVID-19 infection. 82 assigned to melatonin 10 mg a day for 14 days and 76 assigned to SOC	Mean age 56.3 ± 7.7, male 72.2%, hypertension 53.2%, diabetes 29.7%, asthma 10.1%, cerebrovascular disease 15.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
MeCOVID trial;[434] García-García et al; peer reviewed; 2021	Healthcare workers exposed to SARS-COV-2. 151 assigned to melatonin 2 mg a day for 12 weeks and 163 assigned to SOC	Median age 40, male 18.8%, hypertension 3.2%, CHD 0.3%, cancer 2.5%, obesity 0.3%	NR	Some Concerns for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	
Alizadeh et al;[435] peer reviewed; 2021	Patients with critical COVID-19 infection. 33 assigned to melatonin 21 mg a day and 34 assigned to SOC	Mean age 63.5, male 64%	NR	Some Concerns for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Fogleman C et al trial;[436] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 32 assigned to melatonin 10 mg a day for 14 days and 34 assigned to SOC	Median age 52, male 44.9%, hypertension 26.5%, diabetes 16.3%	Vaccinated 2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Ameri et al;[437] peer reviewed; 2022	Patients with severe COVID-19 infection. 109 assigned to melatonin 10 mg a day for 7 days and 117 assigned to SOC	Mean age 54.6, male 42.3%, hypertension 26.5%, diabetes 29.2%, asthma 4.9%, CHD 6.2%, cancer 5.3%	Corticosteroids 44.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Mefenamic acid

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
MEFECOVID-19 trial;[438] Guzman-Esquivel et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 19 assigned to mefenamic acid 1500 mg a day for 7 days and 17 assigned to SOC	Mean age 39.5 ± 15.4, male 33.3%, diabetes 5.6%, asthma 2.8%, obesity 47.2%	Corticosteroids 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Mesenchymal stem-cell transplantation **Mesenchymal stem-cell transplantation may reduce mortality. However, certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Shu et al;[439] peer-reviewed; 2020	Patients with severe COVID-19 infection. 12 assigned to mesenchymal stem cell 2 × 10^6 cells/kg one infusion and 29 assigned to standard of care	Median age 61 ± 10, male 58.5%, hypertension 22%, diabetes 19.5%	Corticosteroids 100%, antibiotics 87.8%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.66 (95%CI 0.47 to 0.92); RD -5.4% (95%CI -8.5% to -1.3%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:**
Shi et al;[440] preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem cell three infusions with 4.0 ×107 cells each and 35 assigned to standard of care	Mean age 60.3 ± 8.4, male 56%, hypertension 27%, diabetes 17%, COPD 2%	Corticosteroids 22%	Low for mortality and mechanical ventilation	
Lanzoni et al;[441] preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell 100±20 ×106 UC-MSC twice and	Mean age 58.7 ± 17.5, male 54.1%, hypertension 66.7%, diabetes 45.8%, coronary heart disease 12.5%, , cancer 4.2%, obesity	Corticosteroids 90.4%, remdesivir 66.7%, hydroxychloroquine 12.5%, tocilizumab 20.8%, convalescent	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	12 assigned to standard of care	66.6%	plasma 29.1%	Notes: Concealment of allocation probably inappropriate.	No information
Dilogo et al;[442] peer reviewed; 2021	Patients with critical COVID-19 infection. 20 assigned to mesenchymal stem cell one 100 ml infusion and 20 assigned to SOC	age >60, 45%, male 75%, hypertension 42.5%, diabetes 50%, CHD 25%, CKD 17.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Zhu et al;[443] peer reviewed; 2021	Patients with severe COVID-19 infection. 29 assigned to mesenchymal stem cell 1 × 106 cells per kilogram body weight, once and 29 assigned to SOC	Median age 65, male 37.9%, hypertension 25.8%, diabetes 13.8%, COPD 1.7%, CHD 10.3%, cerebrovascular disease 8.6%	Corticosteroids 67.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Fathi-Kazerooni et al;[444] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to mesenchymal stem cell 5 ml a day for 5 days and 15 assigned to SOC	Mean age 50 ± , male 65.5%, hypertension 31%, diabetes 24.1%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Rebelatto et al;[445] peer reviewed; 2021	Patients with critical COVID-19 infection. 11 assigned to mesenchymal stem cell three doses of 5 × 105 cells/kg UC-MSCs and 6 assigned to SOC	Mean age 56, male 70.5%, hypertension 52.9%, diabetes 41.2%, COPD 5.9%, CKD 5.9%, obesity 52.9%		Some Concerns for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
DW-MSC trial;[446] Karyana et al; peer reviewed;	Patients with mild COVID-19 infection. 6	Age range 31 to 47, male 66.6%	NR	Low for mortality and mechanical ventilation; low for	

2021	assigned to mesenchymal stem cell 5.0 × 10^7 cells to 1.0 × 10^8 cells and 3 assigned to SOC			symptom resolution, infection and adverse events	
Farkhad et al;[447] preprint; 2022	Patients with severe COVID-19 infection. 10 assigned to mesenchymal stem cell 3 intravenous infusions of UC-MSCs (1 × 10^6 cells/kg BW per injection) every other day and 10 assigned to SOC	Mean age 61.7, male 65%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Malueka et al;[448] preprint; 2023	Patients with severe COVID-19 infection. 21 assigned to mesenchymal stem cell 1x10 6 cells per kilogram of body weight and 21 assigned to SOC	Mean age 56	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Metformin

Metformin may not reduce hospitalizations. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
TOGETHER 2 trial;[449] Reis et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 215 assigned to MTF 1500 mg a day and 203 assigned to SOC	Median age 52, male 42.8%, hypertension 40%, diabetes 14.6%, COPD 1.2%, asthma 8.1%, CHD 3%, CKD 0.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

DMMETCOV19-2 trial;[450] Ventura-López et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 10 assigned to metformin 1240 mg a day for 14 days and 10 assigned to SOC	Mean age 47.5, male 85%, hypertension 20%, diabetes 20%, COPD 10%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.92 (95%CI 0.61 to 1.37); RD -0.4% (95%CI -1.9% to 1.8%); Low certainty ⊕⊕◯◯
COVID-OUT trial;[262] Bramante et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 663 assigned to metformin 1500 mg a day for 14 days and 398 assigned to SOC	Median age 45.5, male 44%, hypertension 26.7%, diabetes 2%, obesity 48.8%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 52.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Methylene blue

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hamidi-Alamdari et al;[451] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to methylene blue 1 mg/kg every 12 to 8 h for 14 days and 40 assigned to SOC	Mean age 54 ± 13, male 52.5%, hypertension 17.5%, diabetes 10%	Corticosteroids 87.5%, azithromycin 92.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information

Metisoprinol

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Borges et al;[452] peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to metisoprinol 1500 mg/kg/day for 14 days and 30 assigned to SOC	Mean age 33.2 ± 16, male 53.3%, COPD 10%, CKD 16.6%, cancer 3.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Metoprolol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
MADRID-COVID trial;[453] Clemente-Moragón et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 12 assigned to metoprolol 15 mg a day for 3 days and 8 assigned to SOC	Median age 60 ± 14.2, male 65%, hypertension 30%, diabetes 10%	Corticosteroids 100%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Metronidazole **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Kazempour et al;[454] peer reviewed; 2021	Patients with moderate COVID-19 infection. 20 assigned to metronidazole 1 g a day for 7 days and 24 assigned to SOC	Mean age 63 ± 16.3, male 59.1%, hypertension 47.7%, diabetes 18.2%, COPD 6.8%, asthma %, CHD 4.5%	Hydroxychloroquine 59%, lopinavir-ritonavir 43.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information **Hospitalization:** No information

Molnupiravir **Molnupiravir probably has no important effect on hospitalizations but probably improves time to symptom resolution in patients with recent onset mild to moderate disease, it may not increase severe adverse events.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Painter et al;[455] Preprint; 2020	Healthy volunteers. 64 assigned to molnupiravir 80 to 1600 mg twice a day for 5.5 days	Mean age 39.6 ± 39, male 82.8%,	NR	Low for adverse events	**Mortality:** RR 0.38 (95%CI 0.11 to 1.35); RD -9.9% (95%CI -14% to 5.6%); Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** RR 0.36 (95%CI 0.11 to 1.12); RD -11.1% (95%CI -15.4% to -2.1%); Very low certainty ⊕◯◯◯ **Symptom**
AGILE trial;[456] Khoo et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 12 assigned to molnupiravir 600-1600 mg a day and 6 assigned to SOC	Median age 56 ± 58, male 27.8%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Fischer et al;[457] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 140 assigned to molnupiravir 200 to 800 mg twice a day for 5 days and 62 assigned to SOC	Age >65 6%±, male 48.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**resolution or improvement:** RR 1.17 (95%CI 1.1 to 1.3); RD 39.4% (95%CI 12.1% to 39.4%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.75 (95%CI 0.48 to 1.19); RD -2.6% (95%CI -5.3% to -1.9%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.66 (95%CI 0.43 to 1.01); RD -1.6% (95%CI -2.7% to 0%); Moderate certainty ⊕⊕⊕◯
MOVe-OUT trial; et al;[458] Bernal et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 709 assigned to molnupiravir 1600 mg a day for 5 days and 699 assigned to SOC	Median age 43, male 48.7%, diabetes 15.9%, COPD 4%, asthma %, CHD 11.7%, CKD 5.9%, cancer 2%, obesity 73.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
HCR/III/MOLCOV/04/2021-01 trial; Hetero et al; other; 2021	Patients with mild COVID-19 infection. 608 assigned to molnupiravir 1600 mg a day for 5 days and 610 assigned to SOC	Male 68.6%	NR	Not assessed	
CR216-21 trial;[459] Tippabhotla et al; preprint; 2021	Patients with mild COVID-19 infection. 610 assigned to molnupiravir 800 mg a day for 5 days and 610 assigned to SOC	Mean age 36.5 ± 11, male 61.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zou et al;[460] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 76 assigned to molnupiravir 1600 mg a day for 5 days and 31 assigned to SOC	Median age 39.8 ± , male 55.5%	Vaccinated 91.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment	

				of allocation probably inappropriate.	
AGILE trial;[461] Khoo et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 90 assigned to molnupiravir 1600 mg a day for 5 days and 90 assigned to SOC	Mean age 42.5 ± , male 42.8%	Vaccinated 50%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
MOVe-IN trial;[462] Ariibas et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 226 assigned to molnupiravir 400 to 1600 mg a day for 5 days and 78 assigned to SOC	Mean age 57, male 66.6%	Corticosteroids 67.1%, remdesivir 23.7%; Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
MOVe-OUT - ph2 trial;[463] Caraco et al; peer reviewed; 2022	Patients with mild COVID-19 infection. 228 assigned to molnupiravir 400 to 1600 mg a day for 5 days and 74 assigned to SOC	Mean age 52.6, male 49.2%, diabetes 16.6%, COPD 3.6%, asthma %, CHD 8.3%, CKD 2.3%, immunosuppression 0%, cancer 1%, obesity 48.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:	
PANORAMIC-Molnu trial;[464] Butler et al; peer reviewed; 2022	Patients with mild COVID-19 infection. 12529 assigned to molnupiravir 1600 mg a day for 5 days and 12525 assigned to SOC	Mean age 56.6 ± 12.6, male 41%, hypertension 22%, diabetes 12%, CHD 8%, CKD 2%, obesity 15%	Vaccinated 99%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	

Montelukast **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Kerget et al;[465] peer reviewed; 2021	Patients with moderate COVID-19 infection. 120 assigned to montelukast 10 to 20 mg a day and 60 assigned to SOC	Mean age 54.6 ± 15.3, male 42.2%, hypertension 30%, diabetes 19%, asthma 1.7%, CHD 1.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

					No information **Hospitalization:** No information

Mouthwash

Mouthwash may improve time to symptom resolution. Uncertainty in potential benefits and harms on other outcomes. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mukhtar et al;[466] preprint ; 2020	Patients with mild to critical COVID-19. 46 assigned to mouthwash with hydrogen peroxide 2% and chlorhexidine gluconate mixed solution three times a day and 46 assigned to standard of care	Mean age 49, male 78.2%, hypertension 37%, diabetes 41.3%, coronary heart disease 6.5%, chronic kidney disease 12%, c obesity 31.5%	Corticosteroids 53.2%, remdesivir 26%, hydroxychloroquine 21.7%, lopinavir-ritonavir 54.3%, azithromycin 57.6%, convalescent plasma 13%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.36 (95%CI 1.04 to 1.78); RD 21.8% (95%CI 2.4% to 47.3%); Low certainty ⊕⊕◯◯
GARGLES trial;[467] Mohamed et al; preprint; 2020	Patients with COVID-19. 10 assigned to mouthwash with povidone iodine or essential oils 3 times a day and 10 assigned to	Median age 28.9, male 80%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	mouthwash with water or no mouthwash			study. Concealment of allocation is probably inappropriate.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
KILLER trial;[468] Guenezan et al; peer reviewed; 2020	Patients with mild COVID-19. 12 assigned to mouthwash with 25 ml of 1% povidone iodine and 12 assigned to SOC	Mean age 45 ± 23, male 33%, hypertension 12.5%, diabetes 4%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elzein et al;[469] preprint; 2021	Patients with mild to severe COVID-19 infection. 52 assigned to mouthwash with povidone or chlorhexidine and 9 assigned to SOC	Mean age 45.3 ± 16.7, male 40.9%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Santos et al;[470] preprint; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to mouthwash with anionic iron tetracarboxyphthalocyanine derivative 5 times a day and 21 assigned to SOC	Mean age 53.7 ± 44.5, male 63%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
BBCovid trial;[471] Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to mouthwash with ß-cyclodextrin-citrox three times a day	Mean age 43.8 ± 15.5, male 45.7%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

	and 78 assigned to SOC				
Huang et al;[472] peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 66 assigned to mouthwash chlorhexidine 0.12% 15 ml twice a day for 4 days and 55 assigned to SOC	Median age 62 ± 66, male 58%	Corticosteroids 100%, remdesivir 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Eduardo et al;[473] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 34 assigned to mouthwash cetylpyridinium chloride, zinc, chlorhexidine, hydrogen peroxide and 9 assigned to SOC	Mean age 54.7, male 74.4%, hypertension 30.2%, diabetes 23.2%, COPD 11.6%, CHD 18.6%, CKD 11.6%, obesity 13.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Di-Domênico et al;[474] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 63 assigned to mouthwash with hydrogen peroxide 1% three time a day and nasal wash with hydrogen peroxide 0.5% and 43 assigned to SOC	Age >60 17%, male 39.6%, hypertension 22.6%, diabetes 11.3%, COPD 5.7%, CHD 3.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant number of patients excluded post-randomization resulting in potential inbalances in baseline risks	
ACPREGCOV trial;[475] Damião Costa et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to mouthwash 15 mL of 0.12% chlorhexidine	Mean age 39 ± 12, male 50%, hypertension 17%, diabetes 4%, obesity 25%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	gluconate and 50 assigned to SOC				
BUCOSARS trial;[476] Ferrer et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 54 assigned to mouthwash with povidone-iodine, hydrogen peroxide, cetylpyridinium chloride or chlorhexidine and 13 assigned to SOC	Mean age 54 - 55 ± , male 67%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Poleti ML et al trial;[477] Poleti et al; ; 2021	Patients with mild COVID-19 infection. 59 assigned to mouthwash with antimicrobial phthalocyanine derivative and 75 assigned to SOC	Mean age 34 ± 21, male 38%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow-up.	
Alemany et al;[478] peer reviewed; 2022	Patients with mild COVID-19 infection. 60 assigned to mouthwash with 0.07% cetylpyridinium and 58 assigned to SOC	Mean age 46, male 41.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Barrueco et al;[479] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 35 assigned to mouthwash with povidone-iodine 2%, hydrogen peroxide 1%, cetylpyridinium chloride 0.07% or chlorhexidine 0.12% and 10 assigned to SOC	Mean age 62.4 ± , male 54.5%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Mupadolimab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Miller et al;[480] preprint; 2021	Patients with moderate to severe COVID-19 infection. 29 assigned to mupadolimab 1-2 mg/kg and 11 assigned to SOC	Median age 55, male 57.5%, any comorbidities 45%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

Mycobacterium w **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ARMY-1 trial;[481] Sehgal et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to Mycobacterium w 0.3 ml SC once a day for 3 days and 20 assigned to SOC	Mean age 56 ± 15, male 69%, hypertension 31%, diabetes 33.3%, COPD 4.8%, asthma 4.8%	Corticosteroids 100%, hydroxychloroquine 26.2%, tocilizumab 12%, convalescent plasma 7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:**

					No information

N-acetylcysteine

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
de Alencar et al;[482] peer-reviewed; 2020	Patients with severe COVID-19. 68 assigned to NAC 21 g once and 67 assigned to standard of care	Mean age 58.5 ± 22.5, male 59.2%, hypertension 46.6%, diabetes 37.7%, cancer 12.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty
Gaynitdinova et al;[483] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 24 assigned to NAC 1200-1500 mg once and 22 assigned to SOC	Mean age 57.9 ± 12.7	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Taher et al;[484] peer reviewed;	Patients with mild to moderate	Mean age 57.6 ± 18.7, male 58.7%,	Corticosteroids 69.6%,	High for mortality and mechanical	

2021	COVID-19 infection. 47 assigned to NAC 40 mg/kg a day for 3 days and 45 assigned to SOC	diabetes 23.9%, COPD 15.2%, asthma %, CHD 28.2%,	hydroxychloroquine 90.2%, azithromycin 51.1%,	ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	⊕◯◯◯ **Hospitalization:** No information

N-acetylcysteine (inhaled)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Delic et al;[111] peer reviewed; 2022	Patients with critical COVID-19 infection. 39 assigned to N-acetylcysteine (inhaled) twice a day and 52 assigned to SOC	Mean age 68.3, male 74.8%, hypertension 61.5%, diabetes 27.5%, COPD %, asthma %, CHD 7.7%, CKD %, cerebrovascular disease 4.4%	Corticosteroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Panahi et al;[485] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 125 assigned to N-acetylcysteine (inhaled) two 200 µg puffs a day and 125 assigned to SOC	Mean age 55.1 ± 16.1, male 55.2%, hypertension 25.2%, diabetes 19.6%, COPD 1.6%, asthma 3.2%, CKD 8.1%, cancer 2.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

					Hospitalization: No information

Nafamostat mesylate

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
DEFINE trial;[486] Quinn et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 21 assigned to nafamostat 0.2 mg/kr/hr for 7 days and 21 assigned to SOC	Mean age 63.6, male 59.5%, hypertension 38.1%, diabetes 21.4%, COPD %, asthma 9.5%, CHD 14.3%, CKD 4.8%, immunosuppression 7.1%, cancer 9.5%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: No information
Namilumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
CATALYST trial;[339] Fisher et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 55 assigned to namilumab and 54 assigned to SOC	Median age 62.8 ± 18, male 68.5%	Corticosteroids 90.7%, remdesivir 53.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

					Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Nano-curcumin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hassaniazad et al;[487] peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 20 assigned to nano-curcumin 160 mg a day for 14 days and 20 assigned to SOC	Mean age 48.5 ± 10.9, male 55%	Corticosteroids 87.5%, hydroxychloroquine 45%, lopinavir-ritonavir 52.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: No information

Nasal hypertonic saline

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Kimura et al;[488] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 14 assigned to nasal hypertonic saline 250 cc twice daily, 14 assigned to nasal hypertonic saline plus surfactant and 17 assigned to standard of care	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%, diabetes 6.6%, chronic lung disease 15.5%, coronary heart disease 4.4%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**
Yildiz et al;[489] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 50 assigned to nasal hypertonic saline and 50 assigned to SOC	Mean age 38.8 ± , male 58%, hypertension 12%, diabetes 6%, COPD/asthma 4%, CHD 15%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment	

				of allocation probably inappropriate.	No information **Hospitalization:** No information
George et al;[490] peer reviewed; 2021	Patients with mild COVID-19 infection. 20 assigned to nasal hypertonic saline (Caclium rich hypertonic salts) and 20 assigned to SOC	Age range 22-45		Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Baxter et al;[491] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 37 assigned to nasal saline 240 ml + povidone-iodine twice a day for 14 days and 42 assigned to nasal saline 240 ml +2.5 mL sodium bicarbonate twice a day for 14 days	Mean age 64 ± 7.9, male 54.4%, hypertension 43.4%, diabetes 11.3%, COPD %, asthma 5.7%, immunocompromised 3.8%, obesity 45%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Neem (*Azadirachta indica* A. Juss)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Nesari et al;[492] other; 2021	Individuals exposed to SARS-CoV-2 infection. 70 assigned to neem 50 mg for 28 days and 84 assigned to SOC	Mean age 37, male %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No

				inappropriate. Significant loss to follow-up.	information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information
Niclosamaide **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Abdulamir et al;[493] preprint; 2021	Patients with mild to critical COVID-19 infection. 75 assigned to niclosamaide 4 g once followed by 3 g a day for 7 days and 75 assigned to SOC	Mean age 49.3 ± 16, male 53.3%, hypertension 12.7%, diabetes 8%, asthma 0.7%, cancer 0.7%, obesity 0.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**
Cairns et al;[494] peer reviewed; 2021	Patients with mild COVID-19 infection. 33 assigned to niclosamide 2 g a day for 7 days and 34 assigned to SOC	Mean age 36.4 ± 13, male 61.2%, hypertension 7.5%, asthma 7.5%, CHD 1.5%, obesity 7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

					Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Nicotine patches **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Labro et al;[495] peer reviewed; 2022	Patients with critical COVID-19 infection. 106 assigned to nicotine patches 14 mg a day for a maximum of 30 days and 112 assigned to SOC	Mean age 61, male 69.7%, hypertension 58.7%, diabetes 41.4%, COPD 3.2%, cerebrovascular disease 8.3%, immunosuppresion 6%,	Corticosteroids 64.5%, tocilizumab 0.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.02 (95%CI 0.67 to 1.57); RD 0.3% (95%CI -5.2% to 5.7%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Nigella sativa +/- Honey **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
HNS-COVID-PK trial;[496] Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + *Nigella sativa* 1 g + 80 mg/kg three times a day for 13 days and 156 assigned to SOC	> 60 age 52 ±, male 56.8%, hypertension 31.6%, diabetes 36.7%	Corticosteroids 26.5%, azithromycin 73.8%, ivermectin 36.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Koshak et al;[497] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 91 assigned to *Nigella sativa* 500 mg twice a day for 10 days and 92 assigned to SOC	Mean age 36 ± 11, male 53%, hypertension 9%, diabetes 8%, asthma 4%, CHD 0.5%, obesity 25%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

					Hospitalization: Very low certainty ⊕◯◯◯
Nirmatrelvir-ritonavir **Nirmatrelvir-ritonavir probably reduces hospitalizations. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
EPIC-HR trial;[498] Hammond et al; peer reviewed; 2021	Patients with COVID-19 infection. 1039 assigned to nirmatrelvir/ritonavir 600/200 mg a day for 5 days and 1046 assigned to SOC	Median age 46, male 51.1%, hypertension 32.9%, diabetes 12.1%, obesity 35.6%	NR; vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.49 (95%CI 0.30 to 0.80); RD -

					5.2% (95%CI -7.1% to -2%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.12 (95%CI 0.06 to 0.25); RD -4.2% (95%CI -4.5% to -3.5%); Moderate certainty ⊕⊕⊕◯

Nitazoxanide

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
SARITA-2 trial;[499] Rocco et al; preprint; 2020	Patients with mild COVID-19. 194 assigned to nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	Age range 18 - 77, male 47%, comorbidities 13.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯
Fontanesi et al;[500] preprint; 2020	Patients with mild to critical COVID-19. 25 assigned to nitazoxanide 1200 mg a day for 7 days and 25 assigned to SOC	Age > 65 46%, male 30%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably	

				inappropriate.	**Hospitalization:** Very low certainty ⊕◯◯◯
Silva et al;[501] preprint; 2021	Patients with mild to moderate COVID-19 infection. 23 assigned to nitazoxanide 2-3 g a day for 14 days and 13 assigned to SOC	Male 72.2%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Vanguard trial;[502] Rossignol et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 184 assigned to nitazoxanide 600 mg a day for 5 days and 195 assigned to SOC	Mean age 40.3 ± 15.4, male 43.5%, comorbidities 34%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
NACOVID trial;[503] Fowotade et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 31 assigned to nitazoxanide 2000 mg plus atazanavir/ritonavir 300/100 mg a day and 26 assigned to SOC	Mean age 38 ± 16, male 67%, obesity 19%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Medhat et al;[504] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 77 assigned to nitazoxanide 2000 mg a day for 14 days and 73 assigned to SOC	Mean age 45, male 45.3%, hypertension 21.3%, diabetes 19.3%	Corticosteroids 44%, hydroxychloroquine 7.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and	

				adverse events outcomes results.	
COVER HCW trial;[505] Sokhela et al; peer reviewed; 2022	Patients with exposed to COVID-19 infection. 280 assigned to nitazoxanide 1000 mg a day for 1 week followed by 2000 mg a day for 24 weeks and 283 assigned to SOC	Median age 24, male 51.9%, hypertension 8.2%, diabetes 1.1%, COPD 2.2%	Vaccinated 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	

Nitric oxide

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Moni et al;[506] preprint; 2021	Patients with severe COVID-19 infection. 14 assigned to inhaled nitric oxide (iNO) pulses of 30 min for 3 days and 11 assigned to SOC	Mean age 59.8 ± 10, male 72%, hypertension 44%, diabetes 56%, COPD 12%, CHD 24%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis**
Winchester et al;[507] peer-reviewed; 2021	Patients with mild COVID-19 infection. 40 assigned to nitric oxide nasal spray (NONS) 4 sprays 5	Mean age 44, male 36.7%, hypertension 6.3%, diabetes 6.3%, COPD 1.2%, CHD 0%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	to 6 times a day for 9 days and 40 assigned to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
NO COV-ED trial;[508] Strickland et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 19 assigned to inhaled nitric oxide (iNO) 5 liters per minute and 15 assigned to SOC	Mean age 41, male 53.2%, hypertension 12.8%, diabetes 6.4%, COPD 14.9%, CHD 2.1%, immunosuppression 4.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Hospitalization:** No information
Tandon et al;[509] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 64 assigned to nitric oxide nasal spray (NONS) 0.45 mL/dose six times a day for 8 days and 69 assigned to SOC	Mean age 37.8, male 64.4%, any commorbidities 12.1%	Vaccinated 46.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Non-steroidal anti-inflammatory drugs (NSAID)

Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However, the certainty of the evidence is very low because of the risk of bias. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mobarak et al;[510] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 39 assigned to naproxen 1000 mg a day and 38	Mean age 47 , male 55.8%, hypertension 9%, diabetes 17%, CHD 13%, CKD 5.2%, obesity 1.3%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

	assigned to SOC				information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Non-RCT					
Eilidh et al;[511] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 54 received NSAID and 1168 received alternative treatment schemes	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%, coronary heart disease 22.3%, chronic kidney disease 38.7%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function).	**Mortality:** OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕◯◯◯
Jeong et al;[512] preprint; 2020	Patients with moderate to severe COVID-19 infection. 354 received NSAID and 1470 received alternative treatment schemes	Age >65 36%, male 41%, hypertension 20%, diabetes 12%, chronic lung disease 16%, asthma 6%, chronic kidney disease 2%, cancer 6%	NR	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and IPTW were implemented to adjust for potential	

				confounders (age, sex, health insurance type, hypertension, hyperlipidemia, diabetes mellitus, malignancy, asthma, chronic obstructive pulmonary disease, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal, conditions, and use of co-medications).	
Lund et al;[513] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 224 received NSAID and 896 received alternative treatment schemes	Median age 54 ± 23, male 41.5%, chronic lung disease 3.9%, asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%	Corticosteroids 7.1%	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and matching were implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, and phase of the outbreak.	
Rinott et al;[514] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 87 received NSAID and 316 received alternative treatment schemes	Median age 45 ± 37, male 54.6%, diabetes 9.4%, coronary heart disease 12.9%,	NR	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. No adjustment for potential confounders.	
Wong et al;[515] preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 535519 received NSAID	Median age 51 ± 23, male 42.7%, hypertension 19.6%, diabetes 9.6%,	Corticosteroids 2.2%, hydroxychloroquine 0.6%	High for mortality Notes: Non-randomized study	

	and 1924095 received alternative treatment schemes	chronic lung disease 2.4%, asthma %, coronary heart disease 0.5%, chronic kidney disease 2.8%, cancer 5.2%,		with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, vaccination, and deprivation).	
Imam et al;[516] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 466 received NSAID and 839 received alternative treatment schemes	Mean age 61 ± 16.3, male 53.8%, hypertension 56.2%, diabetes 30.1%, chronic lung disease 8.2%, asthma 8.8%, coronary heart disease 15.9%, chronic kidney disease 17.5%, immunosuppression 1%, cancer 6.4%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified).	
Esba et al;[517] preprint; 2020	Patients with mild to severe COVID-19 infection. 146 received NSAID and 357 received alternative treatment schemes	Median age 41.7 ± 30, male 57.2%, hypertension 20.4%, diabetes 22.5%, chronic lung disease 5.2%, chronic kidney disease 3.2%, cancer 1.4%	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age; sex; comorbidities: hypertension, diabetes mellitus (DM), dyslipidemia, asthma, or chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), renal or liver impairment, and malignancy).	

Norelgestromin and Ethinylestradiol

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cortés-Algara et al;[518] peer reviewed; 2021	Patients with moderate COVID-19 infection. 30 assigned to norelgestromin and ethinylestradiol 6 mg/ 0.6 mg and 14 assigned to SOC	Mean age 58.6 , male 38.6%, hypertension 29.5%, diabetes 34.1%, obesity 6.8%	Corticosteroids 65.9%, hydroxychloroquine 65.9%, azithromycin 93.2%, vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:**

					No information

Novaferon

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zheng et al;[418] preprint; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:**

					No information

Nutritional support Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Leal et al;[519] preprint; 2021	Patients with severe COVID-19 infection. 40 assigned to nutritional support with spirulin, folic acid, glutamine, vegetable protein, vitamin C, zinc, selenium, vitamin D, resveratrol, omega-3, L-arginine, magnesium and probiotics and 40 assigned to SOC	Mean age 52.7 ± 10.8, male 65%, CHD 33.7%, obesity 33.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

					Hospitalization: No information
Omega-3 fatty acids **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Sedighiyan et al;[520] Preprint; 2020	Patients with mild to moderate COVID-19. 15 assigned to omega-3 670 mg three times a day for 2 weeks and 15 assigned to SOC	Mean age 66.7 ± 2.5, male 60%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Doaei et al;[521] peer reviewed; 2021	Patients with critical COVID-19 infection. 28 assigned to omega-3 1000 mg a day and 73 assigned to SOC	Mean age 64 ± 14, male 59.4%	NR	Some concerns for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding is probably	

				inappropriate. Significant loss to follow-up.	**Hospitalization:** No information
COVID-Omega-F trial;[522] Arnardottir et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to omega-3 10 g a day for 5 days and 12 assigned to SOC	Mean age 81.1 ± 6.1, male 45%, hypertension 64%, diabetes 41%, COPD 13%, CHD 64%, CKD 23%, cancer 18%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

OP-101

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PRANA trial;[523] Gusdon et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 17 assigned to OP-101 2 to 8 mg/kg once and 7 assigned to SOC	Median age 61, male 70.8%, hypertension 45.8%, diabetes 58.3%	Corticosteroids 100%, remdesivir 75%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

					Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Opaganib

Opaganib may not reduce mortality or mechanical ventilation; it may not increase severe adverse events but it may increase symptom resolution or improvement. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ABC-110 trial;[524] Winthrop et al; peer-reviewed; 2021	Patients with moderate to severe COVID-19 infection. 22 assigned to opaganib 1000 mg a day for 14 days and 18 assigned to SOC	Median age 58 ± 29.8, male 64.3%	Corticosteroids 92.8%, remdesivir 45.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.94 (95%CI 0.66 to 1.34); RD -0.9% (95%CI -5.5% to -5.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.68 to 1.24); RD -1% (95%CI -5.5% to -4.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.1 (95%CI 0.95 to 1.27); RD 6% (95%CI -3% to -16.4%); Low certainty ⊕⊕◯◯
Carvalho Neuenschwander et al;[525] preprint; 2022	Patients with severe COVID-19 infection. 230 assigned to opaganib 500 mg a day for 14 days and 233 assigned to SOC	Mean age 56.5, male 65.4%, diabetes 35%	Corticosteroids 94.2%, remdesivir 17.3%, convalescent plasma 1.7%; Vaccinated 0.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** RR 0.96 (95%CI 0.69 to 1.34); RD -0.4% (95%CI -3.2% to -3.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Otilimab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
OSCAR trial;[526] Patel et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 386 assigned to otilimab 90 mg once and 393 assigned to SOC	Mean age 59.6 ± 12, male 71.6%, hypertension 49.7%, diabetes 36.7%, CHD 11.9%	Corticosteroids 83%, remdesivir 34%, tocilizumab 1.2%, convalescent plasma 6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

					Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ozone

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PROBIOZOVID trial;[527] Araimo et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 14 assigned to ozone 250 ml ozonized blood and 14 assigned to standard of care	Mean age 61.7 ± 13.2, male 50%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information
SEOT trial;[528] Shah et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to ozone 150 ml rectal insufflation plus 5 ml with venous	Mean age 43.8 ± 9, male 80%, diabetes 10%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	blood once a day for 10 days and 30 assigned to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
P2Y12 inhibitors **P2Y12 in combination with full or prophylactic dose anticoagulants may not reduce mortality, may not improve time to symptom resolution, and may increase severe adverse events. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ACTIV-4a trial;[529] Berger et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 293 assigned to P2Y12 inhibitors (ticagrelor 120 mg a day or prasugrel 5 to 10 mg a day or clopidogrel 75 mg a day) in combination with full dose anticoagulants and 269 assigned to SOC in combination with full dose anticoagulants	Mean age 52.7, male 58.5%, hypertension 48.4%, diabetes 25.8%, COPD 5.4%, asthma 11.2%, CKD 3.9%, cerebrovascular disease 0.7%	Corticosteroids 64.1%, remdesivir 52%, tocilizumab 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 1.02 (95%CI 0.64 to 1.62); RD 0.3% (95%CI -5.7% to 9.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.97 (95%CI 0.94

REMAP-CAP - P2Y12 trial;[69] Bradbury et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 455 assigned to P2Y12 inhibitors clopidogrel 75 mg a day or ticagrelor 120 mg a day or prsugrel 60 mg once followed by 5 to 10 mg a day for 14 days and 529 assigned to SOC	Median age 57, male 67.2%, hypertension %, diabetes 39.3%, CHD 5.1%, CKD 3.9%	Corticosteroids 97.4%, remdesivir 22%, tocilizumab 43.7%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	to 1.02); RD -1.8% (95%CI -3.6% to 1.2%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 3.1 (95%CI 1.32 to 7.29); RD 21.4% (95%CI -3.3% to 64.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Palmitoylethanolamide **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Fessler et al;[530] peer reviewed; 2022	Patients with mild COVID-19 infection. 30 assigned to Palmitoylethanolamide 230 to 300 mg twice a day for 4 weeks and 30 assigned to SOC	Mean age 25.5, male %, hypertension 3.3%, asthma 6.6%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No

					information **Adverse events:** No information **Hospitalization:** No information
Peg-interferon (IFN) alfa **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
PEGI.20.002 trial;[531] Pandit et al; Peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to pegylated interferon alfa 1 µg/kg once and 19 assigned to SOC	Mean age 49.2 ± 13.5, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis**
Bushan et al;[532] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 119	Mean age 49.9 ± 15.3, male 70.8%	Corticosteroids 59.9%, remdesivir 21.5%,	High for mortality and mechanical ventilation; high for symptom resolution,	

	assigned to Peg Interferon Alfa 1 µg/kg subcutaneous [SC] injection once and 123 assigned to SOC			infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**studies):** No information **Adverse events:** No information **Hospitalization:** No information

Peg-interferon (IFN) lamda

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ILIAD trial;[533] Feld et al; preprint; 2020	Patients with mild to severe COVID-19. 30 assigned to peg-IFN lambda 180 µg subcutaneous injection once and 30 assigned to standard of care	Median age 46 ± 22, male 58%, comorbidities 15%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis**
COVID-Lambda trial;[534] Jagannathan et al; preprint; 2020	Patients with mild COVID-19. 60 assigned to peg-IFN lambda 180 mcg subcutaneous injection once and 60 assigned to standard of care	Median age 36 ± 53, male 68.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study which might have introduced bias to symptoms and adverse events outcomes results.	**studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Chung et al; NCT04343976; other; 2022	Patients with moderate to severe COVID-19 infection. 7 assigned to Peg-IFN lambda 180 µg once and 7 assigned to SOC	Mean age 54.5, male 78.6%,	NR	NA	
PROTECT trial; NCT04344600; Sulkowski et al; other; 2022	Patients with exposed to COVID-19 infection. 2 assigned to Peg-IFN lambda 180 µg once and 4 assigned to SOC	Age >65 50, male 16.7%	NR	NA	

Pembrolizumab

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COPERNICO trial;[535] Sanchez-Conde et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 7 assigned to pembrolizumab 200 mg on days 1 and 21 and 5 assigned to SOC	Mean age 68, male 75%	Corticosteroids 100%, remdesivir 33%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Pentoxifylline **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Maldonado et al;[536] peer-reviewed; 2020	Patients with severe to critical COVID-19. 26 assigned to pentoxifylline 400 mg three times a day while hospitalized and 12 assigned to standard of care	Mean age 57.5 ± 11.7, male 55.2%, hypertension 39.4%, diabetes 50%, obesity 55.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**No information **Symptomatic**
Azizi et al;[537] peer reviewed; 2021	Patients with moderate to severe COVID-19	Mean age 59, male 35%, hypertension 18%, diabetes 32%,	Corticosteroids 55.5%,	High for mortality and mechanical ventilation; high for	

	infection. 40 assigned to pentoxifylline 1200 mg a day for 10 days and 32 assigned to SOC	CHD 12.5%, cerebrovascular disease 5.5%		symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	**infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Pirfenidone **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zhang et al;[538] peer reviewed; 2022	Patients with severe COVID-19 infection. 73 assigned to pirfenidone 1200 mg a day for 28 days and 73 assigned to SOC	Mean age 62, male 64.4%, hypertension 34.3%, diabetes 12.3%, COPD 6.2%, CHD 5.5%, CKD 1.4%, cerebrovascular disease 3.4%, cancer 2.7%,	Corticosteroids 84.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Plitidepsin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
APLICOV-PC trial;[539] Varona et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 45 assigned to plitidepsin three doses of 1.5 to 2.5 mg	Mean age 51, male 66.6%, hypertension 20%, diabetes 17.8%, COPD 6.7%, asthma 11.1%, CHD 4.4%, CKD 2.2%, obesity 22.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
PNB001 (CCK-A antagonist) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BCR-PNB-001 trial;[540] Lattaman et al; preprint; 2021	Patients with moderate COVID-19 infection. 20 assigned to PNB001 200 mg a day for 14 days and 20 assigned to SOC	Mean age 52, 65% male	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information

Polymerized type I collagen (PT1C)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mendez-Flores et al;[541] preprint; 2021	Patients with mild to moderate COVID-19 infection. 44 assigned to PT1C 25 mg intramuscular for 3 days followed by 12.5 mg for another 4 days and 43 assigned to SOC	Mean age 48.5 ± 14.1, male 41.6%, hypertension 20.2%, diabetes 16.9%, COPD 2.3%, asthma 4.5%, CHD 0%, cancer 0%, obesity 28.1%	Corticosteroids 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Potassium canrenoate **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
SpiroCOVID19 trial;[542] Karolak et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 24 assigned to potassium canrenoate 400 mg a day for 7 days and 25 assigned to SOC	Mean age 62, male 53.1%, hypertension 63.2%, diabetes 28.6%, COPD %, asthma %, CHD 14.2%, cerebrovascular disease 2%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Povidone iodine spray **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Seet et al;[303] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 735 assigned to povidone iodine spray 3 times a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Probiotics

Probiotics may increase symptom resolution or improvement. The effect on other outcomes is uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Wang et al;[543] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 98 assigned to probiotics 2 lozenges a day for 30 days and 95 assigned to SOC	Mean age 36 ± 8, male 29%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information
PROCOV-19-2020 trial;[544]	Patients with moderate to critical	Mean age 64 ± , male 46%	NR	High for mortality and mechanical	

Ivashkin et al; peer reviewed; 2021	COVID-19 infection. 99 assigned to probiotics three times a day for 14 days and 101 assigned to SOC			ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptomatic infection (prophylaxis studies):** RR 1.89 (95%CI 1.4 to 2.56); RD 53.9.8% (95%CI 24.2% to 94.5%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Hospitalization:** No information
PROTECT-EHC trial;[545] Wischmeyer et al; peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 91 assigned to probiotics 1 capsule a day for 28 days and 91 assigned to SOC	Age 18-64 62%, male 36.8%, hypertension 12.1%, diabetes 3.8%, COPD 1.1%, cancer 2.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
ABB-COVID19 trial;[546] Gutiérrez-Castrellón et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 147 assigned to probiotics 1 capsule a day for 30 days and 146 assigned to SOC	Median age 37 ± , male 46.3%, hypertension 19.6%, diabetes 10.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Saviano et al;[547] peer reviewed; 2022	Patients with severe COVID-19 infection. 40 assigned to probiotics (*Bifidobacterium lactis* LA 304, *Lactobacillus salivarius* LA 302)and *Lactobacillus acidophilus* LA 201) twice a day for 10 days and 40 assigned to SOC	Mean age 59.6, male 55%, hypertension 38.7%, diabetes 17.5%, COPD 8.7%	Corticosteroids 100%; vaccinated 18.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Progesterone

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication	Patients and interventions	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard

status	analyzed				of care and GRADE certainty of the evidence
RCT					
Ghandehari et al;[548] preprint; 2020	Patients with severe COVID-19. 18 assigned to progesterone 100 mg twice a day for 5 days and 22 assigned to standard of care	Mean age 55.3 ± 16.4, male 100%, hypertension 48%, diabetes 25%, obesity 45%	Corticosteroids 60%, remdesivir 60%, hydroxychloroquine 2.5%, tocilizumab 12.5%, azithromycin 50%, convalescent plasma 5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Prolectin-M

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Prolectin-M trial;[549] Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 g a day and 5 assigned	Mean age 28.5 ± 3.85, male 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and	**Mortality:** No information **Invasive mechanical**

	to standard of care			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Propolis **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Bee-Covid trial;[550] Duarte Silveira et al; Preprint; 2020	Patients with moderate to critical COVID-19. 82 assigned to propolis 400–800 mg a day for 7 days and 42 assigned to SOC	Mean age 50 ± 12.8, male 69.4%, hypertension 45.2%, diabetes 21%, COPD 7.3%, asthma %, obesity 51.6%	Corticosteroids 80.6%, hydroxychloroquine 3.2%, azithromycin 95.2%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Prostacyclin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COMBAT-COVID trial;[551] Johansson et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 41 assigned to prostacyclin 1 ng/kg/min for 3 days and 39 assigned to SOC	Mean age 67, male 66.2%, hypertension 61.2%, COPD 12.5%, CKD 2.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Prostacyclin (inhaled)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ThIlo trial;[552] Haeberle et al; preprint; 2021	Patients with critical COVID-19 infection. 72 assigned to prostacyclin (inhaled) 3 times a day for 5 days and 72 assigned to SOC	Mean age 60, male 75%, hypertension 58.6%, diabetes 28.5%, COPD 7.6%, asthma 4.9%, CKD 6.9%, cancer 2.8%	Corticosteroids 51.4%, remdesivir 42.4%, tocilizumab 16%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.05 (95%CI 0.64 to 1.7); RD 0.8% (95%CI -5.7% to 11.2%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No

					information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Proxalutamide **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Cadegiani et al;[553] Preprint; 2020	Patients with mild COVID-19. 114 assigned to proxalutamide 200 mg a day for 15 days and 100 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Randomization and concealment methods probably not appropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**
AB-DRUG-SARS-004	Patients with mild to moderate	Mean age 45.3 ± 13, male 54.2%,	NR	High for mortality and mechanical	

trial;[554] Cadegiani et al; peer reviewed; 2020	COVID-19 infection. 171 assigned to proxalutamide 200 mg a day for 15 days and 65 assigned to SOC	hypertension 22.5%, diabetes 8.9%, COPD 0%, asthma 5%, CKD 0.4%, cancer 17%, obesity 15.7%		ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.07 (95%CI 0.01 to 0.52); RD -4.5% (95%CI -4.7% to -2.3%); Very low certainty ⊕◯◯◯
KP-DRUG-SARS-003 trial;[555] Cadegiani et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 423 assigned to proxalutide 300 mg a day for 14 days and 355 assigned to SOC	Median age 51 ± , male 59.6%, hypertension 27.6%, diabetes 12.5%, COPD 2.3%, asthma %, CHD %, CKD 0%	Steroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Randomization scheme was modified during the study.	
AB-DRUG-SARS-005 trial;[556] Cadegiani et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 75 assigned to proxalutamide 200 mg a day for 7 days and 102 assigned to SOC	Mean age 44.2 ± 12.1, male 0%, hypertension 31.1%, diabetes 8.5%, COPD 0.6%, obesity 18.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Randomization process presented as "Blocked" but described as a cluster randomization.	

Pyridostigmine

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PISCO trial;[557] Fragoso-Saavedra et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 94	Median age 52 ± 20, male 59.6%, hypertension 35.1%, diabetes 36.2%,	Corticosteroids 74.5%, tocilizumab 5.3%	High for mortality and mechanical ventilation; high for symptom resolution,	**Mortality:** Very low certainty ⊕◯◯◯

	assigned to pyridostigmine 60 mg a day for 14 days and 94 assigned to SOC	COPD 4.3%, asthma %, CHD 2.1%, obesity 43.1%		infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Quercetin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Onal et al;[558] peer review; 2020	Patients with moderate to severe COVID-19. 49 assigned to quercetin 1000 mg and 380 assigned to SOC	Age > 50 65.7%, male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma 13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:**

Di Pierro et al;[559] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to quercetin 400-600 mg a day for 14days and 21 assigned to SOC	Mean age 49.3 ± 19.5, male 47.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Shohan et al;[560] peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 30 assigned to quercetin 1000 mg a day for 7 days and 30 assigned to SOC	Mean age 51.8, male 56.6%, hypertension 20%, asthma 6.6%, CHD 15%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes:	
Rondanelli et al;[561] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 60 assigned to quercetin 500 mg a day and 60 assigned to SOC	Mean age 49.3 ± 12.9, male 52.5%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Raloxifene

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Nicastri et al;[562] peer reviewed;	Patients with moderate COVID-	Mean age 56.7 ± 10.1, male 54.1%,	Corticosteroids 14.7%, remdesivir	Low for mortality and mechanical	**Mortality:** Very low certainty

2021	19 infection. 42 assigned to raloxifene 60 to 120 mg for 14 days and 19 assigned to SOC	hypertension 26.2%, diabetes 0.66%, COPD %, asthma 1.6%	1.6%	ventilation; low for symptom resolution, infection and adverse events	⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Ramipril **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
RASTAVI trial;[563] Amat-Santos et al; preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 50 assigned to ramipril 2.5 mg a day progressively increased to 10 mg a day and 52 assigned to standard of care	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%, diabetes 20.65%, chronic lung disease 7.35%, coronary heart disease 22.45%, chronic kidney disease 34.15%, cerebrovascular disease 11.15%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information
RD-X19 (light therapy) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
EB-P12-01 trial;[564] Stasko et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to RD-X19 light dose of 16 J/cm2 twice a day and 11 assigned to SOC	Median age 40 ± 20.6, male 52%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information

Recombinant super-compound interferon

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Li et al;[565] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 46 assigned to recombinant super-compound interferon 12 million IU twice daily (nebulization) and 48 assigned to interferon alfa	Median age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, chronic lung disease 1.1%, coronary heart disease 7.4%, cerebrovascular disease 5.3%, liver disease 6.4%	Corticosteroids 9.6%, ATB 22.3%, intravenous immunoglobulin 3.2%, lopinavir-ritonavir 44.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information

Regdanvimab (monoclonal antibody)

Regdabivimab may improve time to symptom resolution. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Streinu-Cercel et al;[566] Peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 204 assigned to regdanvimab 40-80 mg/kg once and 103 assigned to SOC	Mean age 51 ± 20, male 44.6%, comorbidities 73%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯
CT-P59 1.2 trial;[567] Kim et al; peer reviewed;	Patients with mild COVID-19 infection. 15	Median age 52 ± 8, male 100%	NR	Low for mortality and mechanical ventilation; low for	**Symptom resolution or improvement:** RR

2021	assigned to regdanvimab 20 to 80 mg once and 3 assigned to SOC			symptom resolution, infection and adverse events Notes:	1.24 (95%CI 1.05 to 1.46); RD 4.2% (95%CI 9% to 80%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

REGEN-COV (casirivimab and imdevimab)

REGEN-COV probably reduces mortality and mechanical ventilation in seronegative severe to critical patients. In mild patients REGEN-COV probably reduces hospitalizations and in exposed individuals it reduces symptomatic infections.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Weinreich et al;[568] preprint; 2020	Patients with recent onset mild disease with risk factors for severe COVID-19 infection. 2091 assigned to REGEN-COV (casirivimab and imdevimab) 1.2 to 2.4 g single infusion and 2089 assigned to SOC	Median age 50 ± 21, male 48.7%, obesity 58%, comorbidities 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.83 (95%CI 0.63 to 1.09); RD -2.7% (95%CI -5.9% to 1.4%); Low certainty ⊕⊕◯◯ **Mortality (seronegative):** RR 0.79 (95%CI 0.71 to 0.89); RD -3.2% (95%CI -

RECOVERY - REGEN-COV trial;[569] Horby et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 4839 assigned to REGEN-COV (Regeneron) 8 g once and 4946 assigned to SOC	Mean age 61.9 ± 14.4, male 63%, diabetes 26.5%, COPD %, CHD 21%, CKD 5%	Corticosteroids 94%, azithromycin 3%, baricitinib 9%; vaccinated 8%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	4.6% to -1.8%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.79 (95%CI 0.54 to 1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation (seronegative):** RR 0.82 (95%CI 0.74 to 0.9); RD -3.1% (95%CI -4.5% to -1.7%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement (seronegative):** RR 1.1 (95%CI 1.06 to 1.14); RD 6% (95%CI 3.6% to 8.5%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.24 (95%CI 0.08 to 0.76); RD -13.2%
O'Brien et al;[570] peer reviwed; 2021	Patients with early asymptomatic COVID-19 infection. 100 assigned to REGEN-COV (Regeneron) 1.2 g once and 104 assigned to SOC	Mean age 40.9 ± 18, male 45.4%, diabetes 7.8%, CKD 2.5%, immunosuppressive therapy 1.5%, obesity 13.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Herman et al;[571] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 841 assigned to REGN-COV2 (Regeneron) 1200 mg once and 842 assigned to SOC	Median age 43 ± 25, male 45.9%, 6.8%, CKD 1.9%, immunosuppresive therapy 1%, obesity 34.1%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
OPTIMISE-C19 trial;[96] McCreary et al; peer reviewed; 2022	Patients with mild COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2 (Regeneron) and 1013 assigned to bamlanivimab +/- etesevimab	Mean age 56 ± 16, male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD 6.5%, immunosuppresive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Somersan-Karakaya et al;[572] peer-reviewed; 2021	Patients with moderate to severe COVID-19 infection. 804 assigned to REGN-COV2 (Regeneron)	Median age 62 ± , male 54.1%	Corticosteroids 74.8%, remdesivir 54.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	2.4 to 8 gr once and 393 assigned to SOC				(95%CI -16% to -4.2%); High certainty ⊕⊕⊕⊕
R10933-10987-COV-20145 trial;[573] Portal Celhay et al; preprint; 2021	Patients with mild COVID-19 infection. 584 assigned to REGN-COV2 (Regeneron) 300 - 2400 mg once and 77 assigned to SOC	Mean age 34.6, male 44.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Adverse events:** RR 0.51 (95%CI 0.38 to 0.67); RD -5% (95%CI -6.3% to -3.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.28 (95%CI 0.19 to 0.42); RD -3.5% (95%CI -3.9% to -2.8%); Moderate certainty ⊕⊕⊕◯
Isa et al;[574] preprint; 2021	Patients with COVID-19 infection. assigned to REGN-COV2 (Regeneron) and assigned to	Median age 48 ± 22, male 55.1%, hypertension 14.7%, asthma 5.2%, CHD 0.8%, CKD 0.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Weinreich et al;[575] preprint; 2021	Patients with mild to moderate COVID-19 infection. 434 assigned to REGN-COV2 (Regeneron) 2400 TO 8000 mg once and 231 assigned to SOC	Median age 42 ± 21, male 47.1%, obesity 37.3%, Risk factor for hospitalization 60.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OPTIMISE-C19 trial;[576] Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD 16%, CKD 4.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
MANTICO trial;[99] Mazzaferri et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 107 assigned to sotrovomab 500 mg once and 106 assigned to bamlanivimab +	Mean age 65 ± 15, male 57.2%, diabetes 2.9%, COPD 16.7%, asthma %, CHD 37.9%, CKD 5.1%, immunosuppression 19.6%, obesity 25.4%	Vaccinated 28.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might	

	etesevimab 700/1400 mg once and 106 assigned to REGEN-COV2 600/600 mg once			have introduced bias to symptoms and adverse events outcomes results.	
PLATCOV - Regen trial;[393] Schilling et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 10 assigned to REGEN-COV 1200 mg once and 41 assigned to SOC	Mean age 27 , male 39%	Corticosteroids %, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated %	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Remdesivir

In hospitalized patients with moderate to critical disease, remdesivir probably reduces mortality and mechanical ventilation, and it may improve time to symptom resolution without increasing severe adverse events. In patients with recent onset mild COVID-19, it may reduce hospitalizations. However, the certainty is low because of risk of bias and imprecision.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ACTT-1 trial; Beigel et al;[577] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 541 assigned to remdesivir intravenously 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 and 522 assigned	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.93 (95%CI 0.89 to 1.03); RD -1.1% (95%CI -1.8% to 0.5%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.76 (95%CI 0.56 to 1.04); RD -4.2% (95%CI -7.6% to 0.7%); Moderate

	to standard of care				certainty ⊕⊕⊕◯
SIMPLE trial; Goldman et al;[578] peer-reviewed; 2020	Patients with severe COVID-19 infection. 200 assigned to remdesivir (5 days) 200 mg once followed 100 mg for 5 days and 197 assigned to remdesivir (10 days)	Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Symptom resolution or improvement:** RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.77 (95%CI 0.46 to 1.29); RD -2.3% (95%CI -5.5% to 3%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.28 (95%CI 0.11 to 0.75); RD -3.4% (95%CI -4.3% to -1.2%); Low certainty ⊕⊕◯◯
CAP-China remdesivir 2 trial;[579] Wang et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 158 assigned to remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions and 79 assigned to standard of care	Median age 65 ± 7.5, male 60.5%, hypertension 43%, diabetes 23.7%, coronary heart disease 7.2%	Corticosteroids 65.6%, lopinavir-ritonavir 28.4%, IFN 32.2%, ATB 91.1%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
SIMPLE 2 trial; Spinner et al;[580] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 384 assigned to remdesivir 200 mg on day 1 followed by 100 mg a day for 5 to 10 days and 200 assigned to standard of care	Median age 57 ± 9, male 61.3%, hypertension 42%, diabetes 40%, asthma 14%, coronary heart disease 56%	Corticosteroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	Some concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY;[290] Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 4146	Age range 50 – 69 years old 46.2%, male 63.4%, diabetes 27.2%,	Steroids 67.7%, convalescent plasma 3.3%, Anti IL6 4.5%	Low for mortality and mechanical ventilation; some Concerns for	

	assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 4129 assigned to SOC	COPD 6.8%, asthma 5.9%, CHD 22.5%		symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.	
Mahajan et al;[581] peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 34 assigned to remdesivir 200 mg once followed by 100 mg once a day for 5 days and 36 assigned to SOC	Mean age 57.7 ± 13.1, male 65.5%, hypertension 45.7%, diabetes 60%, asthma 1.4%, CHD 12.9%, CKD 4.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Abd-Elsalam et al;[582] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 100 assigned to SOC	Mean age 53 ± 15, male 59.5%, hypertension 33%, diabetes 34%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Sarhan et al;[583] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 52 assigned to remdesivir 200 mg once followed by 100 mg a day for 5 days plus tocilizumab and 56 assigned to HCQ 400 mg once followed by 200 mg a day for 5 days plus tocilizumab	Mean age 57, male 72%, hypertension 61.7%, diabetes 47.6%, COPD 2.8%, asthma 13.1%, CHD 21.5%, CKD 4.7%,	Hydroxychloroquine 52.3%, tocilizumab 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

PINETREE trial;[584] Gottlieb et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 279 assigned to remdesivir 200 mg once followed by 100 mg on days two and three and 283 assigned to SOC	Mean age 50 ± 15, male 53.1%, hypertension 47.7%, diabetes 61.6%, COPD 24%, CKD 3.2%, immunosuppresion 4.1%, cancer 5.3%, obesity 55.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CATCO trial;[585] Ali et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 170 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 153 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Remdesivir (inhaled)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Gilead et al; NCT04539262; other; 2021	Patients with mild to moderate COVID-19 infection. 109 assigned to remdesivir (inh) 31 to 62 mg a day for 3 to 5 days and 45 assigned to SOC	Age > 60 years old 12.9%, male 50%	NR	NA	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Severe Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Reparixin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
REPAVID-19 trial;[586] Landoni et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 36 assigned to reparixin 3600 mg a day for 7 days and 19 assigned to SOC	Mean age 61.7, male 76.4%, hypertension 43.6%, diabetes 23.6%, COPD %, CHD 12.7%, CKD 7.3%, obesity 20%	Corticosteroids 92.7%, remdesivir 23.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: No information

Reseveratrol

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
McCreary et al;[587] peer-reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to resveratrol 4 g a day for 7 days and 50 assigned to SOC	Mean age 56 ± 9, male 43%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No
Reszinate trial;[588] Kaplan et al; preprint; 2021	Patients with mild COVID-19 infection. 14 assigned to	Mean age 42.4, male 40%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution,	

	resveratrol + zinc 4000/150 mg once a day for five days and 16 assigned to SOC			infection, and adverse events	information **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
rhG-CSF (in patients with lymphopenia) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Cheng et al;[589] peer-reviewed; 2020	Patients with moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100 assigned to standard of care	Mean age 45 ± 15, male 56%	Lopinavir-ritonavir 15.5%, IFN 9%, umifenovir 18%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty

					⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
rhG-CSF (inhaled) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
SARPAC trial;[590] Lambrecht et al; preprint; 2021	Patients with severe COVID-19 infection. 40 assigned to rhG-CSF (inhaled) 125 µg twice daily for 5 days and 41 assigned to SOC	Mean age 60 ± 20, male 61%, hypertension 17.1%, diabetes 17.1%, CHD 2.4%, CKD 2.4%, cancer 4.9%	Corticosteroids 22%, hydroxychloroquine 63.4%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**

					Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
rhu-pGSN **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BTI-202 trial;[591] DiNubile et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 31 assigned to rhu-pGSN 12 mg/kg three times and 30 assigned to SOC	Mean age 62.1 ± 11.6, male 57.4%, hypertension 41%, diabetes 32.8%	Corticosteroids 100%, remdesivir 98.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No

					information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Ribavirin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al;[419] preprint; 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 g IV loading dose followed by orally 400-600 mg every 8 h for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

	ribavirin plus lopinavir-ritonavir				**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ribavirin plus interferon beta-1b

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Hung et al;[592] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 86 assigned to ribavirin plus interferon beta-1b 400 mg every 12 hours (ribavirin), and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]) on alternate days, for 14 days and 41 assigned to standard of care	Median age 52 ± 15, male 54%, hypertension 18.3%, diabetes 13.3%, coronary heart disease 7.9% cerebrovascular disease 1.5%, cancer 1.5%	Corticosteroids 6.2%, ATB 53.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ruxolitinib

Ruxolitinib may reduce mortality. However the certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cao et al;[593] peer-reviewed; 2020	Patients with severe COVID-19 infection. 22 assigned to ruxolitinib 5 mg twice a day and 21 assigned to standard of care	Mean age 63 ± 10, male 58.5%, hypertension 39%, diabetes 19.5%, coronary heart disease 7.3%,	Corticosteroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.72 (95%CI 0.59 to 0.89); RD -4.5% (95%CI -6.5% to -1.7%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯
RUXCOVID trial;[594] Han et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 287	Mean age 56.5 ± 13.3, male 54%, diabetes 21.9%, obesity 47%	NR	Low for mortality and mechanical ventilation; low for symptom resolution,	

	assigned to ruxolitinib 10 mg a day for 14 to 28 days and 145 assigned to SOC			infection and adverse events	**Symptom resolution or improvement:** RR 1.05 (95%CI 0.89 to 1.24); RD 3% (95%CI -6.7% to 14.5%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
RUXCOVID-DEVENT trial; NCT04377620; other; 2021	Patients with critical COVID-19 infection. 164 assigned to ruxolitinib 10 to 30 mg a day and 47 assigned to SOC	Mean age 63.4 ± 12.7, male 64.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Sabizabulin

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Barnette et al;[595] peer reviewed;	Patients with severe COVID-19	Mean age 59.7 ± 14.7, male 68%,	Corticosteroids 82.7%, remdesivir	High for mortality and mechanical	**Mortality:** Very low certainty

2022	infection. 98 assigned to sabizabulin 9 mg for up to 21 days and 52 assigned to SOC	hypertension 60%, diabetes 37.3%, COPD %, CHD 4.7%, CKD 10%, cancer 5.3%, obesity 32.4%	32.7%, tocilizumab 10%, baricitinib 12%; vaccinated 44.7%,	ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Sarilumab

Sarilumab may not reduce mortality nor mechanical ventilation requirements, and probably does not improve time to symptom resolution. Sarilumab probably does not increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

REMAP-CAP - tocilizumab trial;[596] Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8 mg/kg once or twice, 48 assigned to sarilumab 400 mg once and 402 assigned to SOC	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%	Corticosteroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.99 (95%CI 0.89 to 1.15); RD -0.2% (95%CI -1.8% to 2.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.68 to 1.42); RD -0.3% (95%CI -5.5% to 7.3%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.97 to 1.06); RD 0.6% (95%CI -1.8% to 3.6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 1.01 (95%CI 0.9 to 1.13); RD 0.1% (95%CI -1% to 1.3%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
Lescure et al;[597] peer-reviewed; 2020	Patients with severe to critical COVID-19. 332 assigned to sarilumab 200-400 mg once and 84 assigned to SOC	Mean age 59 ± 18, male 62.7%, hypertension 42.5%, diabetes 26.4%, COPD 4.3%, asthma 4.1%, CHD 5.3%, CKD 4.3%, cancer 10.1%, obesity 20.7%	Corticosteroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Sarilumab-COVID19 Study trial;[598] Sivapalasingam, et al; preprint; 2021 (two studies reported)	Patients with severe to critical COVID-19 infection. 1148 assigned to sarilumab 200-400 mg once and 376 assigned to SOC	Critical patient population: mean age 61 ± 20, male 68.4%, hypertension 52.1%, diabetes 18.7%, obesity 46.5%	Corticosteroids 34.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
CORIMUNO-SARI trial;[599] Mariette, et al, peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 68 assigned to sarilumab 400 mg once and 76 assigned to SOC	Median age 62, male %, hypertension 25.1%, diabetes 30.5%, COPD 6.3%, asthma 8%, CKD 11.8%, cancer 3%,	Steroids 20.1%, remdesivir 0%, hydroxychloroquine 14.6%, azithromycin 39.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	
CORIMUNO-SARI ICU trial;[600] Hermine et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 48 assigned to sarilumab 400 mg once and 33 assigned to SOC	Median age 61, male 76.5%, diabetes 31.2%, COPD 3.7%, asthma 4.9%, CKD 13.5%, cancer 1.2%,	Steroids 19.7%, remdesivir 0%, hydroxychloroquine 4.9%, lopinavir-ritonavir 1.2%, azithromycin 2.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	

				study which might have introduced bias to symptoms and adverse events outcomes results.	
SARCOVID trial;[601] García Vicuña et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to sarilumab 400 mg once and 10 assigned to SOC	Median age 61.5, male 67%, hypertension 43%, diabetes 17%, COPD 7%, CHD 10%, CKD 13%, obesity 10%	Steroids 83%, remdesivir 0%, hydroxychloroquine 20%, lopinavir-ritonavir 17%, tocilizumab %, azithromycin 60%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SARICOR trial;[602] Merchante et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 76 assigned to sarilumab 200-400 mg once and 39 assigned to SOC	Median age 59, male 68%, hypertension 41%, diabetes 15%, COPD 13%, CHD 4%, CKD 2%,	Steroids 90%, remdesivir 12%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SARTRE trial;[603] Sancho-Lopez et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 99 assigned to sarilumab 200-400 mg once and 102 assigned to SOC	Median age 60, male 70.2%, hypertension 40.8%, diabetes 16.4%, COPD 9.5%, CHD 12.4%, CKD 3%, cancer 3%, obesity 3.5%	Steroids 100%, remdesivir 1%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
IRB 3305 trial;[604] Branch-Elliman	Patients with moderate to severe COVID-19	Mean age 72.3 ± 12.7, male 92%, hypertension 86%,	Corticosteroids 86%, remdesivir 80%,	Low for mortality and mechanical ventilation; low for	

et al; peer reviewed; 2021	infection. 20 assigned to sarilumab 200 to 400 mg (subcutaneous) once and 30 assigned to SOC	diabetes 50%, COPD 32%, asthma 16%, CHD 70%, CKD 18%, cancer 48%, obesity 62%	hydroxychloroquine 4%, tocilizumab 2%, convalescent plasma 2%;	symptom resolution, infection and adverse events	
ESCAPE trial;[605] Mastrorosa et al; preprint; 2022	Patients with severe COVID-19 infection. 121 assigned to sarilumab 400 mg once or twice and 55 assigned to SOC	Mean age 60.3, male 76.1%, hypertension 3.9%, diabetes 2.8%, COPD 30%, CKD 0.6%, cancer 0%	Corticosteroids 39.8%, remdesivir 17%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Secukinumab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BISHOP trial;[606] Gomes Resende et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 25 assigned to secukinumab 300 mg once and 23 assigned to SOC	Mean age 54 ± 21.5, male 52%, hypertension 48%, diabetes 34%, CHD 8%, obesity 48%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Senicapoc Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COVIPOC trial;[607] Granfeldt et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to senicapoc 50 mg twice and 26 assigned to SOC	Median age 66, male 65.2%, hypertension 34.8%, diabetes 28.3%, COPD 26%, CKD 4.5%, cancer 15.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Sentinox Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Panatto et al;[608] peer reviewed; 2022	Patients with mild COVID-19 infection. 36 assigned to sentinox 0.005% 3 to 5 times a day and 18 assigned to SOC	Mean age 40.1 ± 13.7, male 81%, any commorbidities 4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Short-wave diathermy Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Tian et al;[609] peer reviewed; 2021	Patients with moderate COVID-19 infection. 27 assigned to short-wave diathermy and 13 assigned to SOC	Median age 65 ± 18, male 62.5%, hypertension 30%, diabetes %, COPD 45%, CHD 30%, CKD 7.5%, cerebrovascular disease 27.5%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Sildenafil Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
UNAB-003 trial;[610] Santamarina et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 20 assigned to sildenafil 75 mg a day for 7 days and 20 assigned to SOC	Median age 57, male 82.5%, diabetes 20%, COPD 0%, asthma 5%	Corticosteroids 82.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Blinding and concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Siltuximab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COV-AID-2 trial;[611] other; 2021	Patients with severe to critical COVID-19 infection. 77 assigned to siltuximab 11 mg/kg once and 72 assigned to SOC	Median age 64	Corticosteroids 59%, remdesivir 3.4%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

Silymarin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Aryan et al;[612] peer reviewed; 2022	Patients with severe COVID-19 infection. 25 assigned to silymarin 210 mg a day for 14 days and 25 assigned to SOC	Mean age 49 ± 11.1, male 48%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Sitagliptin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Asadipooya et al;[613] preprint; 2021	Patients with moderate to severe COVID-19 infection. 66 assigned to sitagliptin 100 mg a day and 87 assigned to SOC	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD 6.4%, cancer 5.9%, obesity 18.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

Sofosbuvir +/- daclatasvir, ledipasvir, ravidasvir, or velpatasvir Sofosbuvir alone or in combination with daclatasvir or ledipasvir may increase mortality and not reduce mechanical ventilation requirements, and probably does not improve time to symptom resolution.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Kasgari et al;[422] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.14 (95%CI 0.83 to 1.56); RD 2.2% (95%CI -2.7% to 9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.02 (95%CI 0.59 to 1.76); RD 0.3% (95%CI -7.1% to 13.1.7%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.95 to 1.08); RD 0.6% (95%CI -3% to 4.8%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Sadeghi et al;[614] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 14 days and 33 assigned to standard of care	Median age 58 ± 13, male 20.21%, hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%, coronary heart disease 15.1%, cancer 4.5%, obesity 25.7%	Corticosteroids 30.2%, lopinavir-ritonavir 48.4%, antibiotics 89.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation is probably inappropriate.	
Yakoot et al;[615] preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 10 days and 45 assigned to standard of care	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %, asthma 1%, coronary heart disease 8%	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is	

				probably inappropriate.	
Roozbeh et al;[616] Peer reviewed; 2020	Patients with moderate COVID-19. 27 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 7 days and 28 assigned to SOC	Median age 53 ± 16, male 47%, comorbidities 38%	Azithromycin 100%, hydroxychloroquine 100%	High for symptom resolution, infection, and adverse events Notes: Blinding method possibly inappropriate which might have introduced bias to symptoms and adverse events outcomes results.	
Sali et al;[420] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to sofosbuvir 400 mg a day and 32 assigned to lopinavir-ritonavir 400/100 mg every 12 hours	Mean age 56.5 ± 14, male 53.7%, diabetes 33%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
DISCOVER trial;[617] Mobarak et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 541 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 10 days and 542 assigned to SOC	Median age 58, male 54%, hypertension 34%, diabetes 26%, COPD 2.1%, asthma 4.8%, CHD 9.1%	Steroids 69.9%, remdesivir 15.6%, hydroxychloroquine 12.8%, lopinavir-ritonavir 33.1%, azithromycin 22.1%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Alavi-moghaddam et al;[618] Preprint; 2021	Patients with severe to critical COVID-19 infection. 27 assigned to sofosbuvir 400 mg a day and 30 assigned to SOC	Mean age 57.2 ±, male 49.1%, hypertension 21%, diabetes 29.8%, COPD 7%, CHD 19.3%, CKD 1.7%, obesity 1.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	

				inappropriate.	
Yadollahzadeh et al;[423] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100 mg twice a day for 7 days	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%, immunosuppression 3.6%, cancer 10.7%	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khalili et al;[619] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 42 assigned to sofosbuvir/ledipasvir 400/90 mg a day for 10 days and 40 assigned to SOC	Median age 62.2 ± 23.1, hypertension 45.1%, diabetes 45.1%, COPD 4.9%, CHD 31.7%, cancer 3.6%	Corticosteroids 8.5%, hydroxychloroquine 10.9%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Elgohary et al;[620] preprint; 2021	Patients with moderate COVID-19 infection. 125 assigned to sofosbuvir/ledipasvir 400/90 mg once a day for 15 days and 125 assigned to SOC	Mean age 43 ±, male 0.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
SOVECOD trial;[621] Sayad et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to sofosbuvir/velpatasvir 400/100 mg once a day for 10	Mean age 54.1 ± 17.8, male 55%, hypertension 30%, diabetes 20%, COPD 10%, CHD 17.5%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	days and 40 assigned to SOC			study which might have introduced bias to symptoms and adverse events outcomes results.	
El-Bendari et al;[622] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 96 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 14 days and 78 assigned to SOC	Mean age 53 ± 15, male 54.6%, hypertension 21.3%, diabetes 37.3%, asthma 1.7%, CHD 10.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abbass et al;[623] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 80 assigned to sofosbuvir/daclatasvir 400/60 a day or sofosbuvir/ravidasvir 400/200 mg a day for 10 days and 40 assigned to SOC	Mean age 44.6 ± 4.7, male 53.3%, diabetes 18.3%, asthma 1.6%, CHD 75.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Table 1 shows more severe patients in SOC (68% vs 59%).	
Medhat et al;[624] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 70 assigned to sofosbuvir/ledipasvir 400/90 mg a day for 14 days and 73 assigned to SOC	Mean age 45, male 51%, hypertension 20.9%, diabetes 20.3%	Corticosteroids 49%, hydroxychloroquine 8.4%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Bozorgmehr et al;[625] peer reviewed; 2022	Patients with severe COVID-19 infection. 50 assigned to sofosbuvir 400 mg a day for 7 days	Mean age 53.8 ± , male 44%, diabetes 7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	and 50 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVER HCW trial;[505] Sokhela et al; peer reviewed; 2022	Patients with exposed to COVID-19 infection. 265 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 24 weeks and 283 assigned to SOC	Median age 24, male 51.9%, hypertension 8.2%, diabetes 1.1%, COPD 2.2%	Vaccinated 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	

Sotrovimab Sotrovimab probably reduces hospitalizations in patients with mild recent onset COVID-19 with risk factors for severe disease.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COMET-ICE trial;[626] Gupta et al; peer reviewed; 2021	Patients with mild to moderate recent onset with risk factors COVID-19 infection. 528 assigned to sotrovimab 500 mg once and 529 assigned to SOC	Median age 53, male 45.9%, hypertension %, diabetes 21.6%, COPD 5.6%, asthma 16.8%, CHD 0.7%, CKD 1.2%, obesity 63.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: Stopped early for benefit	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.34 (95%CI 0.16 to 0.68); RD -6.7% (95%CI -8.6% to -3.3%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.20 (95%CI 0.08 to 0.48); RD -3.8% (95%CI -4.6% to -2.5%); Moderate certainty ⊕⊕⊕◯
OPTIMISE-C19 trial;[576] Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD 16%, CKD 4.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
MANTICO trial;[99] Mazzaferri et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 107 assigned to sotrovomab 500 mg once and 106 assigned to bamlanivimab + etesevimab 700/1400 mg once and 106 assigned to REGEN-COV2 600/600 mg once	Mean age 65 ± 15, male 57.2%, diabetes 2.9%, COPD 16.7%, asthma %, CHD 37.9%, CKD 5.1%, immunosuppression 19.6%, obesity 25.4%	Vaccinated 28.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Spironolactone Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Asadipooya et al;[613] preprint; 2021	Patients with moderate to severe COVID-19 infection. 50 assigned to spironolactone 100 mg a day and 87 assigned to SOC	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD 6.4%, cancer 5.9%, obesity 18.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information
Bharti et al;[627] preprint; 2022	Patients with severe COVID-19 infection. 74 assigned to spironolactone 50 mg once followed by 25 mg a day for 21 days and 46 assigned to SOC	Mean age 48.8 ± 14.3, male 61.7%, hypertension 28.3%, diabetes 34.2%, COPD 1.7%, asthma 3.3%, CHD 5.8%, CKD 0.8%, cancer 0.8%	Corticosteroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow up. Selective reporting: Patients with symptom progression were excluded.	

Spirulin

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Javid et al;[628] preprint; 2022	Patients with severe COVID-19 infection. 68 assigned to spirulina 5 gr a day for 14 days and 58 assigned to SOC	Mean age 57.5, male 57.9%, hypertension 40.5%, diabetes 19.8%, COPD 0.8%, CHD 23%	Corticosteroids 53.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes:	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

Statins

Statins may reduce mortality; however, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

RESIST trial;[66] Ghati et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 221 assigned to atorvastatin 40 mg once a day for 10 days and 219 assigned to SOC	Mean age 53.1 ± 9.2, male 73.3%, hypertension 28.6%, diabetes 27.7%, CHD 1.1%, CKD 2.4%	Corticosteroids 27.3%, remdesivir 20.6%, hydroxychloroquine 9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** RR 0.91 (95%CI 0.73 to 1.14); RD -1.4% (95%CI -4.3% to 2.2%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
INSPIRATION/INSPIRATION-S trial;[629] Bikdeli et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 290 assigned to atorvastatin 20 mg a day for 30 days and 297 assigned to SOC	Median age 57 ± , male 56.4%, hypertension 31.5%, diabetes 16.7%, COPD 8%	Corticosteroids 93.4%, remdesivir 66.3%, hydroxychloroquine 7.5%, lopinavir-ritonavir 0.7%, tocilizumab 14.5%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Ghafouri et al;[630] peer reviewed; 2021	Patients with severe COVID-19 infection. 76 assigned to statin atorvastatin 20 mg for 7 to 14 days and 78 assigned to SOC	Mean age 51.8 ± 17.4, male 50.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
INTENSE-COV trial;[39] Bonnet et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 98 assigned to statin atorvastatin 20 mg a day for 10 days and 96 assigned to SOC	Mean age 37, male %, hypertension 6.2%, diabetes 2.6%, COPD %, asthma 7.2%, CHD 0.5%, CKD 0%, cerebrovascular disease %, immunosuppresive therapy %, cancer 0.5%, obesity %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Stem-cell nebulization

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
SENTAD-COVID trial;[631] Carmenate et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 69 assigned to stem-cell nebulization twice, 24 h apart, and 70 assigned to SOC	Mean age 45.1 ± 10.4, male 46.5%, hypertension 26.6%, diabetes 22.3%, COPD %, asthma 10.7%, CHD 9.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Steroids (corticosteroids)

Corticosteroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Corticosteroids may not significantly increase the risk of severe adverse events. Higher doses (i.e., dexamethasone 12 mg a day) are probably not more effective than standard doses (i.e., dexamethasone 6 mg a day).

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

GLUCOCOVID trial;[632] Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone 40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	Mean age 69.5 ± 11.5, male 61.9%, hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%, cerebrovascular disease 12.7%	Hydroxychloroquine 96.8%, lopinavir-ritonavir 84.1%, azithromycin 92%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.90 (95%CI 0.80 to 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.87 (95%CI 0.73 to 1.04); RD -2.2% (95%CI -4.7% to 0.7%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information
Metcovid trial;[633] Prado Jeronimo et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 194 assigned to methylprednisolone 0.5 mg/kg twice a day for 5 days and 199 assigned to standard of care	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease 0.5%, asthma 2.5%, coronary heart disease 6.9%, alcohol use disorder 27%, liver disease 5.5%	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
RECOVERY - Dexamethasone trial;[634] Horby et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 2104 assigned to dexamethasone 6 mg once daily for 10 days and 4321 assigned to standard of care	Mean age 66.1 ± 15.7, male 64%, diabetes 24%, chronic lung disease 21%, asthma NR%, coronary heart disease 27%, chronic kidney disease 8%, liver disease 2%, any comorbidities 56%	Corticosteroids NA%, remdesivir 0.08%, hydroxychloroquine 1%, lopinavir-ritonavir 0.5%, tocilizumab 3%, azithromycin 25%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
DEXA-COVID19 trial;[635] Villar et al; unpublished; 2020	Patients with severe to critical COVID-19. Seven assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day for 5 days and 12 assigned to standard of care	NR	NR	Low for mortality and invasive mechanical ventilation Notes: RoB judgment from published SR.	

CoDEX trial;[636] Tomazini et al; peer-reviewed; 2020	Patients with critical COVID-19. 151 assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day for 5 days and 148 assigned to standard of care	Mean age 61.4 ± 14.4, male 62.5%, hypertension 66.2%, diabetes 42.1%, coronary heart disease 7.7%, chronic kidney disease 5.3%, obesity 27%	hydroxychloroquine 21.4%, azithromycin 71.2%, ATB 87%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
REMAP-CAP trial;[637] Arabi et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 278 assigned to hydrocortisone 50 mg every 6 hours for 7 days and 99 assigned to standard of care	Mean age 59.9 ± 13, male 71%, diabetes 32%, chronic lung disease 20.3%, coronary heart disease 7.5%, chronic kidney disease 9.2%, immunosuppression 4.9%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVID STEROID trial;[638] Munch et al; PEER-REVIEWED; 2022	Patients with severe to critical COVID-19. 16 assigned to hydrocortisone 200 mg a day for 7 days and 14 assigned to standard of care	NR	NR	Low for mortality and invasive mechanical ventilation Notes: Risk of bias judgment from published SR.	
CAPE COVID trial;[639] Dequin et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 76 assigned to hydrocortisone 200 mg a day progressively reduced to 50 mg a day for 7 to 14 days and 73 assigned to standard of care	Median age 64.7 ± 19.3, male 69.8%, hypertension %, diabetes 18.1%, chronic lung disease 7.4%, immunosuppression 6%	Remdesivir 3.4%, hydroxychloroquine 46.9%, lopinavir-ritonavir 14.1%, tocilizumab 2%, azithromycin 34.2%	Low for mortality and invasive mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Corticosteroids-SARI trial;[635]	Patients with severe to critical	NR	NR	Low for mortality and invasive mechanical	

Unpublished; 2020	COVID-19. 24 assigned to methylprednisolone 40 mg twice a day for 5 days and 23 assigned to standard of care			ventilation Notes: Risk of bias judgment from published SR.	
Farahani et al;[640] preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to methylprednisolone 1000 mg/day for three days followed by prednisolone 1 mg/kg for 10 days, and 15 assigned to standard of care	Mean age 64 ± 13.5	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Edalatifard et al;[641] peer-reviewed; 2020	Patients with severe COVID-19. 34 assigned to methylprednisolone 250 mg/day for 3 days and 28 assigned to standard of care	Mean age 58.5 ± 16.6, male 62.9%, hypertension 32.3%, diabetes 35.5%, chronic lung disease 9.7%, coronary heart disease 17.7%, chronic kidney disease 11.3%, cancer 4.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Tang et al;[642] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 43 assigned to methylprednisolone 1 mg/kg for 7 days and 43 assigned to SOC	Median age 56 ± 27, male 47.7%, hypertension 36%, diabetes 9.3%, COPD 3.5%, asthma 2.4%, CHD 7%, CKD 1.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Jamaati et al;[643] Peer-reviewed; 2020	Patients with moderate to severe COVID-19. 25 assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day until	Median age 62 ± 16.5, male 72%, hypertension 50%, diabetes 54%, COPD 20%, CHD 14%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded	

	day 10 and 25 assigned to SOC			study. Concealment of allocation is probably inappropriate.	
Rashad et al;[644] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 75 assigned to dexamethasone 4 mg/kg a day for 3 days followed by 8 mg a day for 10 days and 74 assigned to TCZ	Mean age 62, male 56.9%, hypertension 47.7%, diabetes 28.4%, COPD 1.8%, asthma 2.7%, CHD 12.8%, CKD 8.2%, cancer 0.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. Significant loss to follow-up as patients who died in the first 3 days after randomization were excluded.	
Ghanei et al;[86] peer reviewed; 2021	Patients with severe COVID-19 infection. 116 assigned to predninoslone 25 mg a day for 5 days and 110 assigned to SOC	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
CORTIVID trial;[645] Les et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 34 assigned to methylprednisolone and 37 assigned to SOC	Mean age 58.4, male 69%, hypertension 32.4%, diabetes 18.3%, COPD 1.4%, asthma 2.8%, CKD 7%	Remdesivir 8.5%, tocilizumab 28.2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Ranjbar et al;[646] Preprint; 2020	Patients with severe to critical COVID-19 infection. 44 assigned to methylprednisolone 2 mg/kg daily for 5	Mean age 58.7 ± 17.4, male 56.9%, hypertension 45.3%, diabetes 32.5%, CHD 30.2%, CKD 2.3%	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and	**Mortality:** RR 1 (95%CI 0.82 to 1.21); RD 0% (95%CI -2.9% to 3.4%); Moderate certainty ⊕⊕⊕◯

	days followed by tapering using same scheme at half dose every 5 days, 42 assigned to dexamethasone 6 mg a day for 10 days			adverse events Notes: Unbalanced prognostic factors (age and gender).	**Invasive mechanical ventilation:** RR 1.11 (95%CI 0.61 to 2.01); RD 1.9% (95%CI -6.7% to 17.5%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 0.98 (95%CI 0.9 to 1.02); RD -1.2% (95%CI -4.2% to 1.2%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.82 (95%CI 0.6 to 1.11); RD -1.8% (95%CI -4.1% to 1.1%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
COVID STEROID 2 trial;[647] Munch et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 497 assigned to dexamethasone 12 mg a day for 10 days and 485 assigned to dexamethasone 6 mg a day for 10 days	Median age 64.5 ± 18, male 69%, diabetes 30.3%, COPD 12%, CHD 14%	Remdesivir 62.8%, tocilizumab 10.1%, convalescent plasma 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Maskin et al;[648] preprint; 2021	Patients with critical COVID-19 infection. 49 assigned to dexamethasone 16 mg a day for 5 days followed by 8 mg a day for 5 days and 49 assigned to dexamethasone 6 mg a day for 10 days	Mean age 61.8 ± 13.4, male 70%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Toroghi et al;[649] peer reviewed; 2021	Patients with severe COVID-19 infection. 86 assigned to dexamethasone 16 to 24 mg a day and 47 assigned to dexamethasone 8 mg a day for up to 10 days	Mean age 58, male 60.2%, hypertension 36%, diabetes 22.5%, COPD 6%, CHD 17.3%, CKD 1.5%, cerebrovascular disease 6%, cancer 2.3%	Remdesivir 75.2%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
HIGHLOWDEXA trial;[650] Taboada	Patients with severe COVID-19	Mean age 64.3 ± 14.3, male 61.8%,	Remdesivir 10%, tocilizumab 12%,	High for mortality and mechanical	

et al; peer reviewed; 2021	infection. 98 assigned to dexamethasone 20 mg once a day for 5 days dexamethasone and 102 assigned to dexamethasone 6 mg once a day for 10 days	hypertension 48%, diabetes 19%, COPD 7%, asthma 5%, CHD 13.5%, CKD 3.5%, obesity 53%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Naik et al;[651] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 21 assigned to dexamethasone 20 mg a day for 3 days and 21 assigned to TCZ 6 mg/kg once	Median age 50.5, male 57.1%, hypertension 57.1%, diabetes 35.7%, COPD 4.8%, asthma 2.4%, CHD %, CKD 0%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
RCT-MP-COVID-19 trial;[652] Salvarani et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 151 assigned to three boluses of 1 g of methylprednisolone intravenously and 150 assigned to SOC	Median age 64 , male 72.1%, hypertension 52.2%, diabetes 14.9%, COPD 4.4%, obesity 22.9%	Corticosteroids 88.4%, remdesivir 15.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
COVIDICUS trial;[653] Bouadma et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 270 assigned to dexamethasone 14 mg a day for 5 days followed by dexamethasone 4 mg a day for 5 days and 276 assigned to dexamethasone 6 mg a day for 10 days	Median age 67, male 75.8%, hypertension 55.4%, diabetes 37%, cancer 11.2%,	Corticosteroids %, remdesivir 17%, hydroxychloroquine 1.1%, lopinavir-ritonavir 2.2%, tocilizumab 1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Dastenae et al;[654] peer reviewed; 2022	Patients with severe to critical COVID-19	Mean age 63, male 55.9%, hypertension 47.6%, diabetes	Remdesivir 88.1%,	High for mortality and mechanical ventilation; high for	

	infection. 73 assigned to methylprednisolone 60 mg a day for 10 days and 71 assigned to dexamethasone 8 mg a day for 10 days	25.9%, COPD 12.6%, asthma %, CHD 11.9%, CKD 6.3%,		symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
MEDEAS trial;[655] Salton et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 337 assigned to methylprednisolone 80 mg a day for 8 days and 340 assigned to dexamethasone 6 mg a day for 10 days	Mean age 63.7, male 69.4%, hypertension 46.5%, diabetes 17.4%, COPD 7.5%, asthma 5%, CHD 7.8%, CKD 4.9%	Remdesivir 20.8%, tocilizumab 8%, baricitinib 4.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
RECOVERY_Steroid_Dose trial;[656] Horby et al; preprint; 2022	Patients with severe COVID-19 infection. 659 assigned to dexamethasone 20 mg daily for 5 days followed by dexamethasone 10 mg for 5 days and 613 assigned to dexamethasone 6 mg a day for 10 days	Mean age 61, male 60.4%, hypertension %, diabetes 19.4%, COPD 21.1%, CKD 3.1%	Remdesivir 34%, tocilizumab 8.1%; Vaccinated 52.3%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Steroids (inhaled corticosteroids)

Inhaled corticosteroids may improve time to symptom resolution but probably do not have an important effect on hospitalizations. Their effects on other important outcomes are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

STOIC trial;[657] Ramakrishnan et al; peer reviewed; 2020	Patients with mild to moderate COVID-19. 71 assigned to inhlaed budesonide 800 µg twice a day and 69 assigned to SOC	Mean age 45 ± 56, male 42.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.09 (95%CI 0.99 to 1.2); RD 5.5% (95%CI -0.6% to 12.1%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Hospitalization:** RR 0.9 (95%CI 0.7 to 1.15); RD -0.5% (95%CI -1.4% to 0.7%); Moderate certainty ⊕⊕⊕◯ **Adverse events:** Very low certainty ⊕◯◯◯
PRINCIPLE trial;[658] Yu et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 787 assigned to inhaled budesonide 800µg twice daily for 14 days and 1069 assigned to SOC	Mean age 64.2 ± 7.6, male 48%, hypertension 44.3%, diabetes 21.4%, COPD 12.6%, CHD 15.8%, cerebrovascular disease 5.6%	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study. Significant loss to follow-up.	
Song et al;[659] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 35 assigned to inhaled ciclesonide 320 µg twice per day for 14 days and 26 assigned to SOC	Median age 53 ± 26, male 47%, hypertension 27.8%, diabetes 14.7%, cerebrovascular disease 3.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ALV-020-001 trial;[660] Clemency et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 197 assigned to inhaled ciclesonide 640 µg a day for 30 days and 203 assigned to SOC	Mean age 43.3 ± 16.9, male 44.8%, hypertension 22.3%, diabetes 7.5%, asthma 6.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

CONTAIN trial;[661] Ezer et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 105 assigned to inhaled ciclesonide 1200 µg + 200 µg intranasal a day and 98 assigned to SOC	Median age 35 ± 19, male 46.3%, hypertension 5.9%, diabetes 2.5%, asthma 5%, CHD 0.5%, cancer 1%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Alsultan et al;[148] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to inhaled steroids budesonide 200 mcg twice a day for 5 days and 21 assigned to SOC	age 60 to 80 65.3, male 38.8%, diabetes 53.1%, CKD 8.2%, cerebrovascular disease 4.1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVERAGE trial;[662] Duvignaud et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 110 assigned to inhaled ciclesonide 640 µg of ciclesonide per day for 10 days and 107 assigned to SOC	Median age 63, male 48.9%, hypertension 41%, diabetes 15.2%, COPD 3.2%, CHD 5%, cerebrovascular disease 8.7%, cancer 5.9%, obesity 29.4%	Vaccinated13.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TACTIC-COVID trial;[663] Agusti et al; other; 2021	Patients with moderate to severe COVID-19 infection. 58 assigned to budesonide (inh) 400 µg/12 h and 62 assigned to SOC	Mean age 51.1 ± 13.7, male 47.1%,	Corticosteroids 17.8%, remdesivir 8.5%, hydroxychloroquine 8.5%, lopinavir-ritonavir 5.9%, tocilizumab 0.8%, azithromycin 9.3%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Terada et al;[125] peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 56 assigned to camostat 600 mg + ciclesonide (inhaled) 1200 µg a day and 61 assigned to SOC	Mean age 58.3, male 64.9%, diabetes 24.8%, COPD 9.4%, CHD 2.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ACTIV-6 - Fluticazone trial;[664] Naggie et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 656 assigned to fluticazone 200 µg once a day for 14 days and 621 assigned to SOC	Median age 45, male 36.8%, hypertension 26.1%, diabetes 9.7%, COPD 1.4%, asthma 13%, CHD 4.7%, CKD 0.8%, cancer 3.4%,	Corticosteroids %, remdesivir 0.1%, monoclonar antibodies 2.7%, paxlovid 0.1%; Vaccinated 65.2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Steroids (nasal corticosteroids)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Yildiz et al;[489] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 50 assigned to nasal steroids and 50 assigned to SOC	Mean age 37.8 ± , male 56%, hypertension 10%, diabetes 7%, COPD/asthma 8%, asthma %, CHD 14%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Sulodexide

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

ERSul trial;[665] Gonzalez Ochoa et al; preprint; 2020	Patients with mild (early within 3 days of onset) COVID-19. 124 assigned to sulodexide 500 RLU twice a day for 3 weeks and 119 assigned to standard of care	Median age 52 ± 10.6, male 47.4%, hypertension 34.2%, diabetes 22.2%, COPD 23%, coronary heart disease 21%	Corticosteroids 62.5%, hydroxychloroquine 33.7%, ivermectin 43%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Tafenoquine

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Dow et al;[666] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 45 assigned to tafenoquine 200 mg a day for 3 days followed by 200 mg once next week and 41 assigned to SOC	Mean age 43 ± 15, male 47.7%	Vaccinated 32.6%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement: :** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

TD-0903 (inhaled JAK-inhibitor)

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Singh et al;[667] Preprint; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to TD-0903 1-10 mg once a day for 7 days and 6 assigned to SOC	Mean age 57.1 ± 12.3, male 68%, hypertension 68%, diabetes 40%	Corticosteroids 92%, remdesivir 12%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Tenofovir + emtricitabine

Tenofovir + emtricitabine may not reduce mortality but may reduce mechanical ventilation. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

AR0-CORONA trial;[668] Parientti et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 30 assigned to tenofovir + emtricitabine 245/200 mg twice a day on day one followed by 245/200 mg a day for 7 days and 30 assigned to SOC	Mean age 42 ± 15, male 43%, hypertension 5%, diabetes 3.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.97 (95%CI 0.49 to 1.92); RD -0.5% (95%CI -8.2% to 14.7%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.76 (95%CI 0.49 to 1.18); RD -4.2% (95%CI -8.8% to 3.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
ARTAN-C19 trial;[669] Lima et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 81 assigned to tenofovir +/- emtricitabine 300/200 mg once a day and 41 assigned to SOC	Mean age 38 ± 14.9, male 35%, hypertension 17%, diabetes 10%, asthma 6%, CHD 3%, cancer 1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	
EPICOS trial;[317] Polo et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 233 assigned to tenofovir +/- emtricitabine 245/200 mg a day and 223 assigned to SOC	Mean age 38.5, male 38%, hypertension 7.4%, diabetes 1.3%, COPD 0%, asthma 3.7%, CHD 0.4%, cancer 1.1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Gaitan-Duarte et al;[154] preprint; 2021	Patients with moderate to severe COVID-19 infection. 160 assigned to emtricitabine/ tenofovir 200/300 mg once a day for 10 days and 161 assigned to SOC	Mean age 55.4 ± 12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%	Corticosteroids 98%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

PanCOVID19 trial;[107] Montejano et al; peer reviewed; 2022	Patients with moderate COVID-19 infection. 177 assigned to tenofovir +/- emtricitabine 400/490 mg once followed by 200/245 mg once a day for 14 days and 178 assigned to SOC	Median age 67, male 64.5%, hypertension 61.1%, diabetes 27.3%, obesity 16.1%	Corticosteroids 100%, remdesivir 12.7%, baricitinib 50.5%; Vaccinated 91%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Thalidomide

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Amra et al;[670]	Patients with	Mean age 62 ± 10,	Corticosteroids	High for mortality and	**Mortality:** Very

preprint; 2021	severe COVID-19 infection. 28 assigned to thalidomide 100 mg a day for 14 days and 23 assigned to SOC	male 54.9%, hypertension 33.3%, diabetes 37.2%, COPD 5.9%, CHD 9.8%	100%, hydroxychloroquine 100%	mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Haghighi et al;[671] preprint; 2021	Patients with moderate to severe COVID-19 infection. 25 assigned to thalidomide 100 mg a day for 14 days and 25 assigned to SOC	Median age 51 ± 18, male 68%, hypertension 24%, diabetes 16%, CHD 8%, cancer 14%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Thymoquinone

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

Benchegroun et al;[672] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 23 assigned to thymoquinone 3000 mg a day and 19 assigned to SOC	Age >55 29.1%, male 43.6%, hypertension 40%, diabetes 18.2%, obesity 38.2%	Vaccinated 16.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Tissue plasminogen activator (tPA)

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

STARS trial;[673] Barret et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 25 assigned to tPa 50 mg bolus with or without drip and heparin and 25 assigned to SOC	Mean age 61, male 74%, hypertension 36%, diabetes 34%, COPD 62%, asthma %, CHD 66%, immunosuppressive therapy 66%	Corticosteroids 52%, remdesivir 40%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
TACOVID trial;[54] Rashidi et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 5 assigned to tPa 50 mg in 24 hs and 5 assigned to UFH 15000 IU a day	Mean age 56.5, male 80%, hypertension 40%, diabetes 10%, CHD 20%, CKD 0%, cancer 0%, obesity 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Tixagevimab–cilgavimab

Tixagevimab-cilgavimab probably reduces mortality, hospitalizations, and SARS-COV-2 infections in exposed individuals, and may not increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PROVENT trial;[674] Levin et	Individuals exposed to SARS-CoV-2	Mean age 53.5 ± 15, male 53.9%,	Vaccinated 0%	Low for mortality and mechanical	**Mortality:** RR 0.72 (95%CI 0.54 to

al; peer reviewed; 2021	infection. 3441 assigned to tixagevimab-cilgavimab 300 mg once and 1731 assigned to SOC	hypertension 35.9%, diabetes 14.1%, COPD 5.3%, asthma 11.1%, CHD 8.1%, CKD 5.2%, immunosuppresive therapy 3.3%, cancer 7.4%, obesity 41.7%		ventilation; High for symptom resolution, infection and adverse events Notes: Most patients were not blinded which might have introduced bias to symptoms and adverse events outcomes results.	0.96); RD -4.5% (95%CI -7.4% to -0.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation** No information **Symptom resolution or improvement:** RR 1.03 (95%CI 0.99 to 1.08); RD 2% (95%CI -0.6% to 4.7%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.18 (95%CI 0.09 to 0.35); RD -14.2% (95%CI -15.8% to -11.2%); Moderate certainty ⊕⊕⊕◯ **Adverse events:** RR 0.95 (95%CI 0.69 to 1.31); RD -0.5% (95%CI -3.2% to 3.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.42 (95%CI 0.24 to 0.74); RD -2.8% (95%CI -3.6% to 1.3%); Moderate certainty ⊕⊕⊕◯
TACKLE trial;[675] Montgomery et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 452 assigned to tixagevimab-cilgavimab 600 mg once and 451 assigned to SOC	Mean age 46.1 ± 15.2, male 50%, hypertension 28%, diabetes 12%, immunosuppression therapy 5%, cancer 4%, obesity 43%	Corticosteroids 2.8%; vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
TICO trial;[676] Lane et al; peer reviewed; 2022	Patients with moderate COVID-19 infection. 710 assigned to tixagevimab-cilgavimab 600 mg once and 707 assigned to SOC	Mean age 46.1 ± 15.2, male 50%, hypertension 28%, diabetes 12%, CHD 9%, CKD 2%, immunosuppression 5%, cancer 4%, obesity 43%	Corticosteroids 73%, remdesivir 63.3%; vaccinated 26.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Tocilizumab

Tocilizumab reduces mortality and mechanical ventilation requirements without increasing severe adverse events.

Study; publication	Patients and interventions	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard

status	analyzed				of care and GRADE certainty of the evidence
RCT					
COVACTA trial; Rosas et al;[677] peer-reviewed; 2020	Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned to standard of care	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, coronary heart disease 28%, obesity 20.5%	Corticosteroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.86 (95%CI 0.79 to 93); RD -2.2% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 0.84 (95%CI 0.79 to 0.91); RD -2.8% (95%CI -3.6% to -1.6%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.08 (95%CI 1.02 to 1.14); RD 4.8% (95%CI 1.2% to 8.5%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.95 (95%CI 0.87 to 1.04); RD -0.5% (95%CI -1.3% to 0.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
Wang et al;[678] preprint; 2020	Patients with moderate to severe COVID-19. 34 assigned to tocilizumab 400 mg once or twice and 31 assigned to standard of care	Median age 63 ± 16, male 50.8%, hypertension 30.8%, diabetes 15.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Zhao et al;[239] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir plus tocilizumab	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RCT-TCZ-COVID-19 trial;[679] Salvarani et al; peer-reviewed; 2020	Patients with severe COVID-19. 60 assigned to tocilizumab 8 mg/kg twice on day 1 and 66 assigned to standard of care	Median age 60 ± 19, male 61.1%, hypertension 44.4%, diabetes 15.1%, COPD 3.2%, obesity 32.2%	Hydroxychloroquine 91.3%, azithromycin 20.6%, antivirals 41.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

				Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BACC Bay Tocilizumab Trial trial;[680] Stone et al; peer-reviewed; 2020	Patients with severe COVID-19. 161 assigned to tocilizumab 8 mg/kg once and 81 assigned to standard of care	Median age 59.8 ± 15.1, male 58%, hypertension 49%, diabetes 31%, COPD 9%, asthma 9%, coronary heart disease 10%, chronic kidney disease 17%, cancer 12%	Corticosteroids 9.5%, remdesivir 33.9%, hydroxychloroquine 3.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CORIMUNO-TOCI 1 trial;[681] Hermine et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 63 assigned to tocilizumab 8 mg/kg once followed by an optional 400 mg dose on day 3 and 67 assigned to standard of care	Median age 63.6 ± 16.2, male 67.7%, diabetes 33.6%, COPD 4.7%, asthma 6.3%, coronary heart disease 31.2%, chronic kidney disease 14%, cancer 7%	Corticosteroids 43%, remdesivir 0.7%, hydroxychloroquine 6.2%, lopinavir-ritonavir 3%, azithromycin 15.4%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
EMPACTA trial;[682] Salama et al; preprint; 2020	Patients with moderate to severe COVID-19. 249 assigned to tocilizumab 8 mg/kg once and 128 assigned to standard of care	Mean age 55.9 ± 14.4, male 59.2%, hypertension 48.3%, diabetes 40.6%, COPD 4.5%, asthma 11.4%, coronary heart disease 1.9%, cerebrovascular disease 3.4%, obesity 24.4%	Corticosteroids 59.4%, remdesivir 54.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
REMAP-CAP - tocilizumab trial;[596] Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8 mg/kg once or twice, 48 assigned to sarilumab	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%	Corticosteroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	400 mg once and 402 assigned to SOC			study which might have introduced bias to symptoms and adverse events outcomes results.	
Veiga et al;[683] peer reviewed; 2020	Patients with severe to critical COVID-19. 65 assigned to TCZ 8 mg/kg once and 64 assigned to SOC	Mean age 57.4 ± 14.6, male 68%, hypertension 49.6%, diabetes 32.6%, COPD 3%, CHD 5.5%, cancer 7%,	Corticosteroids 71.3%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY-TCZ trial;[684] Horby et al; peer reviewed; 2020	Patients with severe to critical COVID-19. 2022 assigned to TCZ 400-800 mg once or twice and 2094 assigned to SOC	Mean age 63.6 ± 13.6, male 67.3%, diabetes 28.5%, COPD 23%, asthma %, CHD 23%, CKD 5.5%	Corticosteroids 82%, hydroxychloroquine 2%, lopinavir-ritonavir 3%, azithromycin 9%	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PreToVid trial;[685] Rutgers et al; preprint; 2021	Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice and 180 assigned to SOC	Median age 66.5 ± 16.5, male 67%, comorbidities 74.3%	Corticosteroids 88.4%, remdesivir 18.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Talaschian et al;[686] preprint; 2021	Patients with severe COVID-19 infection. 17 assigned to TCZ 8 mg/kg once or twice and 19 assigned to SOC	Mean age 61.7 ± 14.2, male 52.7%, hypertension 50%, diabetes 36.1%, COPD 8.3%, asthma %, CHD 44.4%, CKD 2.8%, cancer 0%	Corticosteroids 33.3%, hydroxychloroquine 63.9%, lopinavir-ritonavir 8.3%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Hamed et al;[687] peer reviewed; 2021	Patients with severe COVID-19 infection. 23 assigned to TCZ 400 mg once and 26 assigned to SOC	Mean age 48 ±, male 85.5%, hypertension 36.8%	Corticosteroids 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
ARCHITECTS trial;[611] other; 2021	Patients with severe to critical COVID-19 infection. 10 assigned to TCZ 8 mg/kg once or twice and 11 assigned to SOC	Median age 61 ±	Corticosteroids 95.2%, remdesivir 90.4%, convalescent plasma 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
CORIMUNO-TOCI ICU trial;[600] Hermine et al; Peer reviewed; 2021	Patients with critcal COVID-19 infection. 49 assigned to TCZ 8 mg/kg once or twice and 43 assigned to SOC	Mean age 64.2 ± , male 71.7%, diabetes 35.5%, COPD 7.8%, asthma 5.5%, CHD %, CKD 6.6%, cancer 2.2%,	Steroids 33.6%, remdesivir 0%, hydroxychloroquine 0%, lopinavir-ritonavir 4.3%, azithromycin 4.3%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

COV-AID trial; et al;[611] other; 2021	Patients with severe to critical COVID-19 infection. 81 assigned to TCZ 8 mg/kg once and 72 assigned to SOC	Median age 63	Corticosteroids 52.6%, remdesivir 5.8%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVIDOSE-2 trial; et al;[611] other; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to TCZ 40-120 mg once and 8 assigned to SOC	Median age 65	Corticosteroids 30%, remdesivir 75%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVIDSTORM trial;[688] Broman et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 57 assigned to TCZ 400 to 800 mg once and 29 assigned to SOC	Median age 58.5 ± 13.9, male 55.8%, hypertension 37.2%, diabetes 24.4%, COPD 3.5%, asthma 14%, CHD 5.81%, cancer 11.6%, obesity 63.5%	Steroids 77%, remdesivir 0%, convalescent plasma 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVITOZ-01 trial; et al;[611] other; 2021	Patients with moderate to severe COVID-19 infection. 17 assigned to TCZ 8 mg/kg once or twice and 9 assigned to SOC	Median age 57	Corticosteroids 100%, remdesivir 52.9%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
HMO-0224-20 trial;[611] other; 2021	Patients with severe to critical COVID-19	Median age 63	Corticosteroids 85.2%, remdesivir 22.2%,	High for mortality and mechanical ventilation; high for	

	infection. 37 assigned to TCZ 8 mg/kg once and 17 assigned to SOC		convalescent plasma 0%	symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
REMDACTA trial; et al;[689] Rosas et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 430 assigned to TCZ 8 mg/kg once or twice and 210 assigned to SOC	Median age 6, male 63.2%, hypertension 61.7%, diabetes 39.5%, CHD 23.4%	Corticosteroids 88.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ImmCoVA trial;[611] other; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to TCZ 8 mg/kg once and 27 assigned to SOC	Median age 24	Corticosteroids 96%, remdesivir 14.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
TOCOVID trial;[611] other; 2021	Patients with moderate to severe COVID-19 infection. 136 assigned to TCZ 400 to 600 mg once and 134 assigned to SOC	Median age 53	Corticosteroids 35%, remdesivir 0.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVINTOC trial; et al;[690] Soin et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91 assigned to TCZ	Median age 55 , male 85.5%, hypertension 39.4%, diabetes 41.1%, COPD 2.2%, CHD	Corticosteroids 91%, remdesivir 41.6%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and	

	6 mg/kg once or twice and 88 assigned to SOC	15%, CKD 4.4%		adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOCIDEX trial;[691] Hermine et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 224 assigned to TCZ 400 mg once and 226 assigned to SOC	Median age 63 ± 21, male 68%, hypertension 37.1%, diabetes 23.8%, COPD %, asthma 8.4%, CHD 13.5%, CKD 7.2%	Corticosteroids 100%, convalescent plasma 1.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Karampitsakos et al;[692] preprint; 2022	Patients with severe COVID-19 infection. 125 assigned to baricitinib 4 mg a day for 14 days and 126 assigned to TCZ 8 mg/kg once	Mean age 72.5, male 59.4%, hypertension 53.8%, cancer 9.2%, obesity 8%	Corticosteroids 100%, remdesivir 100%; vaccinated 20.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
MARIPOSA trial;[693] Kumar et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 49 assigned to TCZ 4 mg/kg and 48 assigned to TCZ 8 mg/kg	Mean age 56.8 ± 14.3, male 58.7%	Corticosteroids 22.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Tofacitinib

Tofacitinib may increase symptom resolution or improvement and may increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
STOP-COVID trial;[694] Guimaraes et al; peer reviewed;	Patients with moderate to severe COVID-19 infection. 144	Mean age 56 ± 14, male 65.1%, hypertension 50.2%, diabetes 23.5%	Corticosteroids 78.5%	Low for mortality and mechanical ventilation; low for symptom resolution,	**Mortality:** Very low certainty ⊕◯◯◯

2021	assigned to tofacitinib 10 mg twice a day for 14 days and 145 assigned to SOC			infection, and adverse events	**Invasive mechanical ventilation:** No information
Murugesan et al;[695] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 50 assigned to tofacitinib 20 mg a day for 14 days and 50 assigned to SOC	Mean age 46.5, male 74%, diabetes 36%, COPD 1%, CHD 5%	Corticosteroids 100%, remdesivir 98%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptom resolution or improvement:** RR 1.1 (95%CI 0.98 to 1.23); RD 6.1% (95%CI 1.2% to 13.9%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information

Tranilast

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Saeedi-Boroujeni et al;[696] peer reviewed; 2021	Patients with severe COVID-19 infection. 30	Mean age 59.5, male 63.3%, hypertension 36.7%, diabetes	NR	High for mortality and mechanical ventilation; high for	**Mortality:** Very low certainty ⨁◯◯◯

	assigned to tranilast 300 mg a day for 7 days and 30 assigned to SOC	26.7%, COPD 16.6%, CKD 6.6%		symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Triazavirin

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Wu et al;[697] peer-reviewed; 2020	Patients with mild to critical COVID-19. 26 assigned to	Median age 58 ± 17, male 50%, hypertension 28.8%,	Corticosteroids 44.2%, hydroxychloroquine	Low for mortality and invasive mechanical ventilation; low for	**Mortality:** Very low certainty ⊕◯◯◯

	triazavirin 250 mg orally three or four times a day for 7 days and 26 assigned to standard of care	diabetes 15.4%, chronic lung disease 5.8%, coronary heart disease 15.4%, cerebrovascular disease 7.7%	26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%, umifenovir 61.5%, ribavirin 28.9%	symptom resolution, infection, and adverse events	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
TXA-127 **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
AAAT0535 trial;[698] Wagener	Patients with severe COVID-19	Mean age 56, male 65%	NR	Low for mortality and mechanical	**Mortality:** Very low certainty

et al; peer reviewed; 2022	infection. 11 assigned to TXA-127 0.5 mg/kg a day for 10 days and 9 assigned to SOC			ventilation; low for symptom resolution, infection and adverse events	⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ultraviolet B phototherapy

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Lau et al;[699] peer reviewed; 2022	Patients with severe COVID-19	Mean age 66.9, male 60%, hypertension	Corticosteroids 93.3%, remdesivir	Low for mortality and mechanical	**Mortality:** Very low certainty

	infection. 15 assigned to UVB escalating protocol for 8 days and 15 assigned to SOC	50%, diabetes 16.7%	76.7%, tocilizumab 30%, vaccinated 33.3%, Regeneron 3.3%	ventilation; Low for symptom resolution, infection and adverse events	⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Umifenovir

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Chen et al;[229] preprint; 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to	Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and	**Mortality:** Very low certainty ⊕◯◯◯

	favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
ELACOI trial;[416] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, IVIG 6.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Nojomi et al;[700] preprint; 2020	Patients with severe COVID-19. 50 assigned to umifenovir 100 mg two twice a day for 7 to 14 days and 50 assigned to lopinavir-ritonavir 400 mg a day for 7 to 14 days	Mean age 56.4 ± 16.3, male 60%, hypertension 39%, diabetes 28%, asthma 2%, coronary heart disease 9%, chronic kidney disease 2%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Yethindra et al;[701] peer-reviewed; 2020	Patients with mild COVID-19. 15 assigned to umifenovir 200 mg three times a day for 1 to 5 days and 15 assigned to standard of care	Mean age 35.5 ± 12.1, male 60%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Ghaderkhani S et al (Tehran University of Medical Sciences) trial;[702] Ghaderkhani et al; preprint; 2020	Patients with mild to moderate COVID-19. 28 assigned to umifenovir 200 mg three times a day for 10 days and 25 assigned to standard of care	Mean age 44.2 ± 19, male 39.6%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
UAIIC trial;[703] Darazam et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 51 assigned to umifenovir 600 mg a day for 10 days and 50 assigned to SOC	Mean age 61.2 ± 15.8, male 56.4%, hypertension 46.4%, diabetes 31.6%, COPD 10%, asthma 6.1%, CHD 11.2%, CKD 7.1%, cancer 1%	Corticosteroids 3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Ramachandran et al;[704] preprint; 2021	Patients with mild to moderate COVID-19 infection. 60 assigned to umifenovir 800 mg twice a day for 14 days and 63 assigned to SOC	Mean age 46.7 ± 1.9, male 74.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Verapamil

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ReCOVery-SIRIO trial;[18]	Patients with moderate to severe	Median age 61.3 , male 62.3%,	Remdesivir 1.9%, hydroxychloroquine	High for mortality and mechanical	**Mortality:** Very low certainty

Navarese et al; peer reviewed; 2022	COVID-19 infection. 72 assigned to verapamil 120 to 480 mg a day and 72 assigned to SOC	diabetes 23.7%, COPD 6.5%, cancer 7%	2.3%, azithromycin 6%, convalescent plasma 1.9%	ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Vidofludimus calcium

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Vehreschild et al;[705] peer	Patients with moderate COVID-	Mean age 54.1, male 54%, diabetes	Corticosteroids 63.6%	Low for mortality and mechanical	**Mortality:** Very low certainty

reviewed; 2022	19 infection. 110 assigned to vidofludimus calcium 45 mg a day and 110 assigned to SOC	17.7%, COPD 7, cancer 0.9%,		ventilation; low for symptom resolution, infection and adverse events	⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.13 (95%CI 0.33 to 3.01); RD 8.1% (95%CI -11.2% to 35.2%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Vilobelimab

Vilobelimab probably reduces mortality and probably does not increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Vlaar et al;[706] peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to vilobelimab 800 mg IV with a maximum of seven doses and	Mean age 60 ± 9, male 73%, hypertension 30%, diabetes 27%, obesity 20%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** RR 0.76 (95%CI 0.6 to 0.98); RD -3.8% (95%CI -6.4% to -0.3%); Moderate certainty ⊕⊕⊕◯

	15 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** No information
PANAMO trial (phase 3);[707] Vlaar et al; peer reviewed; 2022	Patients with critical COVID-19 infection. 177 assigned to vilobelimab 800 mg (six infusions) and 191 assigned to SOC	Mean age 56.3, male 68.5%, hypertension 46.2%, diabetes 29.6%, COPD 2%, CHD 7%, CKD 6.2%, cancer 1.1%, obesity 40.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.94 (95%CI 0.8 to 1.11); RD -0.6% (95%CI -2% to 1.1%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information

Vitamin B

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Majidi et al;[708] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 40 assigned to Vit B	Mean age 61.2	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse	**Mortality:** No information **Invasive mechanical**

	IM thiamine (10 mg), riboflavin (4 mg), nicotinamide (40 mg), and dexpanthenol (6 mg) once a day for 14 days and 45 assigned to SOC			events Notes: Concealment of allocation probably inappropriate.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Vitamin C

Vitamin C may reduce mortality and increase symptom resolution or improvement. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zhang et al;[709] preprint; 2020	Patients with severe COVID-19 infection. 26 assigned to vitamin C 12 g twice a day	Mean age 67.4 ± 12.4, male 66.7%, hypertension 44.4%, diabetes 29.6%, chronic lung disease	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and	**Mortality:** Very low certainty ⊕◯◯◯

	for 7 days and 28 assigned to standard of care	5.6%, coronary heart disease 22.2%, chronic kidney disease 1.85%, cancer 5.6%, nervous system disease 20.4%		adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.16 (95%CI 1.01 to 1.33); RD 9.7% (95%CI 0.6% to 20%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Kumari et al;[710] Peer reviewed; 2020	Patients with severe COVID-19. 75 assigned to Vit C 50 mg/kg a day and 75 assigned to SOC	Mean age 52.5 ± 11.5	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Jamali Moghadam Siahkali et al;[711] Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5 g a day for 5 days and 30 assigned to SOC	Mean age 59.2 ± 17, male 50%, hypertension 41.6%, diabetes 38.3%, COPD 10%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVIDAtoZ - Vit C trial;[712] Thomas et al; peer reviewed; 2020	Patients with mild COVID-19. 48 assigned to Vit C 8000 mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Corticosteroids 8.4%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
VCACS trial;[713] Tehrani et al;	Patients with severe COVID-19	Mean age 59.5, male 59%, hypertension	NR	High for mortality and mechanical	

peer reviewed; 2021	infection. 18 assigned to Vit C 8 gr a day for 5 days and 26 assigned to SOC	40.9%, diabetes 34%, COPD 7%, CHD 22.7%, CKD 9.1%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Beigmohammadi et al;[714] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin vitamin D 600000 UI once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000 mg a day in addition to others for 7 days. and 30 assigned to SOC	Mean age 52 ± 9, male 51.6%, hypertension 33.3%, diabetes 18.3%, asthma 13.3%, cancer 5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Majidi et al;[715] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 31 assigned to vitamin C 500 mg a day and 69 assigned to SOC	Mean age 62.4 ± , male 60%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
ALLIANCE trial;[716] Ried et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 162 assigned to vitamin C 400 mg/kg a day for 7 days and 75 assigned to SOC	Mean age 62.3 ± 15.7, male 50%, diabetes 35%, COPD 34%, CHD 36%, cancer 4%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Coppock et al;[717] peer reviewed; 2021	Patients with severe COVID-19 infection. 44	Mean age 60, male 50%, hypertension 62.1%, diabetes	Corticosteroids 77.3%, remdesivir 92.4%	High for mortality and mechanical ventilation; high for	

	assigned to vitamin C 0.3 to 0.9 g/kg a day for 5 days and 22 assigned to SOC	34.8%, COPD 19.7%		symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Fogleman C et al trial;[436] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 32 assigned to vitamin C 1000 mg a day for 14 days and 34 assigned to SOC	Median age 52, male 44.9%, hypertension 26.5%, diabetes 16.3%	Vaccinated 2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Kumar et al;[718] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 30 assigned to Vit C 3 gr a day for 4 days and 30 assigned to SOC	Mean age 60.2, male 78.3%, hypertension 43.3%, diabetes 0%, asthma 5%, CHD 6.7%, CKD 0%, cerebrovascular disease 8.3%	Corticosteroids 100%, remdesivir 90%, tocilizumab 8.3%, convalescent plasma 66.6%;	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	

Vitamin D

Vitamin D does not reduce SARS-COV-2 infections in exposed individuals and probably does not reduce hospitalizations. Vitamin D effects on other important outcomes are uncertain.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					

COVIDIOL trial; Entrenas Castillo et al;[719] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to vitamin D 0.532 once followed by 0.266 twice and 26 assigned to standard of care	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, coronary heart disease 3.9%, immunosuppression 9.2%	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** RR 1.06 (95%CI 0.91 to 1.24); RD 1% (95%CI -1.6% to 4.2%); High certainty ⊕⊕⊕⊕ **Adverse events:** RR 1.03 (95%CI 0.84 to 1.26); RD 0.3% (95%CI -1.6% to 2.7%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 1.2 (95%CI 0.83 to 1.74); RD 1% (95%CI -0.8% to 3.6%); Moderate certainty ⊕⊕⊕◯
SHADE trial;[720] Rastogi et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 16 assigned to vitamin D 60000 IU a day for 7 days and 24 assigned to standard of care	Mean age 48.7 ± 12.4, male 50%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Murai et al;[721] peer-reviewed; 2020	Patients with severe COVID-19. 117 assigned to vitamin D 200,000 IU once and 120 assigned to standard of care	Mean age 56.3 ± 14.6, male 56.3%, hypertension 52.5%, diabetes 35%, COPD %, asthma 6.3%, coronary heart disease 13.3%, chronic kidney disease 1%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Lakkireddy et al;[722] preprint; 2021	Patients with mild to moderate with low plasmatic vitamin D COVID-19 infection. 44 assigned to vitamin D 60000 IU a day for 8 to 10 days and 43 assigned to SOC	Mean age 45.5 ± 13.3, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Sabico et al;[723] peer reviewed;	Patients with moderate to critical	Mean age 49.8 ± 14.3, male 49.3%,	NR	Low for mortality and mechanical	

2021	COVID-19 infection. 36 assigned to vitamin D 5000 IU for 14 days and 33 assigned to vitamin D 1000 IU for 14 days	hypertension 55%, diabetes 51%, COPD %, asthma 4%, CHD 6%, CKD 7%, obesity 33%		ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Maghbooli et al;[724] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 53 assigned to vitamin D3 25 µg a day for 30 days and 53 assigned to SOC	Mean age 49.1 ± 14.1, male 60.4%, hypertension 31.1%, diabetes 23.6%, COPD 10.3%, CHD 12.3%, CKD 2.8%	Corticosteroids 46.2%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Beigmohammadi et al;[725] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin vitamin D 600000 UI once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000 mg a day in addition to others for 7 days, and 30 assigned to SOC	Mean age 52 ± 9, male 51.6%, hypertension 33.3%, diabetes 18.3%, asthma 13.3%, cancer 5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
REsCue trial;[726] Bishop et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 65 assigned to vitamin D calcifediol 300 mcg a day for three days followed by 60 mcg a day for 27 days and 69 assigned to SOC	Mean age 43, male 41%, hypertension 21.6%, diabetes 6%, asthma 2.2%, CKD 3%, obesity 40%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Karonova et al;[727] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 45 assigned to cholecalciferol 50,000 IU/week for 2 weeks followed by 500 UI/day for 3 months and 46 assigned to cholecalciferol 5000 IU/day for 3 months	Mean age 35 ± 2, male 15.3%, obesity 16.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-VIT-D trial;[728] Cannata-Andía et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 274 assigned to vitamin D Cholecalciferol 100.000UI once and 269 assigned to SOC	Median age 58, male 65%, hypertension 43.8%, diabetes 24.7%, COPD 4.2%, asthma 5.5%, CHD 21.2%	Corticosteroids 29.9%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
CORONAVIT trial;[729] Jolliffe et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 3030 assigned to vitamin D 800 to 3200 UI a day and 2949 assigned to SOC	Median age 60.2, male 67%, hypertension 3.7%, diabetes 4.2%, COPD 1.8%, asthma 15.3%, CHD 19.5%, obesity 20.1%	NR; Vaccinated 1.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Villasis-Keever et al;[730] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 150 assigned to vitamin D 4,000 IU cholecalciferol a day for 30 days and 152 assigned to SOC	Median age 37.5 ± 26, male 30%, hypertension 29.6%, diabetes 4.1%, obesity 25.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to	

				follow up.	
CARED-TRIAL trial;[731] Mariani et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 115 assigned to vitamin D 500 000 IU of vitamin D3 once and 103 assigned to SOC	Mean age 59.1 ± 10.6, male 52.8%, hypertension 43.1%, diabetes 26.6%, COPD 11.9%, CHD 4.6%, cancer 0.9%, obesity 39.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
COVIT-TRIAL trial;[732] Annweiler et al; peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 127 assigned to vitamin D cholecalciferol 400.000 UI once and 127 assigned to vitamin D 50.000 UI	Median age 88 , male 46%, hypertension 70%, diabetes 21%, COPD 7%, CHD 43%, CKD 17%, cerebrovascular disease 19%, cancer 7%, obesity 22%	Corticosteroids 15%, hydroxychloroquine 0.4%,azithromycin 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Karonova et al;[733] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 65 assigned to vitamin D cholecalciferol 100,000 IU and 64 assigned to SOC	Mean age 60.5, male 59.2%, hypertension 73.6%, diabetes 31.8%, COPD %, CHD 23.3%, obesity 38.8%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	
Romero-Ibarguengoitia et al;[734] preprint; 2022	Individuals exposed to SARS-CoV-2 infection. 43 assigned to vitamin D 52,000 IU a month for 6 months and 42 assigned to SOC	Mean age 44.4 ± 11.1, male 58.8%, hypertension 10%, diabetes 7%, asthma 4.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Cervero et al;[735] peer reviewed; 2022	Patients with severe COVID-19 infection. 41 assigned to vitamin D cholecalciferol 10000 IU a day for	Median age 65 ± , male 71%, hypertension 48%, diabetes 22%	Corticosteroids 87%, remdesivir 15%, tocilizumab 25%, azithromycin 44%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	14 days and 44 assigned to Vit D 2000 IU a day for 14 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abroug et al;[736] preprint; 2022	Patients with mild with persistently positive PCR test at 14 days COVID-19 infection. 57 assigned to vitamin D cholecalciferol 200,000 IU once and 60 assigned to SOC	Mean age 42.7 ± 14, male 55.6%, hypertension 6.8%, diabetes 12%, asthma 6.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
D-COVID trial;[737] De Niet et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 21 assigned to cholecalciferol 25.000 UI a day for 4 days followed by 25.000 UI a week for 6 weeks and 22 assigned to SOC	Mean age 66, male 53.5%, hypertension 55.8%, diabetes 37.2%, COPD 32.6%, CKD 18.6%	Corticosteroids 100%, remdesivir 100%; Vaccinated 14%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Brunvoll et al;[738] peer reviewed; 2022	Patients with exposed to COVID-19 infection. 17278 assigned to Vit D 400 IU a day in the form of cod liver oil for 164 days (median) and 17323 assigned to SOC	Mean age 44.9 ± 13.4, male 35.4%, comorbidities 22.2%	Vaccinated 35.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Van Helmond et al;[739] preprint; 2022	Patients with exposed COVID-19 infection. 299 assigned to cholecalciferol 5000 IU a day and 578 assigned to SOC	Mean age 49, male 21.2%, diabetes 6.6%, cancer 5.5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Vv116 (oral remdesivir) vv116 is as efective as nirmatrelvir/ritonavir in attaining symptom resolution. Its effects on other patient important outcomes are uncertain. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Cao et al;[740] peer reviewed; 2022	Patients with mild COVID-19 infection. 384 assigned to vv116 (oral remdesivir) 1200 mg once followed by 600 mg a day for 5 days and 387 assigned to Nirmatrelvir/ritonavir 600/200 mg a day for 5 days	Median age 53, male 49.8%, hypertension 35.1%, diabetes 10.1%, COPD 5.7%, CKD 1.4%, immunosuppressive therapy 0.1%, cancer 4.2%, obesity 32.9%	Vaccinated 75.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.09 (95%CI 0.95 to 1.25); RD 5.6% (95%CI -2.9% to 15.3%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

XAV-19 (swine glyco-humanized polyclonal antibodies) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**

RCT					
POLYCOR trial;[741] Gaborit et al; preprint; 2021	Patients with severe COVID-19 infection. 12 assigned to XAV-19 0.5 to 2 mg/kg on days 1 and 5 and 5 assigned to SOC	Mean age 71 ± 24, male 64.7%, hypertension 47.1%, diabetes 11.8%, COPD %, asthma 17.6%, CHD 29.4%, CKD 5.9%, cancer 11.8%, obesity 17.6%	Corticosteroids 100%, remdesivir 47.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Zafirlukast

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Ghobain et al;[742] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 20 assigned to zafirlukast 40 mg a day for 10 days and 20 assigned to SOC	Mean age 51 ± 12.5, male 50%, hypertension 30%, diabetes 50%, CHD 7.5%, CKD 2.5%, obesity 42%	Corticosteroids 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom**

					resolution or improvement: No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Zilucoplan **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ZILU-COV trial;[743] Leeuw et al; peer-reviewed; 2021	Patients with severe COVID-19 infection. 54 assigned to zilucoplan 32.4 mg a day, subcutaneously, for 14 days and 24 assigned to SOC	Median age 63, male 87%, hypertension 46%, diabetes 23%, asthma %, CHD 24%, CKD 5%	Corticosteroids 86%, remdesivir 12%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: No information

Zinc

Zinc may not improve symptom resolution. However, the certainty of the evidence was low because of imprecision. Its effects on other clinical important outcomes are uncertain. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hassan et al;[744] preprint; 2020	Patients with mild to critical COVID-19. 49 assigned to zinc 220 mg twice a day and 56 assigned to standard of care	Mean age 45.9 ± 17.5, male 58.2%, hypertension 10.4%, diabetes 11.2%, coronary heart disease 3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.91 to 1.12); RD 0.6% (95%CI -5.4% to 7.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis**
Abd-Elsalam et al;[745] peer-reviewed; 2020	Patients with mild to critical COVID-19. 96 assigned to zinc 220 mg twice a day for 15 days and 95 assigned to standard of care	Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Abdelmaksoud et al;[746] Peer reviewed; 2020	Patients with mild to critical COVID-19. 49 assigned to Zinc 220 mg twice a day and 56 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
COVIDAtoZ - Zinc trial;[712] Thomas et al; peer reviewed; 2020	Patients with mild COVID-19. 58 assigned to Zinc 50 mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Corticosteroids 8.4%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ZINC COVID trial;[747] Patel et al; Peer reviewed; 2020	Patients with severe to critical COVID-19. 15 assigned to Zinc 0.24 mg/kg a day for 7 days and 18 assigned to SOC	Mean age 61.8 ± 16.9, male 63.6%, hypertension 48.4%, diabetes 18.2%, COPD 6%, CHD 21.2%,	Corticosteroids 75.8%, remdesivir 30.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Seet et al;[303] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 634 assigned to zinc 80 mg and 500 mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Reszinate trial;[588] Kaplan et al; preprint; 2021	Patients with mild COVID-19 infection. 14 assigned to resveratrol + zinc 4000/150 mg once a day for five days and 16 assigned to SOC	Mean age 42.4, male 40%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes:	
Stambouli et al;[213] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 59 assigned to zinc 15 mg a day for 6 weeks and 56 assigned to SOC	Mean age 38.4 ± 10.7, male 61%, hypertension 4.1%, diabetes 2.3%, COPD 0.6%, asthma 1.2%	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Abdallah et al;[748] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 231 assigned to Zinc 50 mg a day for 15 days and 239 assigned to SOC	Mean age 54.1, male 53%, hypertension 23.4%, diabetes 19.4%, COPD 2.3%, asthma 2.3%, CHD %, CKD 1%	Corticosteroids 37.7%; Vaccinated 23%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

α-lipoic acid

Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zhong et al;[749] preprint; 2020	Patients with critical COVID-19 infection. 8 assigned to α-lipoic acid 1200 mg infusion once daily for 7 days and 9 assigned to standard of care	Median age 63 ± 7, male 76.5%, hypertension 47%, diabetes 23.5%, coronary heart disease 5.9%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No

				outcomes results.	information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Appendix 1. Summary of findings tables

Summary of findings Table 1. (Interactive online version)

Population: Patients with severe COVID-19 disease
Intervention: Corticosteroids
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 0.9 (CI 95% 0.8 - 1.01) Based on data from 8000 participants in 12 studies	**160** per 1000	**144** per 1000 Difference: **16 fewer per 1000** (CI 95% 32 fewer - 2 more)	**Moderate** Due to serious imprecision[1]	Steroids probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 5942 participants in 6 studies Follow up 28	**172** per 1000	**150** per 1000 Difference: **22 fewer per 1000** (CI 95% 48 fewer - 9 more)	**Moderate** Due to serious imprecision[2]	Steroids probably decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.27 (CI 95% 0.98 - 1.65) Based on data from 646 participants in 5 studies	**606** per 1000	**770** per 1000 Difference: **164 more per 1000** (CI 95% 12 fewer - 394 more)	**Moderate** Due to serious risk of bias[3]	Steroids probably increases symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.89 (CI 95% 0.68 - 1.17) Based on data from 833 participants in 6 studies	**102** per 1000	**91** per 1000 Difference: **11 fewer per 1000** (CI 95% 33 fewer - 17 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Steroids may have little or no difference on severe adverse events
Mortality (High vs standard dose) 28 days	Relative risk: 1.0 (CI 95% 0.82 - 1.21) Based on data from 4439 participants in 10 studies	**160** per 1000	**160** per 1000 Difference: **0 fewer per 1000** (CI 95% 29 fewer - 34 more)	**Moderate** Due to serious imprecision[5]	High dose steroids (i.e dexamethasone 12mg a day) probably does not decrease mortality in comparison to standard dose steroids (i.e dexamethasone 6mg a day)
Severe adverse events (High vs. standard dose) 28 days	Relative risk: 0.82 (CI 95% 0.6 - 1.11) Based on data from 1280 participants in 2 studies	**102** per 1000	**84** per 1000 Difference: **18 fewer per 1000** (CI 95% 41 fewer - 11 more)	**Low** Due to very serious imprecision[6]	High dose steroids (i.e dexamethasone 12mg a day) may not increase severe adverse events in comparison to standard dose steroids (i.e dexamethasone 6mg a day)

1. **Imprecision: serious.** 95%CI includes no mortality reduction;
2. **Imprecision: serious.** 95%CI include no IVM reduction;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;

4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;
5. **Imprecision: serious.** 95%CI includes no mortality decrease;
6. **Imprecision: very serious.** Low number of patients, Wide confidence intervals;

Summary of findings Table 2. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Remdesivir
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mechanical ventilation 28 days	Relative risk: 0.76 (CI 95% 0.56 - 1.04) Based on data from 9730 participants in 7 studies Follow up Median 28 days	**173** per 1000	**131** per 1000 Difference: **42 fewer per 1000** (CI 95% 76 fewer - 7 more)	**Moderate** Due to serious imprecision[1]	Remdesivir probably decrease mechanical ventilation requirements
Mortality 28 days	Relative risk: 0.93 (CI 95% 0.89 - 1.03) Based on data from 10855 participants in 8 studies Follow up Median 28 days	**160** per 1000	**149** per 1000 Difference: **11 fewer per 1000** (CI 95% 18 fewer - 5 more)	**Moderate** Due to serious imprecision[2]	Remdesivir probably reduces mortality
Symptom resolution or improvement 28 days	Relative risk: 1.1 (CI 95% 0.96 - 1.28) Based on data from 1981 participants in 4 studies Follow up 28 days	**606** per 1000	**667** per 1000 Difference: **61 more per 1000** (CI 95% 24 fewer - 170 more)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Remdesivir may improve symptom resolution or improvement
Severe adverse events	Relative risk: 0.77 (CI 95% 0.46 - 1.29) Based on data from 2430 participants in 4 studies	**102** per 1000	**79** per 1000 Difference: **23 fewer per 1000** (CI 95% 55 fewer - 30 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Remdesivir may have little or no difference on severe adverse events
Hospitalization (in patients with non-severe disease) 28 days	Relative risk: 0.28 (CI 95% 0.11 - 0.75) Based on data from 562 participants in 1 study Follow up Median 28 days	**48** per 1000	**13** per 1000 Difference: **35 fewer per 1000** (CI 95% 43 fewer - 12 fewer)	**Low** Due to very serious imprecision[5]	Remdesivir may decrease hospitalizations (in patients with non-severe disease)

1. **Imprecision: serious.** Wide confidence intervals;
2. **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits ;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95%ci included significant severe adverse events increase;
5. **Imprecision: very serious.**

Summary of findings Table 3. (Interactive online version)

Population: Patients with COVID-19 infection or exposed to COVID-19
Intervention: Hydroxychloroquine (HCQ)
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 15 days	Relative risk: 1.09 (CI 95% 1 - 1.19) Based on data from 10904 participants in 16 studies	**160** per 1000	**171** per 1000 Difference: **14 more per 1000** (CI 95% 0 fewer - 30 more)	**Moderate** Due to serious risk of bias[1]	HCQ probably increases mortality
Mechanical ventilation 15 days	Relative risk: 1.08 (CI 95% 0.93 - 1.25) Based on data from 8667 participants in 10 studies	**173** per 1000	**187** per 1000 Difference: **14 more per 1000** (CI 95% 12 fewer - 43 more)	**Moderate** Due to serious risk of bias[2]	Hcq probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.01 (CI 95% 0.93 - 1.1) Based on data from 6601 participants in 10 studies Follow up 28 days	**606** per 1000	**612** per 1000 Difference: **6 more per 1000** (CI 95% 42 fewer - 61 more)	**Moderate** Due to serious inconsistency[3]	Hcq probably has little or no difference on symptom resolution or improvement
COVID-19 infection (in exposed individuals)	Relative risk: 0.85 (CI 95% 0.73 – 0.98) Based on data from 11088 participants in 14 studies	**174** per 1000	**148** per 1000 Difference: **26 fewer per 1000** (CI 95% 47 fewer - 3 fewer)	**Moderate** Due to serious incosistency[4]	Hcq probably has little or no difference on covid-19 infections (in exposed individuals)
Hospitalizations (in patients with non-severe disease)	Relative risk: 0.82 (CI 95% 0.61 - 1.1) Based on data from 4255 participants in 9 studies	**48** per 1000	**39** per 1000 Difference: **9 fewer per 1000** (CI 95% 19 fewer - 5 more)	**Low** Due to very serious imprecision[5]	Hcq may have little or no difference on hospitalizations in patients with non-severe disease
Severe adverse events	Relative risk: 0.9 (CI 95% 0.66 - 1.22) Based on data from 10381 participants in 20 studies	**102** per 1000	**92** per 1000 Difference: **10 fewer per 1000** (CI 95% 35 fewer - 22 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Hcq may have little or no difference on severe adverse events

1. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
3. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious.** I2 82%; **Imprecision: no serious.** Secondary to inconsistency;
4. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies
5. **Imprecision: very serious.** 95%CI includes significant benefits and harms;

6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table 4. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Lopinavir-ritonavir (LPV)
Comparator: Standard of care

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		SOC	LPV		
Mortality 28 days	Relative risk: 1.01 (CI 95% 0.92 - 1.11) Based on data from 8059 patients in 4 studies Follow-up median 28 days	**160** per 1000	**162** per 1000	**Moderate** Due to serious imprecision[1]	LPV probably has little or no difference on mortality
		Difference: **2 more per 1000** (CI 95% 13 fewer - 18 more)			
Mechanical ventilation 28 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 7622 patients in 4 studies Follow-up median 28 days	**173** per 1000	**185** per 1000	**High**	LPV does not reduce mechanical ventilation
		Difference: **12 more per 1000** (CI 95% 3 fewer - 29 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.03 (CI 95% 0.92 - 1.15) Based on data from 5239 patients in 2 studies Follow-up 28 days	**606** per 1000	**624** per 1000	**Moderate** Due to serious risk of bias[2]	LPV probably has little or no difference on symptom resolution or improvement
		Difference: **18 more per 1000** (CI 95% 48 fewer - 91 more)			
Symptomatic infection (exposed individuals)	Relative risk: 1.4 (CI 95% 0.78 - 2.54) Based on data from 318 patients in 1 study	**174** per 1000	**244** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether LPV increases or decreases symptomatic infection in exposed individuals
		Difference: **70 more per 1000** (CI 95% 38 fewer - 268 more)			
Severe adverse events	Relative risk: 0.6 (CI 95% 0.37 - 0.98) Based on data from 199 patients in 1 study	**102** per 1000	**61** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[4]	LPV may have little or no difference on severe adverse events
		Difference: **41 fewer per 1000** (CI 95% 64 fewer - 2 fewer)			
Hospitalization	Relative risk: 1.22 (CI 95% 0.61 - 2.47)	**48** per 1000	**59** per 1000	**Very low**	We are uncertain whether LPV

	Based on data from 591 patients in 2 studies	Difference: **11 more per 1000** (CI 95% 18 fewer - 71 more)	Due to very serious imprecision[5]	increases or decreases hospitalization

1. **Imprecision: Serious.** 95%CI includes significant mortality reduction and increase;
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: No serious.** Secondary to inconsistency;
3. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: Very serious.** 95%CI includes significant benefits and harms;
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients;
5. **Imprecision: Very serious.** 95%CI includes significant benefits and harms.

Summary of findings Table 5. (Interactive online version)
Population: Patients with COVID-19 infection
Intervention: Convalescent plasma
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	CP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mechanical ventilation 28 days	Relative risk: 1.03 (CI 95% 0.94 - 1.11) Based on data from 14363 participants in 22 studies Follow up Median 28 days	**173** per 1000	**176** per 1000 Difference: **5 more per 1000** (CI 95% 10 fewer - 19 more)	**High**	Convalescent plasma has little or no difference on mechanical ventilation
Mortality 28 days	Relative risk: 0.98 (CI 95% 0.93 - 1.03) Based on data from 24156 participants in 50 studies Follow up Median 28 days	**160** per 1000	**157** per 1000 Difference: **3 fewer per 1000** (CI 95% 11 fewer - 5 more)	**High** [1]	Convalescent plasma has little or no difference on mortality
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.95 - 1.02) Based on data from 14487 participants in 13 studies Follow up 28 days	**606** per 1000	**600** per 1000 Difference: **6 fewer per 1000** (CI 95% 30 fewer - 12 more)	**High**	Cp has little or no difference on symptom resolution or improvement
Hospitalizations	Relative risk: 0.77 (CI 95% 0.57 - 1.03) Based on data from 2642 participants in 4 studies	**48** per 1000	**37** per 1000 Difference: **11 fewer per 1000** (CI 95% 21 fewer - 1 more)	**Moderate** Due to serious imprecision[2]	Coucalescent plasma probably has little or no difference on hospitalizations
Severe adverse events	Relative risk: 1.05 (CI 95% 0.9 - 1.22) Based on data from 7451 participants in 17 studies	**102** per 1000	**104** per 1000 Difference: **5 more per 1000** (CI 95% 10 fewer - 22 more)	**Low** Due to serious imprecision, Due to serious risk of bias[3]	Convalescent may have little or no difference on severe adverse events
Symptomatic infection	Relative risk: 0.92 (CI 95% 0.32 - 2.62) Based on data from 168 participants in 1 study	**174** per 1000	**160** per 1000 Difference: **14 fewer per 1000** (CI 95% 118 fewer - 282 more)	**Very low** Due to extremely serious imprecision[4]	We are uncertain whether cp increases or decreases symptomatic infection
Specific severe adverse events	Based on data from 20000 participants in 1 study	Observed risk of severe adverse events were: TRALI 0.1%, TACO 0.1%, severe allergic reactions 0.1%		**Very low** Due to very serious risk of bias[5]	We are uncertain whether Ipv increases or decreases severe adverse events

1. **Inconsistency: no serious.** Point estimates vary widely;
2. **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals;
4. **Imprecision: ~extreme_serious.** Wide confidence intervals;
5. **Risk of Bias: very serious.** Although adverse events were rare, we assume that some might have been missed and assumed as related to disease progression. RCT are needed to determine interventions safety.**Summary of findings Table 6.** (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Tocilizumab (TCZ)
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	TCZ	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 0.86 (CI 95% 0.79 - 0.93) Based on data from 8541 participants in 21 studies Follow up Median 28 days	**160** per 1000	**136** per 1000 Difference: **22 fewer per 1000** (CI 95% 34 fewer - 11 fewer)	**High**	TCZ decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.84 (CI 95% 0.79 - 0.91) Based on data from 7655 participants in 21 studies Follow up Median 28 days	**173** per 1000	**145** per 1000 Difference: **28 fewer per 1000** (CI 95% 36 fewer - 16 fewer)	**High** [1]	TCZ decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.08 (CI 95% 1.02 - 1.14) Based on data from 7077 participants in 11 studies Follow up 28 days	**606** per 1000	**648** per 1000 Difference: **48 more per 1000** (CI 95% 12 more - 85 more)	**Low** Due to serious imprecision, Due to serious risk of bias[2]	TCZ may increase symptom resolution or improvement
Severe adverse events	Relative risk: 0.95 (CI 95% 0.86 - 1.04) Based on data from 5412 participants in 17 studies	**102** per 1000	**97** per 1000 Difference: **5 fewer per 1000** (CI 95% 14 fewer - 4 more)	**Moderate** Due to serious risk of bias[3]	Tcz probably has little or no difference on severe adverse events

1. **Imprecision: no serious.** 95% included significant and trivial reduction mechanical ventilation requirement reduction ;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits ;
3. **Risk of Bias: serious. Imprecision: no serious.** 95%ci included significant severe adverse events increase.

Summary of findings Table 7. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention & comparator: Anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day); anticoagulants in full dose (i.e., enoxaparin 1 mg/kg twice a day); anticoagulants in prophylactic dose (i.e., enoxaparin 40 mg a day); no anticoagulants

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	ACO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (full or intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.99 (CI 95% 0.81 - 1.21) Based on data from 9118 participants in 17 studies	**160** per 1000	**158** per 1000 Difference: **2 fewer per 1000** (CI 95% 30 fewer - 34 more)	**Moderate** Due to serious imprecision[1]	Anticoagulantes in intermediate or full dose probably have little or no difference on mortality in comparison with prophylactic dose
Venous thromboembolic events (full dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.56 (CI 95% 0.44 - 0.72) Based on data from 5892 participants in 9 studies	**70** per 1000	**39** per 1000 Difference: **31 fewer per 1000** (CI 95% 39 fewer - 20 fewer)	**High**	Anticoagulantes in intermediate or full dose probably decreases venous thromboembolic events (full dose)
Major bleeding (full or intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 1.63 (CI 95% 1.16 - 2.33) Based on data from 8196 participants in 13 studies	**19** per 1000	**31** per 1000 Difference: **12 more per 1000** (CI 95% 3 more - 25 more)	**High**	Anticoagulantes in intermediate or full dose increase major bleeding
Hospitalization (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 0.94 (CI 95% 0.55 - 1.59) Based on data from 1549 participants in 4 studies	**48** per 1000	**45** per 1000 Difference: **3 fewer per 1000** (CI 95% 22 fewer - 28 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Anticoagulants may have little or no difference on hospitalization
Symptom resolution or improvement (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 1.08 (CI 95% 0.92 - 1.27) Based on data from 444 participants in 1 studies	**606** per 1000	**654** per 1000 Difference: **48 more per 1000** (CI 95% 48 fewer - 164 more)	**Low** Due to very serious imprecision[3]	Anticoagulants may have little or no difference on symptom resolution or improvement
Venous thromboembolic events (intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.82 (CI 95% 0.46 - 1.46) Based on data from 2317 participants in 5 studies	**70** per 1000	**57** per 1000 Difference: **13 fewer per 1000** (CI 95% 38 fewer - 32 more)	**Low** Due to very serious imprecision[4]	Anticoagulants in intermediate dose may slightly reduce venous thromboembolic events
Clinically important bleeding (prophylactic dose	Relative risk: 2.5 (CI 95% 0.49 - 12.8)	**9** per 1000	**23** per 1000	**Very low** Due to very serious imprecision[5]	It is uncertain if anticoagulantes in prophylactic dose

vs. no anticoagulants in mild ambulatory patients)	Based on data from 444 participants in 1 studies	Difference: **14 more per 1000** (CI 95% 5 fewer - 106 more) Difference: **163 more per 1000** (CI 95% 48 fewer - 768 more)		increase or decrease clinically important bleeding

1. **Imprecision: serious.** Low number of patients;
2. **Risk of Bias: serious. Imprecision: serious.** 95%CI includes harms and absence of harms;
3. **Imprecision: very serious.** 95%CI includes harms and absence of harms;
4. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
5. **Imprecision: very serious.** 95%CI includes harms and absence of harms;

Summary of findings Table 8. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Non-corticosteroids anti-inflammatory drugs (NSAID)
Comparator: Standard of care

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		SOC	NSAID		
Mortality 28 days	Odds Ratio: 0.83 (CI 95% 0.66 - 1.05) Based on data from 2465490 patients in 6 studies	**160** per 1000	**137** per 1000	**Very low** Due to very serious risk of bias[1]	We are uncertain whether NSAID increases or decreases mortality
		Difference: **23 fewer per 1000** (CI 95% 48 fewer - 7 more)			

1. **Risk of bias: Very serious.**

Summary of findings Table 9. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Interferon beta-1a (IFN-B-1a)
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	IFN	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 0.99 (CI 95% 0.75 - 1.31) Based on data from 6869 patients in 6 studies Follow up Median 28 days	**160** per 1000	**171** per 1000 Difference: **2 fewer per 1000** (CI 95% 40 fewer - 50 more)	**Moderate** Due to serious imprecision[1]	IFN probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 1.01 (CI 95% 0.87 - 1.18) Based on data from 5052 patients in 4 studies Follow up 28 days	**173** per 1000	**168** per 1000 Difference: **2 more per 1000** (CI 95% 22 fewer - 31 more)	**Moderate** Due to serious imprecision[2]	IFN probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 0.96 (CI 95% 0.92 - 0.99) Based on data from 969 patients in 1 study Follow up 28 days	**606** per 1000	**582** per 1000 Difference: **24 fewer per 1000** (CI 95% 48 fewer - 6 fewer)	**Moderate** Due to serious imprecision[3]	IFN probably has little or no difference on symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.94 (CI 95% 0.65 - 1.37) Based on data from 877 patients in 1 study Follow up 28 days	**102** per 1000	**96** per 1000 Difference: **6 fewer per 1000** (CI 95% 36 fewer - 38 more)	**Low** Due to very serious imprecision[4]	IFN may have little or no difference on severe adverse events
Symptom resolution or improvement (inhaled)[5] 30 days	Hazard Ratio: 2.19 (CI 95% 1.03 - 4.69) Based on data from 81 patients in 1 study Follow up 28 days	**606** per 1000	**870** per 1000 Difference: **264 more per 1000** (CI 95% 11 more - 381 more)	**Low** Due to very serious imprecision[6]	IFN (inhaled) may increase symptom resolution or improvement

1. **Imprecision: serious.** 95%CI includes significant mortality reduction and increase;
2. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95% included significant mechanical ventilation requirement reduction and increase;
3. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
4. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;
5. Nebulizations;
6. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits.

Summary of findings Table 10. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Bamlanivimab +/- etesevimab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Bamlanivimab +/- etesevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.68 (CI 95% 0.17 - 2.8) Based on data from 2315 patients in 3 studies	**160** per 1000	**109** per 1000 Difference: **51 fewer per 1000** (CI 95% 133 fewer - 288 more)	**Very low** Due to serious imprecision, Due to very serious imprecision[1]	We are uncertain whether bamlanivimab increases or decreases mortality
Symptom resolution or improvement[2]	Relative risk: 1.02 (CI 95% 0.99 - 1.06) Based on data from 1750 patients in 3 studies	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 6 fewer - 36 more)	**Moderate** Due to serious imprecision[3]	Bamlanivimab probably has little or no difference on symptom resolution or improvement
Symptomatic infection	Relative risk: 0.56 (CI 95% 0.39 - 0.81) Based on data from 961 patients in 1 study Follow up 28 days	**174** per 1000	**97** per 1000 Difference: **77 fewer per 1000** (CI 95% 106 fewer - 33 fewer)	**Moderate** Due to serious imprecision[4]	Bamlanivimab probably decreases symptomatic infection
Severe adverse events[5]	Hazard Ratio: 1.12 (CI 95% 0.75 - 1.66) Based on data from 3661 patients in 6 studies	**102** per 1000	**114** per 1000 Difference: **12 more per 1000** (CI 95% 24 fewer - 62 more)	**Low** Due to very serious imprecision[6]	Bamlanivimab may not increase severe adverse events
Hospitalization[7]	Hazard Ratio: 0.37 (CI 95% 0.21 - 0.65) Based on data from 1804 patients in 3 studies	**48** per 1000	**18** per 1000 Difference: **30 fewer per 1000** (CI 95% 38 fewer - 17 fewer)	**Moderate** Due to serious imprecision[8]	Bamlanivimab +/- etesevimab probably decreases hospitalization

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. Symptomatic infection in persons at risk or exposed to SARS-COV2;
3. **Imprecision: serious.** 95%CI includes benefits and absence of benefits;
4. **Imprecision: serious.** OIS not met;
5. Symptomatic infection in persons at risk or exposed to SARS-COV2;
6. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
7. Symptomatic infection in persons at risk or exposed to SARS-COV2;
8. **Imprecision: serious.** Low number of patients

Summary of findings Table 11. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Favipiravir
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Favipravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 1.08 (CI 95% 0.77 - 1.5) Based on data from 3247 participants in 12 studies Follow up Median 28 days	**160** per 1000	**173** per 1000 Difference: **13 more per 1000** (CI 95% 37 fewer - 80 more)	**Low** Due to very serious imprecision[1]	Favipiravir may increase mortality
Mechanical ventilation 28 days	Relative risk: 1.27 (CI 95% 0.91 - 1.76) Based on data from 1632 participants in 6 studies Follow up Median 28 days	**173** per 1000	**220** per 1000 Difference: **47 more per 1000** (CI 95% 16 fewer - 131 more)	**Low** Due to very serious imprecision[2]	Favipravir may increase mechanical ventilation
Symptom resolution or improvement (Low RoB studies) 28 days	Relative risk: 1.01 (CI 95% 0.97 - 1.05) Based on data from 2029 participants in 4 studies Follow up 28 days	**606** per 1000	**612** per 1000 Difference: **6 more per 1000** (CI 95% 18 fewer - 30 more)	**High**	Favipiravir has little or no difference on symptom resolution or improvement
Hospitalization (in patients with non-severe disease)	Relative risk: 1.33 (CI 95% 0.64 - 1.78) Based on data from 824 participants in 5 studies Follow up 28 days	**48** per 1000	**64** per 1000 Difference: **16 more per 1000** (CI 95% 17 fewer - 37 more)	**Low** Due to very serious imprecision[3]	Favipravir may have little or no difference on hospitalization (in patients with non-severe disease)
Severe adverse events 30 days	Relative risk: 0.92 (CI 95% 0.56 - 1.52) Based on data from 2557 participants in 9 studies	**606** per 1000	**558** per 1000 Difference: **48 fewer per 1000** (CI 95% 267 fewer - 315 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[4]	We are uncertain whether favipiravir increases or decreases severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant mortality reduction and increase;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits ;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
   Imprecision: very serious. 95%CI includes significant benefits and absence of benefits ;

Summary of findings Table 12. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Ivermectin
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (Low risk of bias studies)	Relative risk: 1 (CI 95% 0.8 - 1.24) Based on data from 6522 participants in 13 studies	**160** per 1000	**158** per 1000 Difference: **0 fewer per 1000** (CI 95% 32 fewer - 38 more)	**Moderate** Due to serious imprecision[1]	Ivermectin probably has little or no difference on mortality
Mechanical ventilation (Low risk of bias studies)	Relative risk: 0.82 (CI 95% 0.58 - 1.17) Based on data from 3288 participants in 9 studies	**173** per 1000	**142** per 1000 Difference: **31 fewer per 1000** (CI 95% 73 fewer - 29 more)	**Very low** Due to very serious imprecision[2]	We are uncertain whether ivermectin increases or decreases mechanical ventilation (low risk of bias studies)
Symptom resolution or improvement (Low risk of bias studies)	Relative risk: 1.04 (CI 95% 0.98 - 1.1) Based on data from 3238 participants in 7 studies	**606** per 1000	**630** per 1000 Difference: **24 more per 1000** (CI 95% 12 fewer - 61 more)	**Moderate** Due to serious imprecision[3]	Ivermectin probably has little or no difference on symptom resolution or improvement
Symptomatic infection (Low risk of bias studies)[4]	Relative risk: 1.01 (CI 95% 0.54 - 1.89) Based on data from 536 participants in 1 study	**174** per 1000	**176** per 1000 Difference: **2 more per 1000** (CI 95% 80 fewer - 155 more)	**Very low** Due to very serious imprecision[5]	We are uncertain whether ivermectin increases or decreases symptomatic infection
Severe adverse events	Relative risk: 1.05 (CI 95% 0.69 - 1.62) Based on data from 2831 participants in 8 studies Follow up 28 days	**102** per 1000	**107** per 1000 Difference: **5 more per 1000** (CI 95% 32 fewer - 63 more)	**Very low** Due to very serious imprecision[6]	Ivermectin may have little or no difference on severe adverse events
Hospitalization (in non-severe patients)	Relative risk: 0.9 (CI 95% 0.74 - 1.1) Based on data from 6315 participants in 11 studies Follow up 28 days	**48** per 1000	**43** per 1000 Difference: **5 fewer per 1000** (CI 95% 12 fewer - 5 more)	**Moderate** Due to serious imprecision[7]	Ivermectin probably has little or no difference on hospitalization

1. **Imprecision: serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: very serious.** Wide confidence intervals;
3. **Imprecision: serious.** Wide confidence intervals;
4. Symptomatic infection in persons at risk or exposed to SARS-COV2;
5. **Imprecision: very serious.** Low number of patients;
6. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;
7. **Imprecision: serious.** Less than 200 events.

Summary of findings Table 13. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Baricitinib
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.73 (CI 95% 0.57 - 0.92) Based on data from 11102 participants in 5 studies	**160** per 1000	**117** per 1000 Difference: **43 fewer per 1000** (CI 95% 69 fewer - 13 fewer)	**High**	Baricitinib decreases mortality
Invasive mechanical ventilation	Relative risk: 0.83 (CI 95% 0.66 - 1.04) Based on data from 9114 participants in 3 studies Follow up 30 days	**173** per 1000	**144** per 1000 Difference: **29 fewer per 1000** (CI 95% 59 fewer - 7 more)	**Moderate** Due to serious imprecision[1]	Baricitinib probably decreases invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.27 (CI 95% 1.13 - 1.42) Based on data from 2659 participants in 3 studies Follow up 30 days	**606** per 1000	**770** per 1000 Difference: **164 more per 1000** (CI 95% 79 more - 255 more)	**Moderate** Due to serious risk of bias[2]	Baricitinib probably improves symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.64 - 0.95) Based on data from 2659 participants in 3 studies Follow up 30 days	**102** per 1000	**80** per 1000 Difference: **22 fewer per 1000** (CI 95% 37 fewer - 5 fewer)	**Moderate** Due to serious risk of bias[3]	Baricitinib probably has little or no difference on severe adverse events

1. **Imprecision: serious.** Wide confidence intervals;
2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up;
3. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up.

Summary of findings Table 14. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Azithromycin
Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates SOC	 Azythromicin	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality	Relative risk: 1.01 (CI 95% 0.92 - 1.1) Based on data from 8967 participants in 6 studies	**160** per 1000	**162** per 1000 Difference: **2 more per 1000** (CI 95% 13 fewer - 16 more)	**Moderate** Due to serious imprecision[1]	Azythromicin probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 0.92 (CI 95% 0.77 - 1.1) Based on data from 8947 participants in 5 studies	**173** per 1000	**159** per 1000 Difference: **14 fewer per 1000** (CI 95% 40 fewer - 17 more)	**Moderate** Due to serious imprecision[2]	Azythromicin probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement[3]	Relative risk: 1.02 (CI 95% 0.99 - 1.04) Based on data from 9690 participants in 6 studies	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 6 fewer - 24 more)	**High**	Azythromicin has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.23 (CI 95% 0.51 - 2.96) Based on data from 439 participants in 1 study Follow up 28 days	**102** per 1000	**125** per 1000 Difference: **23 more per 1000** (CI 95% 50 fewer - 200 more)	**Very low** Due to very serious imprecision, Due to very serious risk of bias[4]	We are uncertain whether azythromicin increases or decreases severe adverse events
Hospitalizations	Relative risk: 0.98 (CI 95% 0.52 - 1.86) Based on data from 493 participants in 2 studies Follow up 21 days	**48** per 1000	**47** per 1000 Difference: **1 fewer per 1000** (CI 95% 23 fewer - 41 more)	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Azythromicin may have little or no difference on hospitalizations

1. **Imprecision: serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: serious.** 95%CI includes significant benefits and harms;
3. Symptomatic infection in persons at risk or exposed to SARS-COV2;
4. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;
5. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits.

Summary of findings Table 15. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Colchicine
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.99 (CI 95% 0.92 - 1.06) Based on data from 18353 patients in 13 studies	**160** per 1000	**158** per 1000 Difference: **2 fewer per 1000** (CI 95% 13 fewer - 10 more)	**Moderate** Due to serious imprecision[1]	Colchicine probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 0.98 (CI 95% 0.89 - 1.07) Based on data from 17053 patients in 7 studies Follow up 30 days	**173** per 1000	**170** per 1000 Difference: **3 fewer per 1000** (CI 95% 19 fewer - 12 more)	**Moderate** Due to serious imprecision[2]	Colchicine probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1 (CI 95% 0.98 - 1.02) Based on data from 11784 patients in 5 studies Follow up 30 days	**173** per 1000	**175** per 1000 Difference: **0 more per 1000** (CI 95% 3 fewer - 3 more)	**High**	Colchicine has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 0.99) Based on data from 4880 patients in 3 studies Follow up 30 days	**102** per 1000	**80** per 1000 Difference: **22 fewer per 1000** (CI 95% 40 fewer - 1 fewer)	**High**	Colchicine has little or no difference on severe adverse events
Pulmonary embolism	Relative risk: 5.55 (CI 95% 1.23 - 25.0) Based on data from 4399 patients in 1 study Follow up 30 days	**0.9** per 1000	**5.0** per 1000 Difference: **4.1 more per 1000** (CI 95% 0.21 more - 21.6 more)	**Low** Due to very serious imprecision[3]	Colchicine may have little or no difference on pulmonary embolism
Hospitalization (in patients with non-severe disease)	Relative risk: 0.81 (CI 95% 0.63 - 1.04) Based on data from 4777 patients in 2 studies Follow up 30 days	**48** per 1000	**39** per 1000 Difference: **9 fewer per 1000** (CI 95% 18 fewer - 2 more)	**Moderate** Due to serious imprecision[4]	Colchicine probably has little or no difference on hospitalization (in patients with non-severe disease)

1. **Imprecision: serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: serious.** 95%CI includes benefits and harms;
3. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits , low number of patients, wide confidence intervals;
4. **Imprecision: serious.** Low number of patients.

Summary of findings Table 16. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir		
Invasive mechanical ventilation (Low RoB studies)	Relative risk: 1.02 (CI 95% 0.59 - 1.76) Based on data from 1163 participants in 2 studies Follow up 30 days	**173** per 1000	**176** per 1000 Difference: **3 more per 1000** (CI 95% 71 fewer - 131 more)	**Low** Due to very serious imprecision[1]	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir may have little or no difference on invasive mechanical ventilation
Mortality (Low RoB studies)	Relative risk: 1.14 (CI 95% 0.83 - 1.56) Based on data from 1163 participants in 2 studies	**160** per 1000	**182** per 1000 Difference: **22 more per 1000** (CI 95% 27 fewer - 90 more)	**Low** Due to very serious imprecision[2]	Sofosbuvir alone or in combination may have little or no difference on mortality
Severe adverse events	Relative risk: 0.35 (CI 95% 0.06 - 2.18) Based on data from 628 participants in 2 studies	**102** per 1000	**36** per 1000 Difference: **66 fewer per 1000** (CI 95% 96 fewer - 120 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir increases or decreases severe adverse events
Symptom resolution or improvement (Low RoB studies)	Relative risk: 1.01 (CI 95% 0.95 - 1.08) Based on data from 1163 participants in 2 studies Follow up 7 days	**606** per 1000	**612** per 1000 Difference: **6 more per 1000** (CI 95% 30 fewer - 48 more)	**Moderate** Due to serious imprecision[4]	Sofosbuvir alone or in combination probably has little or no difference on symptom resolution or improvement
Symptomatic infection	Relative risk: 0.52 (CI 95% 0.3 - 0.89) Based on data from 548 participants in 1 study	**174** per 1000	**90** per 1000 Difference: **84 fewer per 1000** (CI 95% 122 fewer - 19 fewer)	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir increases or decreases symptomatic infection

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious. Imprecision: very serious.** Wide confidence intervals;
4. **Inconsistency: serious. Imprecision: serious.** Wide confidence intervals;
5. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious. Imprecision: very serious.** Wide confidence intervals.

Summary of findings Table 17. (Interactive online version)

Patients with COVID-19 infection
Intervention: REGEN-COV (casirivimab and imdevimab)
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** REGEN-COV (casirivimab and imdevimab)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.83 (CI 95% 0.63 - 1.09) Based on data from 16845 participants in 4 studies	**160** per 1000	**133** per 1000 Difference: **27 fewer per 1000** (CI 95% 59 fewer - 14 more)	**Low** Due to serious inconsistency, Due to serious imprecision[1]	Regen-cov (casirivimab and imdevimab) may decrease mortality
Mortality (seronegative)	Relative risk: 0.79 (CI 95% 0.71 - 0.89) Based on data from 3673 participants in 2 studies	**160** per 1000	**126** per 1000 Difference: **34 fewer per 1000** (CI 95% 46 fewer - 18 fewer)	**Moderate** Due to serious indirectness[2]	Regen-cov (casirivimab and imdevimab) probably decreases mortality in seronegative patients
Invasive mechanical ventilation	Relative risk: 0.79 (CI 95% 0.54 - 1.14) Based on data from 14575 participants in 3 studies Follow up 30 days	**173** per 1000	**137** per 1000 Difference: **36 fewer per 1000** (CI 95% 80 fewer - 24 more)	**Low** Due to very serious imprecision[3]	Regen-cov (casirivimab and imdevimab) may decrease invasive mechanical ventilation
Invasive mechanical ventilation (seronegative)	Relative risk: 0.82 (CI 95% 0.74 - 0.9) Based on data from 3603 participants in 2 studies	**173** per 1000	**142** per 1000 Difference: **31 fewer per 1000** (CI 95% 45 fewer - 17 fewer)	**Moderate** Due to serious indirectness, Due to serious imprecision[4]	Regen-cov (casirivimab and imdevimab) probably decreases invasive mechanical ventilation in seronegative patients
Symptom resolution or improvement	Relative risk: 1.06 (CI 95% 1.0 - 1.12) Based on data from 14746 participants in 3 studies	**606** per 1000	**642** per 1000 Difference: **36 more per 1000** (CI 95% 0 fewer - 73 more)	**Low** Due to serious imprecision, Due to serious inconsistency[5]	Regen-cov (casirivimab and imdevimab) may increase symptom resolution or improvement
Symptom resolution or improvement (seronegative)	Relative risk: 1.1 (CI 95% 1.06 - 1.14) Based on data from 6277 participants in 3 studies Follow up 30 days	**606** per 1000	**667** per 1000 Difference: **61 more per 1000** (CI 95% 36 more - 85 more)	**Moderate** Due to serious indirectness[6]	Regen-cov (casirivimab and imdevimab) probably increases symptom resolution or improvement in seronegative patients
Hospitalization (in patients with non-severe disease)	Relative risk: 0.28 (CI 95% 0.19 - 0.42) Based on data from 6732 participants in 4 studies Follow up 30 days	**48** per 1000	**13** per 1000 Difference: **35 fewer per 1000** (CI 95% 39 fewer - 28 fewer)	**Moderate** Due to serious imprecision[7]	Regen-cov (casirivimab and imdevimab) probably reduces hospitalization in patients with recent onset non-severe disease

Symptomatic infection (in exposed individuals)	Relative risk: 0.24 (CI 95% 0.08 - 0.76) Based on data from 2856 participants in 3 studies Follow up 30 days	**174** per 1000 **42** per 1000 Difference: **132 fewer per 1000** (CI 95% 160 fewer - 42 fewer)	**High** [8]	Regen-cov (casirivimab and imdevimab) decreases symptomatic infection in exposed individuals
Severe adverse events	Relative risk: 0.51 (CI 95% 0.38 - 0.67) Based on data from 12360 participants in 6 studies	**102** per 1000 **52** per 1000 Difference: **50 fewer per 1000** (CI 95% 63 fewer - 34 fewer)	**Moderate** Due to serious imprecision[9]	Regen-cov (casirivimab and imdevimab) probably has little or no difference on severe adverse events

1. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.; **Imprecision: serious.** Wide confidence intervals;
2. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis; **Imprecision: very serious.**
3. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: very serious.** Wide confidence intervals;
4. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis;
5. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies; **Imprecision: serious.** Wide confidence intervals;
6. **Indirectness: serious.** Subgroup analysis;
7. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: serious.** Low number of events;
8. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up;
9. **Imprecision: serious.** Wide confidence intervals.

Summary of findings Table 18. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Sotrovimab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Standard of care	Sotrovimab		
Mortality	Relative risk: 0.2 (CI 95% 0.01 - 4.16) Based on data from 1057 participants in 1 study	**160** per 1000	**32** per 1000 Difference: **128 fewer per 1000** (CI 95% 158 fewer - 506 more)	**Very low** Due to extremely serious imprecision[1]	We are uncertain whether sotrovimab increases or decreases mortality
Mechanical ventilation	Relative risk: 0.11 (CI 95% 0.01 - 2.06) Based on data from 1057 participants in 1 study	**174** per 1000	**19** per 1000 Difference: **155 fewer per 1000** (CI 95% 172 fewer - 184 more)	**Very low** Due to extremely serious imprecision[2]	We are uncertain whether sotrovimab increases or decreases mechanical ventilation
Hospitalization	Relative risk: 0.2 (CI 95% 0.08 - 0.48) Based on data from 1057 participants in 1 study	**48** per 1000	**10** per 1000 Difference: **38 fewer per 1000** (CI 95% 44 fewer - 25 fewer)	**Moderate** Due to serious imprecision[3]	Sotrovimab probably decreases hospitalization
Hospitalization (sotrovimab vs. REGEN-COV)	Relative risk: 1.07 (CI 95% 0.88 - 1.3) Based on data from 3558 participants in 1 study	**48** per 1000	**51** per 1000 Difference: **3 more per 1000** (CI 95% 6 fewer - 14 more)	**High**	Sotrovimab has little or no difference on hospitalization compared to REGEN-COV
Severe adverse events	Relative risk: 0.34 (CI 95% 0.18 - 0.68) Based on data from 1057 participants in 1 study	**102** per 1000	**35** per 1000 Difference: **67 fewer per 1000** (CI 95% 84 fewer - 33 fewer)	**Moderate** Due to serious imprecision[4]	Sotrovimab probably has little or no difference on severe adverse events

1. **Imprecision: ~extremely_serious.** Very low number of events;
2. **Imprecision: ~extremely_serious.** Very low number of events;
3. **Imprecision: serious;**
4. **Imprecision: serious.** Low number of patients.

Summary of findings Table 19. (Interactive online version)

Patients with COVID-19 infection
Intervention: Inhaled corticosteroids
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** Inhaled coticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Symptom resolution or improvement[1]	Relative risk: 1.09 (CI 95% 0.99 - 1.2) Based on data from 3919 participants in 8 studies	**606** per 1000	**661** per 1000 Difference: **55 more per 1000** (CI 95% 6 fewer - 121 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Inhaled coticosteroids may increase symptom resolution or improvement
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.44 - 1.98) Based on data from 1560 participants in 1 study	**173** per 1000	**163** per 1000 Difference: **10 fewer per 1000** (CI 95% 97 fewer - 170 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether inhaled corticosteroids increases or decreases invasive mechanical ventilation
Mortality	Relative risk: 0.82 (CI 95% 0.44 - 1.53) Based on data from 2345 participants in 5 studies	**160** per 1000	**131** per 1000 Difference: **29 fewer per 1000** (CI 95% 90 fewer - 85 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether inhaled corticosteroids increases or decreases mortality
Severe adverse events	Relative risk: 0.5 (CI 95% 0.23 - 1.12) Based on data from 2014 participants in 4 studies	**102** per 1000	**51** per 1000 Difference: **51 fewer per 1000** (CI 95% 79 fewer - 12 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether inhaled coticosteroids increases or decreases severe adverse events
Hospitalizations	Relative risk: 0.9 (CI 95% 0.7 - 1.15) Based on data from 3953 participants in 5 studies	**48** per 1000	**43** per 1000 Difference: **5 fewer per 1000** (CI 95% 14 fewer - 7 more)	**Moderate** Due to serious risk of bias[6]	Inhaled coticosteroids probably has little or no difference on hospitalizations

1. Symptomatic infection in persons at risk or exposed to SARS-COV2
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and harms;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and harms;
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits , Wide confidence intervals;
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.

Summary of findings Table 20. (Interactive online version)

Patients with COVID-19 infection
Intervention: Fluvoxamine
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Fluvoxamine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Symptom resolution	Relative risk: 0.99 (CI 95% 0.96 - 1.02) Based on data from 1135 participants in 1 studies	**606** per 1000	**600** per 1000 Difference: **6 fewer per 1000** (CI 95% 24 fewer - 12 more)	**High**	Fluvoxamine has little or no difference on symptom resolution
Mortality	Relative risk: 0.69 (CI 95% 0.36 - 1.27) Based on data from 1497 participants in 1 studies	**160** per 1000	**110** per 1000 Difference: **50 fewer per 1000** (CI 95% 102 fewer - 43 more)	**Very low** Due to very serious imprecision[1]	There were too few who experienced the mortality, to determine whether fluvoxamine made a difference
Mechanical ventilation	Relative risk: 0.77 (CI 95% 0.45 - 1.3) Based on data from 1497 participants in 1 studies	**160** per 1000	**123** per 1000 Difference: **37 fewer per 1000** (CI 95% 88 fewer - 48 more)	**Very low** Due to very serious imprecision[2]	There were too few who experienced the mortality, to determine whether fluvoxamine made a difference
Hospitalizations	Relative risk: 0.78 (CI 95% 0.6 - 1.02) Based on data from 2302 participants in 3 studies	**48** per 1000	**37** per 1000 Difference: **11 fewer per 1000** (CI 95% 19 fewer - 1 more)	**Moderate** Due to serious imprecision[3]	Fluvoxamine probably has little or no difference on hospitalizations
Severe adverse events[4]	Relative risk: 0.81 (CI 95% 0.54 - 1.22) Based on data from 1649 participants in 2 studies	**102** per 1000	**83** per 1000 Difference: **19 fewer per 1000** (CI 95% 47 fewer - 22 more)	**Low** Due to very serious imprecision[5]	Fluvoxamine may not increase severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
4. Symptomatic infection in persons at risk or exposed to SARS-COV2
5. **Imprecision: very serious.** Wide confidence intervals;

Summary of findings Table 21. (Interactive online version)

Patients with COVID-19 infection
Intervention: Molnupiravir
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Standard of care	Molnupiravir		
Mechanical ventilation	Relative risk: 0.36 (CI 95% 0.11 - 1.12) Based on data from 1610 participants in 1 studies	**173** per 1000	**62** per 1000 Difference: **111 fewer per 1000** (CI 95% 154 fewer - 21 more)	**Very low** Due to very serious imprecision[1]	We are uncertain whether molnupiravir increases or decreases mortality
Mortality	Relative risk: 0.38 (CI 95% 0.11 - 1.35) Based on data from 27202 participants in 5 studies	**160** per 1000	**61** per 1000 Difference: **99 fewer per 1000** (CI 95% 142 fewer - 56 more)	**Very low** Due to very serious imprecision[2]	We are uncertain whether molnupiravir increases or decreases mortality
Symptom resolution	Relative risk: 1.88 (CI 95% 1.2 - 2.95) Based on data from 26513 participants in 3 studies Follow up 5	**606** per 1000	**1000** per 1000 Difference: **394 more per 1000** (CI 95% 121 more - 394 more)	**Moderate** Due to serious risk of bias[3]	Molnupiravir probably increases symptom resolution
Hospitalization	Relative risk: 0.66 (CI 95% 0.43 - 1.01) Based on data from 29050 participants in 7 studies	**48** per 1000	**32** per 1000 Difference: **16 fewer per 1000** (CI 95% 27 fewer - 0 fewer)	**Moderate** Due to serious imprecision[4]	Molnupiravir probably does not have an important effect on hospitalization
Severe adverse events	Relative risk: 0.75 (CI 95% 0.48 - 1.19) Based on data from 2219 participants in 4 studies Follow up 29	**102** per 1000	**77** per 1000 Difference: **25 fewer per 1000** (CI 95% 53 fewer - 19 more)	**Low** Due to very serious imprecision[5]	Molnupiravir may have little or no difference on severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms, Low number of patients;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms, Low number of patients;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
4. **Imprecision: serious.** Wide confidence intervals;
5. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;

Summary of findings Table 22. (Interactive online version)

Patients with COVID-19 infection
Intervention: Nirmatrelvir-ritonavir
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Standard of care	Nirmatrelvir-ritonavir		
Mortality	Relative risk: 0.04 (CI 95% 0.0 - 0.68) Based on data from 2085 participants in 1 study	**160** per 1000	**6** per 1000 Difference: **154 fewer per 1000** (CI 95% 160 fewer - 51 fewer)	**Very low** Due to very serious imprecision[1]	We are uncertain whether nirmatrelvir-ritonavir increases or decreases mortality
Hospitalization	Relative risk: 0.12 (CI 95% 0.06 - 0.25) Based on data from 2085 participants in 1 study	**48** per 1000	**6** per 1000 Difference: **42 fewer per 1000** (CI 95% 45 fewer - 36 fewer)	**Moderate** Due to serious imprecision[2]	Nirmatrelvir-ritonavir probably decreases hospitalizations
Severe adverse events	Relative risk: 0.49 (CI 95% 0.3 - 0.8) Based on data from 2224 participants in 1 study Follow up 29	**102** per 1000	**50** per 1000 Difference: **52 fewer per 1000** (CI 95% 71 fewer - 20 fewer)	**Moderate** Due to serious imprecision[3]	Nirmatrelvir-ritonavir probably has little or no difference on severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms, low number of patients;
2. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
3. **Imprecision: serious.** Low number of events.

Summary of findings Table 23. (Interactive online version)

Patients with COVID-19 infection
Intervention: Ruxolitinib
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care	Molnupiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.72 (CI 95% 0.59 - 0.89) Based on data from 686 participants in 3 studies	**160** per 1000	**21** per 1000 Difference: **45 fewer per 1000** (CI 95% 66 fewer - 18 fewer)	**Low** Due to serious imprecision and incosistency[1]	Ruxolitinib may reduce mortality
Mechanical ventilation	Relative risk: 0.99 (CI 95% 0.49 - 1.99) Based on data from 474 patients in 2 study	**173** per 1000	**171** per 1000 Difference: **2 fewer per 1000** (CI 95% 32 fewer - 171 more)	**Very low** Due to very serious imprecision[2]	It is uncertain if ruxolitinib increases or decreases mechanical ventilation
Severe adverse events	Relative risk: 1.12 (CI 95% 0.69 - 1.82) Based on data from 679 participants in 3 studies	**102** per 1000	**114** per 1000 Difference: **12 more per 1000** (CI 95% 79 fewer - 100 more)	**Very low** Due to very serious imprecision[2]	It is uncertain if ruxolitinib increases or decreases mechanical ventilation
Symptom resolution	Relative risk: 1.05 (CI 95% 0.89 – 1.24) Based on data from 685 participants in 3 studies	**606** per 1000	**606** per 1000 Difference: **30 more per 1000** (CI 95% 66 fewer - 145 more)	**Low** Due to very serious imprecision[2]	Ruxolitinb may no increase symptom resolution

1. **Imprecision: serious.** Low number of patients; **Inconsistency: serious.** Significant not explained heterogeneity;
2. **Imprecision: very serious.** 95%CI including important benefits and harms.

Summary of findings Table 24. (Interactive online version)

Patients with COVID-19 infection
Intervention: CD24Fc
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	CD24Fc	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.9 (CI 95% 0.49 - 1.69) Based on data from 234 participants in 1 study Follow up 29 days	**160** per 1000	**144** per 1000 Difference: **16 fewer per 1000** (CI 95% 82 fewer - 110 more)	**Very low** Due to extremely serious imprecision[1]	We are uncertain whether CD24Fc increases or decreases mortality
Invasive mechanical ventilation	Relative risk: 0.57 (CI 95% 0.34 - 0.96) Based on data from 234 participants in 1 study Follow up 29 days	**173** per 1000	**99** per 1000 Difference: **74 fewer per 1000** (CI 95% 114 fewer - 7 fewer)	**Low** Due to serious imprecision, Due to very serious imprecision[2]	CD24Fc may decrease invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.18 (CI 95% 1.0 - 1.39) Based on data from 234 participants in 1 study Follow up 29 days	**606** per 1000	**715** per 1000 Difference: **109 more per 1000** (CI 95% 0 fewer - 236 more)	**Low** Due to very serious imprecision[3]	CD24Fc may increase symptom resolution or improvement
Severe adverse events	Relative risk: 0.98 (CI 95% 0.61 - 1.57) Based on data from 234 participants in 1 study Follow up 29 days	**102** per 1000	**100** per 1000 Difference: **2 fewer per 1000** (CI 95% 40 fewer - 58 more)	**Very low** Due to extremely serious imprecision[4]	We are uncertain whether CD24Fc increases or decreases severe adverse events

1. **Imprecision: ~extreme_serious.** Low number of patients, Wide confidence intervals;
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients;
3. **Imprecision: very serious;**
4. **Imprecision: ~extreme_serious.** Wide confidence intervals, Low number of patients.

Summary of findings Table 25. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Vitamin D
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Vitamin D	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Symptom resolution or improvement	Relative risk: 1.78 (CI 95% 1.1 - 2.94) Based on data from 43 participants in 1 studies	**606** per 1000	**1079** per 1000 Difference: **473 more per 1000** (CI 95% 61 more - 1176 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[1]	We are uncertain whether vitamin d increases or decreases invasive mechanical ventilation
Mortality	Relative risk: 1.24 (CI 95% 0.8 - 1.91) Based on data from 1234 participants in 6 studies	**160** per 1000	**198** per 1000 Difference: **38 more per 1000** (CI 95% 32 fewer - 146 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[2]	We are uncertain whether vitamin D increases or decreases mortality
Invasive mechanical ventilation	Relative risk: 0.55 (CI 95% 0.31 - 1.0) Based on data from 561 participants in 3 studies	**173** per 1000	**95** per 1000 Difference: **78 fewer per 1000** (CI 95% 119 fewer - 0 fewer)	**Very low** Due to very serious imprecision, Due to serious risk of bias[3]	We are uncertain whether vitamin d increases or decreases invasive mechanical ventilation
Symptomatic infection (Excluding high RoB studies)	Relative risk: 1.06 (CI 95% 0.91 - 1.24) Based on data from 40580 participants in 2 studies	**174** per 1000	**184** per 1000 Difference: **10 more per 1000** (CI 95% 16 fewer - 42 more)	**High**	Vitamin D has little or no difference on symptomatic infection (excluding high rob studies)
Hospitalization	Relative risk: 1.2 (CI 95% 0.83 - 1.74) Based on data from 40882 participants in 3 studies	**48** per 1000	**58** per 1000 Difference: **10 more per 1000** (CI 95% 8 fewer - 36 more)	**Moderate** Due to serious imprecision[4]	Vitamin D probably does not reduce hospitalizations
Severe adverse events	Relative risk: 1.03 (CI 95% 0.84 - 1.89) Based on data from 6197 participants in 2 studies Follow up 29 days	**102** per 1000	**105** per 1000 Difference: **3 more per 1000** (CI 95% 16 fewer - 91 more)	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Vitamin D may not increase severe adverse events

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Wide confidence intervals, Low number of patients;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Low number of patients, Wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Wide confidence intervals, Low number of patients;
4. **Imprecision: serious.** Low number of patients;
5. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals, Low number of patients;

Summary of findings Table 26. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Tixagevimab–Cilgavimab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** Tixagevimab–Cilgavimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Symptom resolution or improvement	Relative risk: 1.03 (CI 95% 0.99 - 1.08) Based on data from 1417 participants in 1 study	**606** per 1000	**624** per 1000 Difference: **18 more per 1000** (CI 95% 6 fewer - 48 more)	**Moderate** Due to serious imprecision[1]	Tixagevimab– cilgavimab probably has little or no difference on symptom resolution or improvement
Mortality	Relative risk: 0.72 (CI 95% 0.54 - 0.96) Based on data from 7492 participants in 3 studies	**160** per 1000	**115** per 1000 Difference: **45 fewer per 1000** (CI 95% 74 fewer - 6 fewer)	**Moderate** Due to serious imprecision[2]	Tixagevimab– cilgavimab probably decreases mortality
Symptomatic infection	Relative risk: 0.18 (CI 95% 0.09 - 0.35) Based on data from 5172 participants in 1 study Follow up 29 days	**174** per 1000	**31** per 1000 Difference: **143 fewer per 1000** (CI 95% 158 fewer - 113 fewer)	**Moderate** Due to serious risk of bias[3]	Tixagevimab– cilgavimab probably decreases symptomatic infection
Severe adverse events	Relative risk: 0.95 (CI 95% 0.69 - 1.31) Based on data from 7492 participants in 3 studies	**102** per 1000	**97** per 1000 Difference: **5 fewer per 1000** (CI 95% 32 fewer - 32 more)	**Low** Due to very serious imprecision[4]	Tixagevimab– cilgavimab may have little or no difference on severe adverse events
Hospitalization	Relative risk: 0.42 (CI 95% 0.24 - 0.74) Based on data from 903 participants in 1 study	**102** per 1000	**43** per 1000 Difference: **59 fewer per 1000** (CI 95% 78 fewer - 27 fewer)	**Moderate** Due to serious imprecision[5]	Tixagevimab– cilgavimab probably decreases hospitalization

1. **Imprecision: serious.** Low number of patients;
2. **Imprecision: serious.** Low number of patients;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
4. **Risk of Bias: serious. Imprecision: very serious.** Wide confidence intervals;
5. **Imprecision: serious.** Low number of patients.

Summary of findings Table 27. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Vilobelimab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Vilobelomab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.76 (CI 95% 0.6 - 0.98) Based on data from 398 participants in 2 studies	**160** per 1000	**122** per 1000 Difference: **38 fewer per 1000** (CI 95% 64 fewer - 3 fewer)	**Moderate** Due to serious imprecision[1]	Vilobelimab probably decreases mortality
Severe adverse events	Relative risk: 0.94 (CI 95% 0.8 - 1.11) Based on data from 298 participants in 2 studies	**102** per 1000	**96** per 1000 **Difference: 6 fewer per 1000** (CI 95% 20 fewer - 11 more)	**Moderate** Due to serious imprecision[2]	Vilobemilab probably makes little or no difference on severe adverse events

1. **Imprecision: serious.** Low number of patients;
2. **Imprecision: serious.** Wide confidence intervals;

Summary of findings Table 28. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Vitamin C
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Vitamin C	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.84 (CI 95% 0.72 - 0.98) Based on data from 566 participants in 6 studies	**160** per 1000	**134** per 1000 Difference: **26 fewer per 1000** (CI 95% 45 fewer - 3 fewer)	**Low** Due to serious imprecision, Due to serious risk of bias[1]	Vitamin C may decrease mortality
Symptom resolution or improvement	Relative risk: 1.16 (CI 95% 1.01 - 1.33) Based on data from 455 participants in 4 studies	**173** per 1000	**201** per 1000 Difference: **28 more per 1000** (CI 95% 2 more - 57 more)	**Low** Due to serious imprecision, Due to serious risk of bias[2]	Vitamin C may increase symptom resolution or improvement
Mechanical ventilation	Relative risk: 0.93 (CI 95% 0.59 - 1.45) Based on data from 264 participants in 3 studies	**606** per 1000	**564** per 1000 Difference: **42 fewer per 1000** (CI 95% 248 fewer - 273 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether vitamin c improves or worsen mechanical ventilation
Severe adverse events	Relative risk: 0.94 (CI 95% 0.8 - 1.11) Based on data from 298 participants in 2 studies	**102** per 1000	**96** per 1000 Difference: **6 fewer per 1000** (CI 95% 20 fewer - 11 more)	**Moderate** Due to serious imprecision[4]	Vitamin c probably makes little or no difference on severe adverse events

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: serious.** Low number of patients;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: serious.** Low number of patients;
3. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Low number of patients;
4. **Imprecision: serious.** Wide confidence intervals;

Summary of findings Table 29. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Sarilumab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mechanical ventilation	Relative risk: 0.98 (CI 95% 0.68 - 1.42) Based on data from 1938 participants in 8 studies	**173** per 1000	**170** per 1000 Difference: **3 fewer per 1000** (CI 95% 55 fewer - 73 more)	**Low** Due to very serious imprecision[1]	Sarilumab may have little or no difference on mechanical ventilation
Mortality	Relative risk: 0.99 (CI 95% 0.89 - 1.15) Based on data from 4674 participants in 11 studies	**160** per 1000	**158** per 1000 Difference: **2 fewer per 1000** (CI 95% 18 fewer - 24 more)	**Low** Due to very serious imprecision[2]	Sarilumab may have little or no difference on mortality
Symptom resolution or improvement	Relative risk: 1.01 (CI 95% 0.97 - 1.06) Based on data from 3036 participants in 8 studies	**606** per 1000	**612** per 1000 Difference: **6 more per 1000** (CI 95% 18 fewer - 36 more)	**Moderate** Due to serious imprecision,[3]	Sarilumab may have little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.01 (CI 95% 0.9 - 1.13) Based on data from 3381 participants in 8 studies	**102** per 1000	**103** per 1000 Difference: **1 more per 1000** (CI 95% 10 fewer - 13 more)	**Moderate** Due to serious imprecision[4]	Sarilumab may have little or no difference on severe adverse events

1. **Imprecision: very serious.** Wide confidence intervals;
2. **Imprecision: very serious.** Low number of patients;
3. **Imprecision: serious.** Wide confidence intervals;
4. **Imprecision: serious.** Wide confidence intervals;

Summary of findings Table 30. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: vv116 (oral remdesivir)
Comparator: Nirmatrelvir-ritonavir

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Nirmatrelvir-ritonavir	vv116		
Symptom resolution or improvement	Relative risk: 1.09 (CI 95% 0.95 - 1.25) Based on data from 771 participants in 1 studies	**606** per 1000	**661** per 1000 Difference: **55 more per 1000** (CI 95% 30 fewer - 152 more)	**High**	vv116 has little or no difference on symptom resolution or improvement compared to nirmatrelvir/ritonavir
Severe adverse events	Relative risk: 0.67 (CI 95% 0.24 - 1.87) Based on data from 771 participants in 1 studies	**102** per 1000	**68** per 1000 Difference: **34 fewer per 1000** (CI 95% 78 fewer - 89 more)	**Very low** Due to very serious serious imprecision[1]	We are uncertain whether sarilumab increases or decreases severe adverse events

1. **Imprecision: very serious.** Wide confidence intervals, Low number of patients

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