

ONGOING LIVING UPDATE OF **COVID-19** THERAPEUTIC OPTIONS

Summary of Evidence • Rapid Review, 31 May 2023

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Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence, Rapid Review. 31 May 2023

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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.

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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 270 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=829) ([interactive online version](#))

Intervention	Overall number of studies including the intervention, n=829	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		67	17	10	10	16	21
Convalescent plasma	NEW	60	51	23	14	1	17
Ivermectin		50	14(*)	9(*)	8(*)	1(*)	10
Favipiravir	NEW	31	8(*)	7	4(*)		9
Tocilizumab		29	21	21	12		17
Anticoagulants	NEW	28	20		1		13(*)
Corticosteroids		27	19(@)	7	6		6
Vitamin D	NEW	24	8	3		2(@@)	2
Lopinavir-Ritonavir		21	4	4	2	1	3
Colchicine		17	15	8	5		5
Sofosbuvir +/- Dacatasvir or others		17	4(*)	2(*)	2(*)		3
ACEIs or ARBs	NEW	16	11(*)	11	3		2
Mouthwash		15	1	1	2		
Mesenchymal stem cells	NEW	13	11	2	3		4
REGEN-COV (casirivimab and imdevimab)		12	2(##)	2(##)	3(##)	3	6
Azithromycin		11	6	5	6		1
Molnupiravir		11	5		4		5
Sanlunab		11	11	8	8		8
Vitamin C		11	8	3	4		1
Corticosteroids (inhaled)		10	5	2	8		4
Remdesivir		10	8	7	4		4
Bamlanivimab +/- etesevimab		9	3		3	1	6
Melatonin		9	4	1	3	1	
Zinc		9	3	1	2	2	1
Anakinra		7	7	3	6		6
Baricitinib		7	5	3	3		3
Interferon beta-1a		7	6	4	2		2
Nitazoxanide		7	2	1	1		3
Umifenovir		7	1	2			1
Aspirin		6	5	4	1		3
Bromhexine Hydrochloride		6	3	1		2	1
Fluvoxamine		6	1	1	1		2
IVIg		6	15	11			2
Peg-IFN lambda		6	1	2			4
Camostat mesilate		5	2	1	3		2
Hyperimmune anti-COVID-19 IVIG		5	4		1		3
Probiotics		5	2	1	1	1	
Statins		5	5	2	1		
Tenofovir + emtricitabine		5	2	2	1	1	3
Doxycycline		4	2	1	2	1	
Hyperbaric oxygen		4	4	3	1		2
Nasal hypertonic saline		4			1		
Nitric oxide		4	2	2	1		
Proxalutamide		4	3	3	2		
Quercetin		4	3		2		1
Ruxolitinib	NEW	4	4	2	4		3
Tixagevimab-Cilgavimab	NEW	4	3		1	1	4
Bicarbonate (inhaled or nasal)		3	2				
Cofactors		3	1		1		1
Famotidine		3	2	2	1		
Icatibant		3	3	1	1		1
Interferon beta-1b		3	2	3	1		
Lactoferrin		3	1	1	1	1	
Leflunomide		3	1	1			1
Low-dose radiation therapy		3	2	1			
Metformin		3	2				1
N-acetylcysteine		3	2	2			1
Omega-3 fatty acids		3	2				
Sotrovimab		3	1	1	1		1
Atazanavir +/- ritonavir		2	2	1	1		1
Beta glucans		2					1
Canakinumab		2	2	1	1		1
Colchicine + statin		2	2	2			1
Domase alfa (inh)		2	1		1		1
Dutasteride		2			1		
Electrolyzed saline		2	2		1		1
Ethanol (inhaled)		2	1		1		1
Interferon beta-1a (inhaled)		2	2	2			2

Intervention	Overall number of studies including the intervention, n=829	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)
Iota-Carrageenan	2	1				2	1
Levamisole	2	1		1			2
Linagliptin	2	2	2				
N-acetylcysteine (inhaled)	2	2					
Nano-curcumin	NEW	2				1	
Nicosamide	2	1	1			1	1
Nigella sativa +/- Honey	2	1		1			1
Nirmatrelvir-ritonavir	2	2	1			2	1
Opaganib	2	2	2	2		2	
P2Y12	2	2	1	1		2	
Peg-IFN alfa	2	2		2			
Pentoxifylline	2	2	2	1			
Povidone iodine	NEW	2	1			1	1
Regdanvimab	2			2		2	1
Resveratrol	2	4	4			4	4
Spirolactone	2	1	1	1			
Thalidomide	2	1	1			1	
Tissue-plasminogen activator (tPA)	2	2				1	
Tofacitinib	2	1		1		1	
TXA-127	2	2	2			1	
Vilobelimab	2	2				2	
99mTc-MDP	1						
Acebilustat	1	1		1		1	
Adalimumab	1	1	1				
Adintrevimab	NEW	1				1	1
Alpha-1 antitrypsin	1	1		1		1	
Amantadine	1	1				1	
Amiodarone	1	1	1			1	
Ammonium chloride	1	1	1				
AMP5A (inhaled)	1	1				1	
Amubarvimab + romlusevimab	1	1				1	1
APMV2020 (aspirin, promethazine, micronutrients)	1	1				1	1
Apremilast	1	1					
Aprepitant	1						
Aprotinin	1	1					
Arbidol	1	1					
ArtemiC	1	1		1		1	
Artemisinin	1			1		1	
Aspirin + Dipyridamole	1	1		1			
Atovaquone	1	1				1	
Auxora	1	1		1		1	
Avdoralimab	1	1				1	
Aviptadil	1	1		1		1	
Ayush-64	1			1		1	1
AZD1656	1	1		1		1	
Azelastine (inhaled)	1					1	
Azvadine	1						
Bactenophage (inh)	NEW	1					
Baloxavir	1			1			
BCG	1	1					
Bebtelovimab	1	1				1	1
Bioven	1	1				1	
Boswellia extract	1			1			
Calcitriol	1	1				1	
Cannabidiol	1	1	1	1		1	1
CD24Fc	1	1	1	1		1	
Celecoxib/Famotidine	1	1					
Cenicriviroc	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	
Corticosteroids (nasal)	1						
Crizanlizumab	1	1	1	1		1	
Curcumin + Piperine	1			1		1	

Intervention	Overall number of studies including the intervention, n=829	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)
Curcumin + Quercetin +/- Vitamin D		1			1		
Danunavir-Cobicistat		1					
Dapagliflozin		1	1	1		1	
Degalactosylated bovine glycoprotein	NEW	1	1	1			1
Degarelix		1		1			1
DFV890		1	1	1	1		1
Dimethyl sulfoxide (DSMO)		1				1	
Doubase C		1					
Dupilumab		1	1				
Edaravone		1	1	1			
Empaglifozin		1	1	1		1	
Endothelial dysfunction protocol		1	1	1			1
Enisamium		1			1		
Ensitrelvir		1	1				1
Ensovibep		1		1			1
Enzalutamide		1	1	1			1
Febuxostat		1					1
Fenofibrate		1	1	1		1	1
Finasteride		1					
Fluoxetine		1		1			
Fluvoxamine + corticosteroids (mh)		1	1	1		1	1
Fostamatinib		1	1		1		1
Gabapentin +/- Montelukast		1			1		1
Galectin inhibitor	NEW	1			1		1
Garadacimab		1	1	1			1
GB0139 (inhaled)		1					1
Gimsilumab (Anti-GM-CSF Monoclonal Antibody)		1	1	1			1
Helium (inhaled)		1					
Hemadsorption		1			1		
Hesperidin		1	1	1	1		1
Hypertonic saline (inhaled)		1	1				
hzVSF-v13		1			1		1
Ibrutinib		1	1	1			1
IC14		1					
Icosapent ethyl		1			1		
IFN-alpha2b + IFN-gamma		1					
Imatinib		1	1	1			1
Indomethacin		1	1	1			1
Infliximab		1			1		1
INM005 (equine antibodies)		1	1	1	1		1
Interferon gamma		1					
Interferon kappa + TFF2		1	1				1
Interferon-2		1			1		1
Isothymol		1	1				
Itolizumab		1	1	1			1
Ivermectin (inhaled)		1			1		
Irekizumab		1			1		1
KB109		1	1		1		1
L-arginine		1					1
Lactococcus Lactis (intranasal)		1			1		1
Lenzilumab		1	1	1			1
Levilumab		1	1	1	1		1
Lincosmycin		1					
Lithium		1					1
Mavrilimumab		1	1	1	1		1
Melenamic acid		1	1				1
Meplazumab		1	1	1			1
Metsoprinol		1					
Methylene blue		1	1				
Metoprolol		1					
Metronidazole		1			1		
Montelukast		1	1				
Mupadolimab		1					1
Mycobacterium w		1	1				
Nafamostat mesylate		1	1				1
Namilumab		1	1		1		1
Neem (Azadirachta Indica A. Juss)		1				1	
Nefinavir	NEW	1			1		1

Intervention	Overall number of studies including the intervention, n=829	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)
Nicotine patches	1	1					1
Norelgestromin and Ethinylestradiol	1						
Novaleron	1						
NSAIDS	1	1		1			1
Nutritional support	1	1	1				
OP-101	1	1	1				1
Otilimab	1	1					1
Pacritinib	1	1	1	1			1
Palmitoylethanolamide	1						
Pembrolizumab	1	1	1	1			1
Pirfenidone	1	1	1	1			1
Plasmapheresis	1	1					
Plitidepsin	1	1	1				1
PNB001 (CCK-A antagonist)	1	1		1			
Polymerized type I collagen (PTIC)	1						1
Potassium Canrenoate	1	1					1
Progesterone	1	1	1				1
Prolectin-M	1	1	1				1
Propolis	1	1	1	1			
Prostacyclin	1	1					1
Prostacyclin (inhaled)	1	1					
Pyridostigmine	1	1	1	1			1
Raloxifene	1	1					1
Ramipril	1	1				1	
Ravulizumab	1	1					1
RD-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
rh-pGSN	1	1	1				1
RP72.14 (DHODH inhibitor)	1						1
SA58 (nasal)	1	1					1
Sabizabulin	1	1					1
Secukinumab	1	1	1				1
Senicapoc	1	1					
Sentinol	1						1
Short-wave diathermy	1	1		1			1
Sildenafil	1	1	1				1
Silver nanoparticles	1	1					1
Silymarin	1			1			
Siltuximab	1	1	1				
Sitagliptin	1	1	1				
Spinulin	1	1					
Stem-cell nebulization	1	1		1			1
Sulodexide	1	1	1				1
Tafenoquine	1			1			1
TD-0903 (inhaled JAK-inhibitor)	1	1					1
Thymoquinone	1						1
Tranilast	1	1		1			
Transcranial direct current stimulation (tDCS)	1						1
Tregs (regulatory T cells)	1						1
Triazavirin	1	1		1			1
TRV-027	1	1	1				1
Ultraviolet light phototherapy	1	1					1
Verapamil	1	1	1				1
Vidofudimus calcium	1	1	1	1			1
Vitamin B	1						
w116 (oral remdesivir)	1			1 (**)			1
XAV-19 (swine polyclonal antibodies)	1	1					1
Zafirlukast	1	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; (**) 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.



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

Intervention	Overall number of studies including the intervention	Mortality (n of studies)	Mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)
NSAID	7	7				



Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=270), as at 31 May 2023

	Intervention	Summary of findings
1	99mTc-MDP	Uncertainty in potential benefits and harms. Further research is needed.
2	Acebilustat	Uncertainty in potential benefits and harms. Further research is needed.
3	Adalimumab	Uncertainty in potential benefits and harms. Further research is needed.
4	Adintrevimab	Adintrevimab may reduce hospitalizations and may not increase severe adverse events. However, certainty of the evidence was low. Further research is needed.
5	ACEIs or ARBs	Continuing or initiating ACEIs or ARBs in patients with COVID-19 increases mortality.
6	Alpha-1 antitrypsin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
7	Amantadine	Uncertainty in potential benefits and harms. Further research is needed.
8	Amiodarone	Uncertainty in potential benefits and harms. Further research is needed.
9	Ammonium chloride	Uncertainty in potential benefits and harms. Further research is needed.
10	AMP5A (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
11	Amubarvimab/romlusevimab	Amubarvimab + romlusevimab probably reduces hospitalizations and p[probably does not increase severe adverse events.
12	Anakinra	Anakinra may increase severe adverse events. However, the certainty of the evidence was low because of risk of bias and imprecision. Its effects on other patient important outcomes are uncertain Further research is needed.
13	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 intermediate or 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 and probably does not reduce hospitalizations.
14	APMV2020 (aspirin, promethazine, micronutrients)	Uncertainty in potential benefits and harms. Further research is needed.
15	Apremilast	Uncertainty in potential benefits and harms. Further research is needed.
16	Aprepitant	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
17	Aprotinin	Uncertainty in potential benefits and harms. Further research is needed.
18	Arbidol	Uncertainty in potential benefits and harms. Further research is needed.
19	ArtemiC (artemisinin, curcumin, frankincense, and vitamin C):	Uncertainty in potential benefits and harms. Further research is needed.
20	Artemisinin	Uncertainty in potential benefits and harms. Further research is needed.
21	Aspirin	Aspirin probably does not reduce mortality, or mechanical ventilation and probably does not increase symptom resolution or improvement. In mild patients it probably has no important effects on hospitalizations. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%).
22	Aspirin + Dipyridamole	Uncertainty in potential benefits and harms. Further research is needed.
23	Atazanavir +/- ritonavir	Uncertainty in potential benefits and harms. Further research is needed.
24	Atovaquone	Uncertainty in potential benefits and harms. Further research is needed.
25	Auxora	Auxora may not increase severe adverse events. The effects of auxora on other important outcomes are uncertain. Further research is needed.
26	Avdoralimab	Uncertainty in potential benefits and harms. Further research is needed.
27	Aviptadil	Uncertainty in potential benefits and harms. Further research is needed.
28	Ayush-64	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
29	AZD1656	AZD1656 may improve time to symptom resolution. The effects of AZD 1656 on other important outcomes are uncertain. Further research is needed.
30	Azelastine	Uncertainty in potential benefits and harms. Further research is needed.
31	Azithromycin	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
32	Azvadine	Uncertainty in potential benefits and harms. Further research is needed.
33	Bacteriophage (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
34	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.
35	Baloxavir	Uncertainty in potential benefits and harms. Further research is needed.
36	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.
37	BCG	Uncertainty in potential benefits and harms. Further research is needed.
38	Bebtelovimab	Uncertainty in potential benefits and harms. Further research is needed.
39	Beta-glucans	Uncertainty in potential benefits and harms. Further research is needed.
40	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.
41	Bioven	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
42	Boswellia extract	Uncertainty in potential benefits and harms. Further research is needed.
43	Bromhexine hydrochloride	Bromhexine may reduce symptomatic infections in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed.
44	Calcitriol	Uncertainty in potential benefits and harms. Further research is needed.
45	Camostat mesilate	Camostat mesilate may not improve time to symptom resolution. Further research is needed.
46	Canakinumab	Uncertainty in potential benefits and harms. Further research is needed.
47	Cannabidiol	Uncertainty in potential benefits and harms. Further research is needed.
48	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.
49	Celecoxib/Famotidine	Uncertainty in potential benefits and harms. Further research is needed.
50	Cenicriviroc	Uncertainty in potential benefits and harms. Further research is needed.
51	CERC-002	Uncertainty in potential benefits and harms. Further research is needed.
52	Chloroquine nasal drops	Uncertainty in potential benefits and harms. Further research is needed.
53	Chlorpheniramine (nasal)	Uncertainty in potential benefits and harms. Further research is needed.
54	CIGB-325	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
55	Clarithromycin	Uncertainty in potential benefits and harms. Further research is needed.
56	Clazakizumab	Clazakizumab may reduce mechanical ventilation and improve time to symptoms resolution. However, certainty of the evidence was low. Further research is needed.
57	Clevudine	Uncertainty in potential benefits and harms. Further research is needed.
58	Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)	Uncertainty in potential benefits and harms. Further research is needed.
59	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 does not have an important effect on hospitalizations.
60	Colchicine + statin	Uncertainty in potential benefits and harms. Further research is needed.
61	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. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%).
62	Crizanlizumab	Uncertainty in potential benefits and harms. Further research is needed.
63	Curcumin + piperine	Uncertainty in potential benefits and harms. Further research is needed.
64	Curcumin + quercetin +/- vitamin D	Uncertainty in potential benefits and harms. Further research is needed.
65	Dapagliflozin	Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.

	Intervention	Summary of findings
66	Darunavir-cobicistat	Uncertainty in potential benefits and harms. Further research is needed.
67	Deagalactosylated bovine glycoprotein	Uncertainty in potential benefits and harms. Further research is needed.
68	Degarelix	Uncertainty in potential benefits and harms. Further research is needed.
69	DFV890	DFV890 may improve time to symptom resolution. The effects of DFV890 on other important outcomes are uncertain. Further research is needed.
70	Dimethyl sulfoxide (DSMO)	Uncertainty in potential benefits and harms. Further research is needed.
71	Dornase alfa (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
72	Doubase C	Uncertainty in potential benefits and harms. Further research is needed.
73	Doxycycline	Doxycycline does not increase symptom resolution or improvement and may not reduce hospitalizations.
74	Dutasteride	Uncertainty in potential benefits and harms. Further research is needed.
75	Dupilumab	Uncertainty in potential benefits and harms. Further research is needed.
76	Edaravone	Uncertainty in potential benefits and harms. Further research is needed.
77	Electrolyzed saline	Uncertainty in potential benefits and harms. Further research is needed.
78	Empaglifozin	Empaglifozin probably does not reduce mortality or mechanical ventilation and probably does not increase symptom resolution.

	Intervention	Summary of findings
79	Endothelial dysfunction protocol	Uncertainty in potential benefits and harms. Further research is needed.
80	Enisamium	Uncertainty in potential benefits and harms. Further research is needed.
81	Ensovibep	Uncertainty in potential benefits and harms. Further research is needed.
82	Ensitrelvir	Uncertainty in potential benefits and harms. Further research is needed.
83	Enzalutamide	Uncertainty in potential benefits and harms. Further research is needed.
84	Ethanol (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
85	Famotidine	Uncertainty in potential benefits and harms. Further research is needed.
86	Favipiravir	Favipiravir may increase mortality and mechanical ventilation requirements; it may increase hospitalizations and it does not improve symptom resolution. Further research is needed.
87	Febuxostat	Uncertainty in potential benefits and harms. Further research is needed.
88	Fenofibrate	Fenofibrate may not increase severe adverse events. The effects of fenofibrate on other important outcomes are uncertain. Further research is needed.
89	Finasteride	Uncertainty in potential benefits and harms. Further research is needed.
90	Fluoxetine	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
91	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 moderate for hospitalizations and very low to low for the other outcomes. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%). Further research is needed.
92	Fluvoxamine + corticosteroids (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
93	Fostamatinib	Uncertainty in potential benefits and harms. Further research is needed.
94	Gabapentin +/- montelukast	Uncertainty in potential benefits and harms. Further research is needed.
95	Galectin inhibitor	Uncertainty in potential benefits and harms. Further research is needed.
96	Garadacimab	Uncertainty in potential benefits and harms. Further research is needed.
97	GB0139 (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
98	Gimsilumab (anti-GM-CSF monoclonal antibody)	Gimsilumab may not reduce mortality or increase symptom resolution. Further research is needed.
99	Helium (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
100	Hemadsorption	Uncertainty in potential benefits and harms. Further research is needed.
101	Hesperidin	Hesperidin may not improve symptom resolution; however, the certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
102	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.
103	Hyperbaric oxygen	Uncertainty in potential benefits and harms. Further research is needed.
104	Hyperimmune anti-COVID-19 intravenous immunoglobulin (C-IVIG)	Hyperimmune IVIG may not increase severe adverse events, however its effects on other outcomes are uncertain. Further research is needed.
105	Hypertonic saline (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
106	hzVSF-v13	Uncertainty in potential benefits and harms. Further research is needed.
107	Ibrutinib	Uncertainty in potential benefits and harms. Further research is needed.
108	IC14	Uncertainty in potential benefits and harms. Further research is needed.
109	Icatibant	Icatibant may not reduce mortality. However, certainty of the evidence was low because of imprecision. Further research is needed.
110	Icosapent ethyl	Uncertainty in potential benefits and harms. Further research is needed.
111	Imatinib	Imatinib may not increase severe adverse events. The effects of imatinib on other important outcomes are uncertain. Further research is needed.
112	Indomethacin	Uncertainty in potential benefits and harms. Further research is needed.
113	Infliximab	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
114	INM005 (polyclonal fragments of equine antibodies)	Uncertainty in potential benefits and harms. Further research is needed.
115	Interferon alpha-2b and interferon gamma	Uncertainty in potential benefits and harms. Further research is needed.
116	Interferon beta-1a	IFN beta-1a probably does not reduce mortality, invasive mechanical ventilation requirements or improve symptom resolution. Further research is needed.
117	Interferon beta-1a (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
118	Interferon beta-1b	Uncertainty in potential benefits and harms. Further research is needed.
119	Interferon gamma	Uncertainty in potential benefits and harms. Further research is needed.
120	Interferon kappa and TFF2	Uncertainty in potential benefits and harms. Further research is needed.
121	Interleukin-2	Uncertainty in potential benefits and harms. Further research is needed.
122	lota-carrageenan	Uncertainty in potential benefits and harms. Further research is needed.
123	Itolizumab	Uncertainty in potential benefits and harms. Further research is needed.
124	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 does not have an important effect on hospitalizations and probably does not increase severe adverse events. It is uncertain if it reduces symptomatic infections when used as prophylaxis.

	Intervention	Summary of findings
125	Ivermectin (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
126	IVIG (intravenous immunoglobulin)	Uncertainty in potential benefits and harms. Further research is needed.
127	Ixekizumab	Uncertainty in potential benefits and harms. Further research is needed.
128	KB109	Uncertainty in potential benefits and harms. Further research is needed.
129	L-arginine	Uncertainty in potential benefits and harms. Further research is needed.
130	<i>Lactococcus lactis</i> (intranasal)	Uncertainty in potential benefits and harms. Further research is needed.
131	Lactoferrin	Uncertainty in potential benefits and harms. Further research is needed.
132	Leflunomide	Leflunomide may increase severe adverse events, its effects on other patient important outcomes are uncertain. Further research is needed.
133	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.
134	Levamisole	Uncertainty in potential benefits and harms. Further research is needed.
135	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.
136	Linagliptin	Uncertainty in potential benefits and harms. Further research is needed.
137	Lincomycin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
138	Lithium	Uncertainty in potential benefits and harms. Further research is needed.
139	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.
140	Low-dose radiation therapy	Uncertainty in potential benefits and harms. Further research is needed.
141	Mavrilimumab	Uncertainty in potential benefits and harms. Further research is needed.
142	Mefenamic acid	Uncertainty in potential benefits and harms. Further research is needed.
143	Melatonin	Uncertainty in potential benefits and harms. Further research is needed.
144	Meplazumab	Meplazumab may not increase symptom resolution. Its effects on other important outcomes are uncertain. Further research is needed.
145	Mesenchymal stem-cells	Mesenchymal stem-cells probably reduce mortality and may not increase severe adverse events in patients with severe to critical COVID-19.
146	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.

	Intervention	Summary of findings
147	Methylene blue	Uncertainty in potential benefits and harms. Further research is needed.
148	Metisoprinol	Uncertainty in potential benefits and harms. Further research is needed.
149	Metoprolol	Uncertainty in potential benefits and harms. Further research is needed.
150	Metronidazole	Uncertainty in potential benefits and harms. Further research is needed.
151	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. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%). Further research is needed.
152	Montelukast	Uncertainty in potential benefits and harms. Further research is needed.
153	Mouthwash	Mouthwash may improve time to symptom resolution. Uncertainty in potential benefits and harms on other outcomes. Further research is needed.
154	Mupadolimab	Uncertainty in potential benefits and harms. Further research is needed.
155	Mycobacterium w	Uncertainty in potential benefits and harms. Further research is needed.
156	N-acetylcysteine	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
157	N-acetylcysteine (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
158	Nafamostat mesylate	Uncertainty in potential benefits and harms. Further research is needed.
159	Namilumab	Uncertainty in potential benefits and harms. Further research is needed.
160	Nano-curcumin	Uncertainty in potential benefits and harms. Further research is needed.
161	Nasal hypertonic saline	Uncertainty in potential benefits and harms. Further research is needed.
162	Neem (<i>Azadirachta indica</i> A. Juss)	Uncertainty in potential benefits and harms. Further research is needed.
163	Nelfinavir	Uncertainty in potential benefits and harms. Further research is needed.
164	Niclosamide	Uncertainty in potential benefits and harms. Further research is needed.
165	Nicotine patches	Uncertainty in potential benefits and harms. Further research is needed.
166	<i>Nigella sativa</i> +/- honey	Uncertainty in potential benefits and harms. Further research is needed.
167	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.
168	Nitazoxanide	Uncertainty in potential benefits and harms. Further research is needed.
169	Nitric oxide	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
170	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.
171	Norelgestromin and ethinylestradiol	Uncertainty in potential benefits and harms. Further research is needed.
172	Novaferon	Uncertainty in potential benefits and harms. Further research is needed.
173	Nutritional support	Uncertainty in potential benefits and harms. Further research is needed.
174	Omega-3 fatty acids	Uncertainty in potential benefits and harms. Further research is needed
175	OP-101	Uncertainty in potential benefits and harms. Further research is needed
176	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.
177	Otilimab	Uncertainty in potential benefits and harms. Further research is needed
178	Ozone	Uncertainty in potential benefits and harms. Further research is needed.
179	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.
180	Pacritinib	Pacritinib may not increase symptom resolution or improvement. However, certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
181	Palmitoylethanolamide	Uncertainty in potential benefits and harms. Further research is needed.
182	Peg-interferon alfa	Uncertainty in potential benefits and harms. Further research is needed.
183	Peg-interferon lambda	Pegylated Interferon lambda may not have an important effect on hospitalizations and may not increase severe adverse events. However, certainty of the evidence was low. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%). Further research is needed.
184	Pembrolizumab	Uncertainty in potential benefits and harms. Further research is needed.
185	Pentoxifylline	Uncertainty in potential benefits and harms. Further research is needed.
186	Pirfenidone	Uncertainty in potential benefits and harms. Further research is needed.
187	Plasmapheresis	Uncertainty in potential benefits and harms. Further research is needed.
188	Plitidepsin	Uncertainty in potential benefits and harms. Further research is needed.
189	PNB001 (CCK-A antagonist)	Uncertainty in potential benefits and harms. Further research is needed.
190	Polymerized type I collagen (PT1C)	Uncertainty in potential benefits and harms. Further research is needed.
191	Potassium canrenoate	Uncertainty in potential benefits and harms. Further research is needed.
192	Povidone iodine (nasal spray)	Uncertainty in potential benefits and harms. Further research is needed.
193	Probiotics	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
194	Progesterone	Uncertainty in potential benefits and harms. Further research is needed.
195	Prolectin-M	Uncertainty in potential benefits and harms. Further research is needed.
196	Propolis	Uncertainty in potential benefits and harms. Further research is needed.
197	Prostacyclin	Uncertainty in potential benefits and harms. Further research is needed.
198	Prostacyclin (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
199	Proxalutamide	Uncertainty in potential benefits and harms. Further research is needed.
200	Pyridostigmine	Uncertainty in potential benefits and harms. Further research is needed.
201	Quercetin	Uncertainty in potential benefits and harms. Further research is needed.
202	Raloxifene	Uncertainty in potential benefits and harms. Further research is needed.
203	Ramipril	Uncertainty in potential benefits and harms. Further research is needed.
204	Ravulizumab	Ravulizumab may not reduce mortality. However, certainty of the evidence was low. Further research is needed.
205	RD-X19 (light therapy)	Uncertainty in potential benefits and harms. Further research is needed.
206	Recombinant super-compound interferon	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
207	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.
208	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.
209	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.
210	Remdesivir (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
211	Reparixin	Uncertainty in potential benefits and harms. Further research is needed.
212	Resveratrol	Uncertainty in potential benefits and harms. Further research is needed.
213	rhG-CSF (in patients with lymphopenia)	Uncertainty in potential benefits and harms. Further research is needed.
214	rhG-CSF (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
215	rhu-pGSN	Uncertainty in potential benefits and harms. Further research is needed.
216	Ribavirin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
217	Ribavirin + interferon beta-1b	Uncertainty in potential benefits and harms. Further research is needed.
218	RP7214 (DHODH inhibitor)	Uncertainty in potential benefits and harms. Further research is needed.
219	Ruxolitinib	Ruxolitinib may reduce mortality but probably does not increase symptom resolution; however, the certainty of the evidence was low. Further research is needed.
220	SA58 (nasal anti-SARS-COV-2 monoclonal antibody)	Uncertainty in potential benefits and harms. Further research is needed.
221	Sabizabulin	Uncertainty in potential benefits and harms. Further research is needed.
222	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.
223	Secukinumab	Uncertainty in potential benefits and harms. Further research is needed.
224	Senicapoc	Uncertainty in potential benefits and harms. Further research is needed.
225	Sentinox	Uncertainty in potential benefits and harms. Further research is needed.
226	Short-wave diathermy	Uncertainty in potential benefits and harms. Further research is needed.
227	Sildenafil	Uncertainty in potential benefits and harms. Further research is needed.
228	Siltuximab	Uncertainty in potential benefits and harms. Further research is needed.
229	Silver nanoparticles	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
230	Silymarin	Uncertainty in potential benefits and harms. Further research is needed.
231	Sitagliptin	Uncertainty in potential benefits and harms. Further research is needed.
232	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.
233	Sotrovimab	Sotrovimab may probably reduce hospitalizations in patients with recent onset mild COVID-19.
234	Spirolactone	Uncertainty in potential benefits and harms. Further research is needed.
235	Spirulin	Uncertainty in potential benefits and harms. Further research is needed.
236	Statins	Statins may reduce mortality but may not have an important effect on mechanical ventilation; however, certainty of the evidence was low. Further research is needed.
237	Stem-cell nebulization	Uncertainty in potential benefits and harms. Further research is needed.
238	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).
239	Steroids (corticosteroids, inhaled)	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.
240	Steroids (corticosteroids, nasal)	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
241	Sulodexide	Uncertainty in potential benefits and harms. Further research is needed.
242	Tafenoquine	Uncertainty in potential benefits and harms. Further research is needed.
243	TD-0903 (inhaled JAK-inhibitor)	Uncertainty in potential benefits and harms. Further research is needed.
244	Tenofovir + emtricitabine	Tenofovir + emtricitabine may not reduce mortality but may reduce mechanical ventilation. However, certainty of the evidence was low. Further research is needed.
245	Thalidomide	Uncertainty in potential benefits and harms. Further research is needed.
246	Thymoquinone	Uncertainty in potential benefits and harms. Further research is needed.
247	Tissue-plasminogen activator (tPA)	Uncertainty in potential benefits and harms. Further research is needed.
248	Tixagevimab–cilgavimab	Tixagevimab–cilgavimab probably reduces mortality, hospitalizations, and SARS-COV-2 infections in exposed individuals and may not increase severe adverse events.
249	Tocilizumab	Tocilizumab reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
250	Tofacitinib	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
251	Tranilast	Uncertainty in potential benefits and harms. Further research is needed.
252	Transcranial direct current stimulation (tDCS)	Uncertainty in potential benefits and harms. Further research is needed.
253	Tregs (regulatory T cells)	Uncertainty in potential benefits and harms. Further research is needed.
254	Triazavirin	Uncertainty in potential benefits and harms. Further research is needed.
255	TRV-027	Uncertainty in potential benefits and harms. Further research is needed.
256	TXA-127	Uncertainty in potential benefits and harms. Further research is needed.
257	Ultraviolet light phototherapy	Uncertainty in potential benefits and harms. Further research is needed.
258	Umifenovir	Uncertainty in potential benefits and harms. Further research is needed.
259	Verapamil	Uncertainty in potential benefits and harms. Further research is needed.
260	Vidofludimus calcium	Uncertainty in potential benefits and harms. Further research is needed.
261	Vilobelimab	Vilobelimab probably reduces mortality and probably does not increase severe adverse events.
262	Vitamin B	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
263	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.
264	Vitamin D	Vitamin D does not reduce infections in exposed individuals and probably does not reduce hospitalizations. Vitamin D effect on other important outcomes is uncertain. Further research is needed.
265	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.
266	XAV-19 (swine glyco-humanized polyclonal antibodies)	Uncertainty in potential benefits and harms. Further research is needed.
267	Zafirlukast	Uncertainty in potential benefits and harms. Further research is needed.
268	Zilucoplan	Uncertainty in potential benefits and harms. Further research is needed.
269	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.
270	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 270 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 are 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. Sixteen 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 60 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. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%).
- **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 suggest 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 seven RCTs assessing anakinra in hospitalized patients with non-severe disease, show inconsistent results on mortality and symptom resolution and

suggest that anakinra may not 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 17 RCTs assessing colchicine, including the COLCORONA study that recruited 4488 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

- **Ivermectin:** Pooled estimates of 50 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 does not have an important effect on hospitalizations in patients with recent onset disease. Ivermectin probably does not increase severe adverse events. It is uncertain if it reduces symptomatic infections when used as prophylaxis.

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

- **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** Seventeen 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 four RCTs show that, in patients with moderate to critical disease, ruxolitinib may reduce mortality but probably does not increase symptom resolution. 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 show 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. Sotrovimab administered by intramuscular route may have similar efficacy to sotrovimab administered by intravenous route, however the certainty of the evidence was low and further research is needed.

- **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 four 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.
- **Amubarvimab + romlusevimab:** The results of one RCT show that, in individuals with recent onset COVID-19, Amubarvimab + romlusevimab probably reduces hospitalizations and probably does not increase 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 suggest 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-cells:** The results of 13 RCTs show that, in patients with severe to critical, mesenchymal stem-cells probably reduce mortality and may not increase severe adverse events.
- **Inhaled corticosteroids:** The results of ten RCTs show that inhaled corticosteroids may improve time to symptom resolution but probably do not have an important effect on hospitalizations. Their effects on other relevant outcomes are uncertain. Further research is needed.

- **Fluvoxamine:** The results of six 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 observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%). The certainty of the evidence was high to low because of imprecision. Further research is needed.
- **Lenzilumab:** The results of one RCT suggest 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 20 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 six RCTs suggest that rivaroxaban or enoxaparin in prophylactic dose may not importantly improve time to symptom resolution or reduce hospitalizations.
- **Aspirin:** Results of six RCTs inform that aspirin probably does not reduce mortality or mechanical ventilation and probably does not increase symptom resolution or improvement. In mild patients it probably has no important effects on hospitalizations. The

observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%).

- **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 ten low-risk of bias RCTs suggest that initiating or continuing ACEIs or ARBs in patients with COVID-19 increase mortality.
- **Molnupiravir:** The results of 11 RCTs show that molnupiravir probably has no important effect on hospitalizations but it probably increases symptom resolution. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%). Molnupiravir may not increase severe adverse events.
- **Nirmatrelvir-ritonavir:** The results of two RCTs show 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 24 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.
- **Peg-Interferon lambda:** The results of six RCTs suggest that Peg-Interferon lambda may not have an important effect on hospitalizations and may not increase severe adverse events. However, certainty of the evidence was low because of imprecision. The observed reduction on hospitalizations would probably be considered important in patients with very high hospitalization risk (>10%). Further research is needed.
- **Empaglifozin:** The results of the RECOVERY study show that empaglifozin probably does not reduce mortality or mechanical ventilation, and probably does not increase symptom resolution. Certainty of the evidence was moderate.

Changes since previous edition

- **Degalactosylated bovine glycoprotein:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **ACEI/ARB:** New evidence included without significant changes.
- **Convalescent plasma:** New evidence included without significant changes.
- **Plasmapheresis:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Vitamin D:** New evidence included without significant changes.
- **SA58 (nasal):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Mesenchymal stem-cells:** 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.
- **Ruxolitinib:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Nelfinavir:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Bacteriophage (inhaled):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Povidone iodine spray:** New evidence included without significant changes.

- **Nano-curcumin:** New evidence included without significant changes.
- **Pentoxifylline:** New evidence included without significant changes.
- **Galectin inhibitor:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Tixagevimab y cilgavimab:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Favipiravir:** New evidence included without significant changes.
- **Adintrevimab:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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 270 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 crítica, 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.

- **Hidroxiclороquina, interferón beta 1-a y lopinavir con ritonavir:** El conjunto de evidencia sobre la hidroxiclороquina, 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 hidroxiclороquina incluso sugiere que su utilización probablemente genere un incremento en la mortalidad. Dieciséis estudios que evaluaron la hidroxiclороquina 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 60 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. Es probable que la reducción observada en las hospitalizaciones se considere importante en pacientes con riesgo muy elevado de ser hospitalizados (>10%).

- **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 siete ECCA que evaluaron la anakinra en pacientes hospitalizados muestran resultados incongruentes en la mortalidad y la resolución de los síntomas y sugieren que podría no 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 17 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.

- **Ivermectina:** Los resultados combinados de 50 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 en paciente con enfermedad de comienzo reciente. La ivermectina probablemente no aumente los eventos adversos graves. Los efectos de la ivermectina sobre la prevención de infecciones sintomáticas cuando se indica de forma profiláctica son inciertos.

- **Favipiravir:** Treinta y un 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 aumentar 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:** Diecisiete 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 cuatro ECCA sugieren que, en pacientes con enfermedad de moderada a grave, el ruxolitinib podría reducir la mortalidad, pero probablemente no aumente la resolución de los síntomas. 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. El sotrovimab administrado por vía intramuscular podría tener una eficacia similar al sotrovimab administrado por vía endovenosa, aunque la certeza es baja y se necesita más información.

- **Regdanvimab:** Los resultados de dos ECCA muestran que, en pacientes con enfermedad de leve a moderada, el regdanvimab 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 cuatro 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, sin aumentar los eventos adversos graves.
- **Amubarvimab y romlusevimab:** Los resultados de un ECCA muestran que el amubarvimab y el romlusevimab probablemente reduzcan las hospitalizaciones y probablemente no aumenten los eventos adversos graves en pacientes con COVID-19 de comienzo reciente.
- **Proxalutamida:** Los resultados de cuatro ECCA indican que la proxalutamida podría tener efectos favorables importantes. 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.
- **Células madre mesenquimatosas:** Los resultados de trece ECCA apuntan que, en pacientes con enfermedad de grave a crítica, las células madre mesenquimatosas probablemente reducen la mortalidad y podría no aumentar los eventos adversos severos.
- **Corticosteroides inhalados:** Los resultados de diez ECCA muestran que los corticosteroides inhalados podrían mejorar 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 seis 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. Es probable que la reducción observada en las hospitalizaciones se considere importante en pacientes con riesgo muy elevado de ser hospitalizados (>10%). La certeza de la evidencia es de baja a alta por imprecisión. Se necesita más información.
- **Lenzilumab:** Los resultados de un ECCA indican 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 tromboprolifácticas. En relación con el mejor esquema tromboprolifáctico, los resultados de 20 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 seis 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 seis 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. En pacientes leves, probablemente no tenga un efecto importante sobre las hospitalizaciones. Es probable que la reducción observada en las hospitalizaciones se considere importante en pacientes con riesgo muy elevado de ser hospitalizados (>10%).
- **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 diez ECCA con riesgo bajo de sesgo muestran que el inicio o continuación de los IECA y los ARB en pacientes con COVID-19 aumenta la mortalidad.
- **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. Es probable que la reducción observada en las hospitalizaciones se considere importante en pacientes con

riesgo muy elevado de ser hospitalizados (>10%). El molnupiravir podría no aumentar los eventos adversos graves.

- **Nirmatrelvir y ritonavir:** Los resultados de dos 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 24 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 incrementa 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.
- **Peginterferón lambda:** Los resultados de seis ECCA sugieren que el peginterferón lambda podría no tener un efecto importante sobre las hospitalizaciones ni aumentar los eventos adversos graves. Sin embargo, la certeza de la evidencia es baja por imprecisión. Es probable que la reducción observada en las hospitalizaciones se considere importante en pacientes con riesgo muy elevado de ser hospitalizados (>10%). Se necesita más información.
- **Empaglifozina:** Los resultados del estudio RECOVERY muestran que la empaglifozina probablemente no reduzca la mortalidad ni la necesidad de ventilación mecánica, y probablemente no incrementa la resolución sintomática. La certeza de la evidencia es moderada.

Cambios respecto a la versión anterior

- **Glicoproteína bovina degalactosilada:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **IECA o ARA:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia
- **Plasma de convalecientes:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia

- **Plasmaféresis:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Vitamina D:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia
- **SA58 (nasal):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Células madre mesenquimatosas:** 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.
- **Ruxolitinib:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Nelfinavir:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Bacteriófago (inhulado):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Iodo povidona en spray:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia
- **Nano-curcumina:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia
- **Pentoxifilina:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia

- **Inhibidor de galectina:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia
- **Tixagevimab y cilgavimab:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia
- **Favipiravir:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia
- **Adintrevimab:** La evidencia nueva incluida modifica la interpretación de los resultados o 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 y las personas inmunocomprometidas, 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§ion=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 31 May 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.

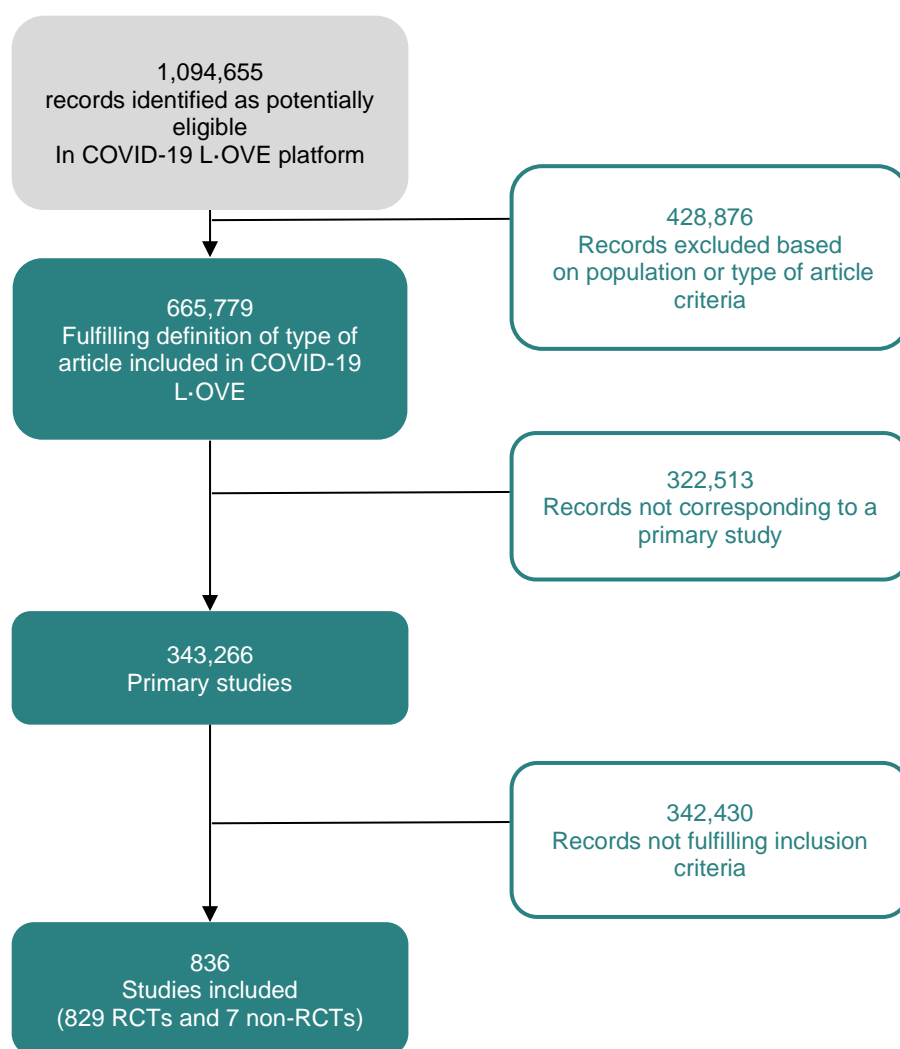
We used MAGIC authoring and publication platform (<https://app.magicapp.org/>) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in Figure 1. A total of 817 studies were selected for inclusion, 810 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	Risk-of-bias arising from randomization process	Risk-of-bias due to deviations from the intended interventions	Risk-of-bias due to missing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result	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	Low	Some Concerns
ACTT-1	Low	Low	Low	Some Concerns	Low	Low	Low
COVID-19 PEP Cavalcanti et al	Low	Low	High	Low	Low	Low	High
Kamran SM et al	High	Some Concerns	Low	Some Concerns	Low	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	Low	High
Chan 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 JF 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
RASTAVI	Low	Some Concerns	Low	High	Low	Low	High
Chan, Zang 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
CONCOVID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
GLUCOCOVID	High	Some Concerns	Low	Low	High	High	High
CloroCOVID19	Low	Low	Low	Some Concerns	Low	Low	Low
Devoudi-Morfarid et al	High	Some Concerns	Low	Low	Low	High	High
Chan et al	High	Some Concerns	Low	Low	Low	High	High
Devoudi 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
Cao 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
Vlaar APJ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Guvenmez 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
Melboub R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zhong et al	Low	Some Concerns	Low	Low	Low	Low	High
Sakoulas 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
Motocoid	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
CARDEA	Low	Low	Low	Low	Low	Low	Low
Abbaspour Kasgan H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sadeghi A et al	High	Some Concerns	Low	Low	Low	High	High
Shu 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-Elaslam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sekhevari E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shouman et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahmani H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ConPlus-19	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
DEXA-COVID19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Steroids-SARI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVID STEROID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
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
LIT 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
Gharebaghi N et al	High	Low	Low	Low	Low	Some Concerns	Some Concerns
TX-COVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
Chang 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
Kimura 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
Edalatfar M et al (Tehran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PREP	Low	Low	Low	Low	Low	Low	Low
Wang M, Hu K et al (Renmin Hospital of Wuhan University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Doi Y et al (Fujita Health University Hospital)	High	Some Concerns	Low	Some Concerns	Low	High	High
Fodder 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

Nejmi et al (Iran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PEP_COVID	Low	Low	Low	Low	Low	Low	Low
de Alencar JCO 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 (Arakbi 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
PLASM-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
Anasari K (Tabriz University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
WHO SOLIDARITY - HQQ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Yethandri V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shi L et al	Low	Low	Low	Low	Low	Low	Low
RCT-T22-COVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BACC Bay Tozilzumab Trial	Low	Low	Low	Low	Low	Low	Low
SARITA-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
Ghaderkhani 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
PROBIOCOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Padmanabhan U et al (Medical Education and Drugs Department)	High	Low	Low	Low	Low	High	High
AlQantari M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khanis 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
Lanzoni 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
Lenze E et al	Low	Low	Low	Low	Low	Low	Low
Monk P et al	Low	Low	Low	Low	Low	Low	Low
SHADE trial	High	Some Concerns	Low	Some Concerns	Low	High	High
Yalkout M et al (Pharco Corporate)	High	Some Concerns	Low	Some Concerns	Low	High	High
Ghandani 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
Tabarsi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAVUS2020 (Promomed, LLC)	High	Some Concerns	Low	Some Concerns	Low	High	High
Murai IH 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
Krolwiecki 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
Hassan 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
Nisoo 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
ITOU-C19-024-00	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elaslam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Protectin-M	High	Some Concerns	Low	Some Concerns	Low	High	High
Maldonado V 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
Roodbeh 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
Balykova LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Babalola et al	Low	Low	Low	Low	Low	Low	Low
REMAP-CAP - tocilizumab	Low	Some Concerns	Low	Some Concerns	Low	High	High
Abdelmaksoud AA et al	High	Some Concerns	Low	Some Concerns	Low	Low	High
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kiri et al	Low	Low	Low	Low	Low	Low	Low
Kumari P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RIKFAV004-Cov/2020	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	Low
RECOVERY-Plasma	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Interferon in COVID (Alavi Dorzgam I et al)	Low	Some Concerns	Low	Some Concerns	Low	High	High
AB-DRUG-SARS-004 (Cadejani FA et al)	High	Some Concerns	Low	Some Concerns	Low	Low	High
JamalMoghdamSiahkhalil S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedghyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Roodjasi A et al	High	Low	Low	Low	Low	High	High
Beo-Covid	Low	Some Concerns	Low	Some Concerns	Low	High	High
SEDT	High	Some Concerns	Low	Some Concerns	Low	High	High
Mohan et al	Low	Low	Low	Low	Low	Low	Low
Shahbaznajat et al	Low	Low	Low	Low	Low	Low	Low
Spoorhi et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Samaha et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Buktari et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Olumusi et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Veiga	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Gottlieb	Low	Low	Low	Low	Low	Low	Low
BRACE CORONA	Low	Some Concerns	Some Concerns	Low	Low	Low	High
CORIMUNO-ANA-1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Thaker A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Onal H et al	High	High	Low	Some Concerns	Low	High	High
Targ 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
Dabbous HM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATTRACT	Low	Some Concerns	Low	Low	Low	Low	Low
Ranbar K et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
EAT-DUTA AndroCoV	Low	Low	High	Low	Low	High	High
Famooah G et al	Some Concerns	Some Concerns	High	Some Concerns	Low	High	High
Khailli H et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Balkoushev VP et al	High	Some Concerns	Low	Some Concerns	Low	High	High
KILLER	High	Some Concerns	Low	Some Concerns	Low	High	High
HYDRA	Low	Some Concerns	Low	Low	Low	Low	Low
Sali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
NITFM032DOR	High	Some Concerns	Low	Some Concerns	Low	High	High
SVU-MED-CHT018-420900	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-TC2	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDatZ- 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
EFC18844	Low	Some Concerns	Low	Low	Low	Low	Low
ARTI-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Purwati	High	Some Concerns	Low	Some Concerns	Low	High	High
VB-NUMG-COVID-19/2020-CT2	High	Some Concerns	Low	Some Concerns	Low	High	High
Jamaali 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-004-2	High	Some Concerns	Low	Some Concerns	Low	High	High
Nouri-Vaakheh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopez-Medina et al	Low	Low	Low	Low	Low	Low	Low
Lakkireddy 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
Bernero Galan et al	Low	Low	Low	Low	Low	Low	Low
Pott-Junior et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mikhaylov	Low	Some Concerns	Low	Some Concerns	Low	Low	High
20AMMA/COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
AAAS624	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.20.002	High	Some Concerns	Low	Some Concerns	Low	High	High
MASH-1-COVID	Low	Some Concerns	Low	Low	Low	Low	Low
INSPIRATION	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Zayechanski	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Santos PSS et al	Low	Some Concerns	Low	Low	Low	Low	Low
Soleymani-Doodran M et al	Low	Some Concerns	Low	Low	Low	Low	Low
TD-0803-0186	High	Some Concerns	Low	Some Concerns	Low	High	High
DISCOVER	Low	Some Concerns	Low	Low	Low	Low	Low
SURG-2020-26683	Low	Some Concerns	Low	Low	Low	Low	Low
Alawi-Moghaddam M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CT-P59 3.2	Low	Some Concerns	Low	Low	Low	Low	Low
Yadolahzadeh 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
Gayritdinova VV et al	High	Some Concerns	Low	Some Concerns	Low	High	High
K031-120	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Beltran Gonzalez JL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Doadi 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
Anra S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ribakov AR et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kushnina N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CERC-002-CV19-201	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
Fouledzadeh M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
HBOT/COVID19	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
CARR-COV-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Seel	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
Saminaghani HR et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CamoCO-19	Low	Some Concerns	Low	Low	Low	Low	Low
BCR-FNB-001	High	Some Concerns	Low	Some Concerns	Low	High	High
ATOMIC2	Low	Some Concerns	Low	Some Concerns	Low	Low	High

Siarni Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CLOTROTRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High
PROSCO	High	Some Concerns	Low	Some Concerns	Low	High	High
Nearan TM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PISCO	High	Some Concerns	Low	Some Concerns	Low	High	High
HNS-COVID-PK	Low	Some Concerns	Low	Low	Low	Low	Low
Rashad A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mori M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
FACCT	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
Handy Salman O et al	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-RT-01	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-ARB	High	Some Concerns	Low	Some Concerns	Low	High	High
Persep 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
Santumab-COVID19 Study	Low	Some Concerns	Low	Low	Low	Low	Low
CAPSID	High	Some Concerns	Low	Some Concerns	Low	Low	High
CHEER	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - Colchicine	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Silvia 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
Elghary MAS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ARMY-1	Low	Some Concerns	Low	Low	Low	Low	Low
Hamdi-Alamdar D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zarehoseinzade E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elaslam S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Biber et al	Low	Low	Some Concerns	Low	Low	Low	Low
Faisal et al	High	Some Concerns	Low	Some Concerns	Low	High	High
SOVECOD	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 - ASA	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
ISMMSCCOVID19	Low	Low	Low	Low	Low	Low	Low
SENTAD-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
Taher A et al	High	Low	Low	Low	Low	Low	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
EIDD-2801-2003	Low	Low	Low	Low	Low	Low	Low
REMP-CAP	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
STOP-COVID	Low	Low	Low	Low	Low	Low	Low
Vellozo 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
Hamid DM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COUNTER-COVID	Low	Low	Low	Low	Low	Low	Low
Abdulamin AS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
KP-DRUG-SARS-003	High	Low	Low	Low	Low	High	High
Aref ZF et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Di Piero 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
COVIT02-01	Low	Low	Low	Low	Low	Low	Low
HMO-G224-20	High	Low	Low	Low	Low	High	High
REMDACTA	Low	Low	Low	Low	Low	Low	Low
ImmCoVA	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-SARI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-SARI ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SARCOVID	Low	Low	Low	Low	Low	Low	Low
SARICOR	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 Sati P3	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
Najmeddin 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
AB-DRUG-SARS-005	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
Gaitan-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
UAIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BISHOP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Asadipooya 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
DOXYCOV	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PRINCIPLE	Low	Low	Low	Low	Low	Low	Low
Patkh D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Covid-19 Phase 3 Prevention Trial - Exposed	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
Abbass S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
C3FO	Low	Low	Low	Low	Low	Low	Low
Kosak et al	High	Some Concerns	Low	Some Concerns	Low	High	High
TOGHETER-Fluvoxamine	Low	Low	Low	Low	Low	Low	Low
TOCDEX	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Fakhran A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HERO-HCQ	Low	Low	Low	Low	Low	Low	Low
Alizadeh Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Bhushan S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
VASCEPA COVID-19 CARDIOLINK-9	High	Some Concerns	Low	Some Concerns	Low	High	High
Shirkat M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rodriguez C et al	Low	Low	Low	Low	Low	Low	Low
Mousavi SA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Strich	Low	Low	Low	Low	Low	Low	Low
MADRID-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
JZW-MC-PYAA	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
Coppola	High	Low	Low	Low	Low	High	High
ALY-020-001	Low	Low	Low	Low	Low	Low	Low
Gales MRI RESPOND-1	Low	Low	Low	Low	Low	Low	Low
ACTIV-2	High	Some Concerns	Low	Some Concerns	Low	Low	Low
CARVIN	Low	Low	Low	Low	Low	Low	Low
Buonfrate et al	Low	Low	Low	Low	Low	Low	Low
McCreary M et al	Low	Low	Low	Low	Low	Low	Low
Ghani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Maskin 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
Hasanzadeh M et al	High	Low	Low	Low	Low	High	High
Ramachandran R et al	Low	Low	Low	Low	Low	Low	Low
CPI-005-002	High	Low	Low	Low	Low	High	High
Di Doménico MB et al	High	Low	Some Concerns	Low	Low	High	High
CT-P59 1.2	Low	Low	Low	Low	Low	Low	Low
ABC-110	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
ARTAN-C19	High	Low	High	Low	Low	High	High
Babalola OE et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESPERIDIN	Low	Low	Low	Low	Low	Low	Low
Resonate	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
BEMICOP	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-IMV	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
Elamir YM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elasam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PROCOV-19-2020	High	Some Concerns	Low	Some Concerns	Low	High	High
Haghighi S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RUX-COVID	Low	Low	Low	Low	Low	Low	Low
ACTT-3	Low	Low	Low	Low	Low	Low	Low
Ameri A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Maghbooli Z et al	High	Low	Low	Low	Low	High	High
INTEREST	Low	Low	Low	Low	Low	Low	Low
Olijnyk O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
EB-P12-01	Low	Low	Low	Low	Low	Low	Low
Mocarak S et al	Low	Low	Low	Low	Low	Low	Low
Leal 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
COVAID-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
CYTCCOV-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Alqhtani FD et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ALPS-COVID	Low	Low	Low	Low	Low	Low	Low
R10503-10967-COV-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

PennCCP2	High	Some Concerns	Low	Some Concerns	Low	High	High
Toroghi N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Isa F et al	Low	Low	Low	Low	Low	Low	Low
MOVe-OUT	Low	Low	Low	Low	Low	Low	Low
Wainraeb_2	Low	Low	Low	Low	Low	Low	Low
Beigholhamadi MT et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sarhan RM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
AP-014	High	Some Concerns	Low	Some Concerns	Low	High	High
Asgardon M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharazmi AB et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COMBAT-COVID	Low	Low	Low	Low	Low	Low	Low
ACPREGCOV	Low	Low	Low	Low	Low	Low	Low
X-Covid 19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hokubar M et al	Low	Low	Low	Low	Low	Low	Low
Malaysian Foviprovir 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
CoV-art & CoV-Early	Low	Low	Low	Low	Low	Low	Low
Raghavan K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shohan et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CSSC-004	Low	Low	Low	Low	Low	Low	Low
Cannellotto M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CRITICAL	Low	Low	Low	Low	Low	Low	Low
Regkirona_Part2							
PINETREE	Low	Low	Low	Low	Low	Low	Low
BUCDSARS	Low	Low	Low	Low	Low	Low	Low
BK-CLV-201	High	Some Concerns	Low	Some Concerns	Low	High	High
HIGHLOWDEKA	High	Some Concerns	Low	Some Concerns	Low	High	High
DEFINE	High	Some Concerns	Low	Some Concerns	Low	High	High
Ahmad B et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Puehkala et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Baxter AL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAVI-COV-US201	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kazempour et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Keret B et al	High	Some Concerns	Low	Some Concerns	Low	High	High
WINCOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Polell M. et al	Low	Low	High	Low	Low	High	High
COP20	Low	Some Concerns	Low	Some Concerns	Low	Low	High
WHIP 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
COVIDENZA	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COLCOVID	Low	Low	Low	Low	Low	Low	Low
Al Sultan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
OPTIMISE-C18	Low	Low	Low	Low	Low	Low	Low
COVID-Omega-F	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-EHC	Low	Low	Low	Low	Low	Low	Low
UNAB-003	High	Some Concerns	Low	Some Concerns	Low	High	High
Tolouan R et al	Low	Low	Low	Low	Low	Low	Low
INSPIRATION/INSPIRATION-S	Low	Low	Low	Low	Low	Low	Low
Abunegara R et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hu O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Avi-Mild	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
Covid19DPPP4I	High	Some Concerns	Low	Some Concerns	Low	High	High
ABS-COVID19	Low	Low	Low	Low	Low	Low	Low
COVID MED	Low	Low	Low	Low	Low	Low	Low
Nak NB et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTN-4a	Low	Low	Low	Low	Low	Low	Low
CATCO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
MEFECOVID-18	Low	Low	Low	Low	Low	Low	Low
Rondanelli 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
Manugesan H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Nanomaiptboon A et al	Low	Low	Low	Low	Low	Low	Low
DOXPREVENT.ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pourdowlat G et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Chupp G et al	Low	Low	Low	Low	Low	Low	Low
NACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
MEDIC-LAUMC	High	Low	Low	Low	Low	High	High
REsCue	Low	Low	Low	Low	Low	Low	Low
ITAC	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
Cairns DM et al	Low	Low	Low	Low	Low	Low	Low
PHYDRA	Low	Low	Low	Low	Low	Low	Low
Nekoukar 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 trial	High	Some Concerns	Low	Some Concerns	Low	High	High
Singh H et al	Low	Low	Low	Low	Low	Low	Low
Barzin Tond S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY	High	Some Concerns	Low	Some Concerns	Low	High	High

RUX-COVID-DEVENT	Low	Low	Low	Low	Low	Low	Low	Low
SAC-COVID	Low	Low	Low	Low	Low	Low	Low	Low
V323042020	Low	Low	Low	Low	Low	Low	Low	Low
Ghaffoor M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
CORTIVID	Low	Low	Low	Low	Low	Low	Low	Low
COVERAGE	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Hassanizad M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
BREATHE	Low	Low	Low	Low	Low	Low	Low	Low
Karanova TL et al	High	Some Concerns	Low	Some Concerns	Low	High	High	Low
MacCOVID	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns	Some Concerns
COVID-VIT-D	High	Some Concerns	Low	Some Concerns	Low	High	High	High
TOGHETER - Ivermectin	Low	Low	Low	Low	Low	Low	Low	Low
FLARE	Low	Low	Low	Low	Low	Low	Low	Low
Brennan CM et al	Low	Low	Some Concerns	Low	Low	High	High	High
IRB 3305	Low	Low	Low	Low	Low	Low	Low	Low
Takaresi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Fathi-Kazeroni M et al	High	Low	Low	Low	Low	High	High	High
Rebclatho CK et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
LIFESAVER	Low	Low	Low	Low	Low	Low	Low	Low
RECOVER	Low	Low	Low	Low	Low	Low	Low	Low
LACOPT	Low	Low	Low	Low	Low	Low	Low	Low
CPC-SARS	Low	Low	Low	Low	Low	Low	Low	Low
Hemick J et al	Low	Low	Low	Low	Low	Low	Low	Low
Tatom G et al	Low	Low	Low	Low	Low	Low	Low	Low
Chowdhury FR et al	Low	Low	Low	Low	Low	Low	Low	Low
PLACO-COVID	Low	Low	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Low	Low	Low	Low	Low	Low
Co-CLARITY	Low	Low	Low	Low	Low	Low	Low	Low
Rego EM et al	Low	Low	Low	Low	Low	Low	Low	Low
PERUCONPLASMA	Low	Low	Low	Low	Low	Low	Low	Low
CP-COVID-19	Low	Low	Low	Low	Low	Low	Low	Low
CONFIDENT	Low	Low	Low	Low	Low	Low	Low	Low
FO-COVID-19	Low	Low	Low	Low	Low	Low	Low	Low
CDP-COVID-19	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
CCAP	Low	Low	Low	Low	Low	Low	Low	Low
COOPCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
COPE - Coalition V	Low	Low	Low	Low	Low	Low	Low	Low
AlQantari M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Omheccall	High	Some Concerns	Low	Some Concerns	Low	High	High	High
CORONAVIT	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Seo H et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Gorisl FI et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
IMPACT-RT	High	Some Concerns	Low	Some Concerns	Low	High	High	High
COVIPOC	High	Some Concerns	Low	Some Concerns	Low	High	High	High
SafeDrop	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Redondo-Calvo FJ et al	Low	Low	Some Concerns	Low	Low	High	High	High
CANDLE	Low	Low	Low	Low	Low	Low	Low	Low
COVID-Compromise	Low	Low	Low	Low	Low	Low	Low	Low
HITCH	Low	Low	Low	Low	Low	Low	Low	Low
Kumar D et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
COVID-19-HBO	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
COVASE	High	Some Concerns	Low	Some Concerns	Low	High	High	High
RCT-MP-COVID-19	Low	Low	Low	Low	Low	Low	Low	Low
COPLA-II	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Coppock D et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Badavi M et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
PROVENT	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Pahwani S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Mostafaie A et al						NA	NA	NA
SILVERGULLET						NA	NA	NA
R-2020-785-176						NA	NA	NA
GS-US-553-8020						NA	NA	NA
DAWn-AZITHRO	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
DW-MSC	Low	Low	Low	Low	Low	Low	Low	Low
CoVIP	Low	Low	Low	High	High	High	High	High
Alizadeh N et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns	Some Concerns
Thilo	Low	Low	Low	Low	Low	Low	Low	Low
ACTT-4	Low	Low	Low	Low	Low	Low	Low	Low
Nicestril E et al	Low	Low	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
COVID-HEP	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
STU-2020-0707	Low	Low	Low	Low	Low	Low	Low	Low
MANTICO	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
CSSC-001	Low	Low	Low	Low	Low	Low	Low	Low
Mukoe H et al	Low	Low	Low	Low	Low	Low	Low	Low
ZILU-COV	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Rahman SMA et al	High	Low	Low	Low	Low	High	High	High
TACTIC-COVID	Low	Low	Low	Low	Low	Low	Low	Low
INSPIRE	Low	Low	Low	Low	Low	Low	Low	Low
MSG-006	Low	Low	Low	Low	Low	Low	Low	Low
REPAVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
NO COV-ED	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Villasis-Koeber MA et al	High	Low	High	Low	Low	High	High	High
CARED-TRIAL	Low	Low	Low	Low	Low	Low	Low	Low
Lonze DE et al	Low	Low	Low	Low	Low	Low	Low	Low
STRUCK	High	Some Concerns	Low	Some Concerns	Low	High	High	High
ACTIV-6	Low	Low	Low	Low	Low	Low	Low	Low
Reza_Mild	Low	Low	Low	Low	Low	Low	Low	Low
Reza_Severe	Low	Low	Some Concerns	Low	Low	High	High	High
Angkasekwinai_Treat	Low	Low	Low	Low	Low	Low	Low	Low
Angkasekwinai_Prev	Low	Low	Low	Low	Low	Low	Low	Low

Mirahmadizadeh et al	Low	Low	Low	Low	Low	Low	Low	Low
George et al	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Rojas et al	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Bargay-Leonart et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
ETHIC	High	Some Concerns	Low	Some Concerns	Low	High	High	High
COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Mukae H et al	Low	Low	Low	Low	Low	Low	Low	Low
Khan et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Molemi et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Stambouli et al	Low	Low	Low	Low	Low	Low	Low	Low
Stambouli et al	Low	Low	Low	Low	Low	Low	Low	Low
Alemamy et al	Low	Low	Low	Low	Low	Low	Low	Low
McMahon et al	Low	Low	Low	Low	Low	Low	Low	Low
Karampitsaika et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Carvalho Neuenschwander et al	Low	Low	Low	Low	Low	Low	Low	Low
Amoushahi et al	High	Low	Low	Low	Low	High	High	High
Castro-Rodriguez et al	High	Some Concerns	High	Some Concerns	Low	High	High	High
Torada et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Modhat et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Prasenohadi et al	Low	Low	Low	Low	Low	Low	Low	Low
TACKLE	Low	Low	Low	Low	Low	Low	Low	Low
TICO	Low	Low	Low	Low	Low	Low	Low	Low
Labro et al	Low	Low	Low	Low	Low	Low	Low	Low
Askari et al	Low	Low	Low	Low	Low	Low	Low	Low
Dow et al	High	Low	Low	Low	Low	High	High	High
Cocconi et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Trinapakuzhi et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Lau et al	Low	Low	Low	Low	Low	Low	Low	Low
COVID-TRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Karouva	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Bencheqroun	Low	Low	Low	Low	Low	Low	Low	Low
Panatto	High	Some Concerns	Low	Some Concerns	Low	High	High	High
UW 20-535	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Barnette	High	Low	Low	Low	Low	High	High	High
Saviano	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Tobback	Low	Low	Low	Low	Low	Low	Low	Low
Barrero	Low	Low	Low	Low	Low	Low	Low	Low
Zeyad	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Self	Low	Low	Low	Low	Low	Low	Low	Low
Kumar	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Zou	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Tandon	Low	Low	Low	Low	Low	Low	Low	Low
COVIDICUS	Low	Low	Low	Low	Low	Low	Low	Low
Dastoez	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Rabbani	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Bharti	Low	Low	Some Concerns	Low	High	High	High	High
Ojeda	High	Low	Low	Low	Low	High	High	High
Bozorgmehr R et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Romero-Ibarquengoitia	High	Some Concerns	Low	Some Concerns	Low	High	High	High
ACTIV-6 - Fluticazone	Low	Low	Low	Low	Low	Low	Low	Low
BLAZE-4	Low	Low	Low	Low	Low	Low	Low	Low
PRANA	Low	Low	Low	Low	Low	Low	Low	Low
Aryan	High	Low	Low	Low	Low	High	High	High
Corvero	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Abroug	High	Low	Low	Low	Low	High	High	High
PLATCOV - Iver	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
PLATCOV - Regen	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
Fogleman C et al	Low	Low	Low	Low	Low	Low	Low	Low
PanCOVID19	Low	Some Concerns	Low	Some Concerns	Low	Low	High	High
AGILE	Low	Low	Low	Low	Low	Low	Low	Low
D-COVID	High	Low	Low	Low	Low	High	High	High
IRICT	Low	Low	Low	Low	Low	Low	Low	Low
Choudhary R et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Khodshahi R et al	Low	Some Concerns	Low	Some Concerns	Low	High	High	High
AAAT0535	Low	Low	Low	Low	Low	Low	Low	Low
ACTIV-3/TICO	Low	Low	Low	Low	Low	Low	Low	Low
Soltani R et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
ANACONDA	Low	Some Concerns	Low	Some Concerns	Low	High	High	High
BTI-202	Low	Low	Low	Low	Low	Low	Low	Low
ReCOvery-SIRIO	High	Some Concerns	Low	Some Concerns	Low	High	High	High
MOVe-IN	Low	Low	Low	Low	Low	Low	Low	Low
MOVe-OUT - ph2	Low	Low	Low	Low	Low	Low	Low	Low
FERMIN	Low	Low	Low	Low	Low	Low	Low	Low
Nimbalai S et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Spuch C et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Delif N et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
DMMETCOV19-2	Low	Low	Low	Low	Low	Low	Low	Low
COVER HCW	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High	High
COVID-OUT	Low	Low	Low	Low	Low	Low	Low	Low
Chung R et al	NA							
PROTECT	NA							
Tovakoli ASJ et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Zhang FO et al	High	Some Concerns	Low	Some Concerns	Low	High	High	High
TACOVID	High	Some Concerns	Low	Some Concerns	Low	High	High	High
Brunvot	Low	Low	Low	Low	Low	Low	Low	Low
Golan	Low	Low	Low	Low	Low	Low	Low	Low
Singstaphat	High	Some Concerns	Low	Some Concerns	Low	High	High	High
PANAMO_vicofinab	Low	Low	Low	Low	Low	Low	Low	Low
Fessler	High	Low	Low	Low	Low	High	High	High
ARCADIA	Low	Low	Low	Low	Low	Low	Low	Low
Medurka	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High	High
Van Helmond	High	High	Low	High	Low	High	High	High

Majidi	High	Low	Low	Low	Low	Low	High	High
PANORAMIC_Malnu	Low	Low	Low	Low	Low	Low	Low	Low
Vehroschild	High	Low	Low	Low	Low	Low	High	High
INTENSE-COV	Low	Low	Low	Low	Low	Low	Low	Low
ACCROS	High	Some Concerns	Low	Some Concerns	Low	Low	High	High
Macloko	High	High	Low	High	Low	Low	High	High
Kumar	High	Low	Low	Low	Low	Low	High	High
MEDEAS	Low	Low	Low	Low	Low	Low	Low	Low
Abdallah	Low	Low	Low	Low	Low	Low	Low	Low
Ameri	High	High	Low	High	Low	Low	High	High
COLVID	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	Low	High
El-Badrawy	High	High	Low	High	Low	Low	High	High
Golberg	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	Low	High
Ghobain	Low	Low	Low	Low	Low	Low	Low	Low
IF-COVID	Low	Low	Low	Low	Low	Low	Low	Low
ESCAPE	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
RECOVERY_Steroid_Dosa	Low	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
ICAT-COVID	High	High	Low	High	Low	Low	High	High
Panahi et al	High	High	Low	High	Low	Low	High	High
Siewiera	High	High	Low	High	Low	Low	High	High
Dhibar	Low	Low	Low	Low	Low	Low	Low	Low
Vila Mendez	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Cao	Low	Low	Low	Low	Low	Low	Low	Low
JavG	Low	Low	Low	Low	Low	Low	Low	Low
ACTIV-6 - Flavocamine	Low	Low	Low	Low	Low	Low	Low	Low
ASCD - Antitrombotics	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Maluska	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Mursidharan	Low	Low	Low	Low	Low	Low	Low	Low
AST	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Ujian	High	High	Low	High	Low	Low	High	High
TOGETHER_IFN	Low	Low	Low	Low	Low	Low	Low	Low
Rahimi	High	High	Low	High	Low	Low	High	High
ACTIV-6 - Iver_High	Low	Low	Low	Low	Low	Low	Low	Low
Liu	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
I-SPY COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
PREVENT	Low	Low	Low	Low	Low	Low	Low	Low
STROMA-CoV-2	Low	Low	Low	Low	Low	Low	Low	Low
Annane	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
COMET-TAIL	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Gladstone	High	High	Low	High	Low	Low	High	High
ANTICOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
FREEDOM	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
COPE Coalition	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Wielar	High	High	Low	High	Low	Low	High	High
Bonn	Low	Low	Low	Low	Low	Low	Low	Low
Pinto	Low	Low	Low	Low	Low	Low	Low	Low
Sedighi	Low	Low	Low	Low	Low	Low	Low	Low
Alemany	Low	Low	Low	Low	Low	Low	Low	Low
Barczyk	Low	Low	Low	Low	Low	Low	Low	Low
Nasri	High	High	Low	High	Low	Low	High	High
Spivak	Low	Low	Low	Low	Low	Low	Low	Low
Llanos-Cuentas	High	High	Low	High	Low	Low	High	High
REVOLUTION	Low	Low	Low	Low	Low	Low	Low	Low
Kim	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Domazet	High	High	Low	High	Low	Low	High	High
LAC	Low	Low	Low	Low	Low	Low	Low	Low
Tanaffa	High	High	Low	High	Low	Low	High	High
COLSTAT	High	High	Low	High	Low	Low	High	High
Castro-Beledo	Low	Low	Low	Low	Low	Low	Low	Low
Ellahan	Low	Low	Low	Low	Low	Low	Low	Low
Ysezi	Low	Low	Low	Low	Low	Low	Low	Low
HALT COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Labrani-Mottagh	Low	Low	Low	Low	Low	Low	Low	Low
Irawan	High	High	Low	High	Low	Low	High	High
Ajit Nar	Low	Low	Low	Low	Low	Low	Low	Low
DEFLECT	Low	Low	Low	Low	Low	Low	Low	Low
Singla	Low	Some Concerns	Low	Some Concerns	Low	Low	Low	High
Levitt	Low	Low	Low	Low	Low	Low	Low	Low
RECOVERY_Empaglifozin	Low	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
ACTIV-2_Amubs	High	Some Concerns	Low	Some Concerns	Low	Low	Low	Low
TOGETHER_Flavo+Bude	Low	Some Concerns	Low	Low	Low	Low	Low	Low
DEFEAT-COVID	High	High	Low	High	Low	Low	High	High
REMAP-CAP_ACEI	Low	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
Soif	Low	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
ANA-COVID-GEAS	Low	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
Amira	High	High	Low	High	Low	Low	High	High
Wang	High	High	Low	High	Low	Low	High	High
Papi	Low	Some Concerns	Low	Low	Low	Low	Low	Low
SPRINTER	Low	Some Concerns	Low	Low	Low	Low	Low	Low
DeNucci	High	High	Low	High	Low	Low	High	High
Wang	High	High	Low	High	Low	Low	High	High
ACDOFACT	Some Concerns	High	Low	High	Low	Low	High	High
Saito	Low	Some Concerns	Low	Low	Low	Low	Low	Some Concerns
Inui	Some Concerns	High	Low	High	Low	Low	High	High
Sadeghi	High	High	Low	High	Low	Low	High	High
Tselim	High	High	Low	High	Low	Low	High	High
Song	Low	Some Concerns	Low	Low	Low	Low	Low	High
REALIST	Low	Some Concerns	Low	Low	Low	Low	Low	Low
PREVENT-HD	Low	Some Concerns	Low	Low	Low	Low	Low	Low
Garcia-Donaos	Low	Some Concerns	Low	Low	Low	Low	Low	High
Miyazaki	Low	Some Concerns	Low	Low	Low	Low	Low	High
Samsee	Low	Some Concerns	Low	Low	Low	Low	Low	Low

Bafiqgu-Karalain	High	High	Low	High	Low	High	High
Sadeghizadeh	High	Low	Low	Low	Low	High	High
Sarhan	High	High	Low	High	Low	High	High
Sigamani	High	Low	Low	Low	Low	High	High
Bender	Low	Some Concerns	Low	Low	Low	Low	Low
Kamali	High	High	Low	High	Low	High	High
Bowditch	Low	Some Concerns	Low	Low	Low	Low	Low
STAMP	Low	Some Concerns	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

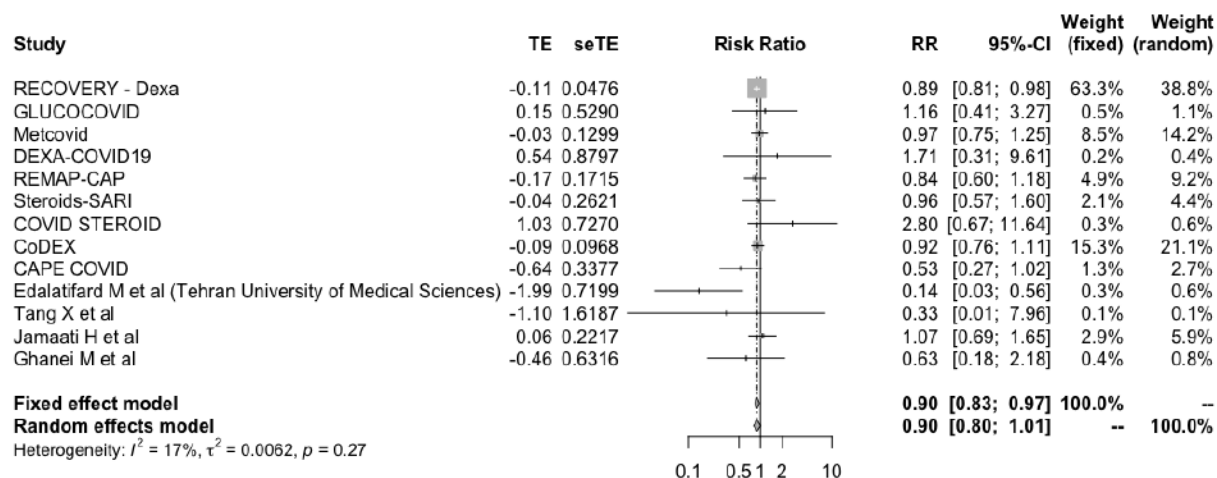


Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

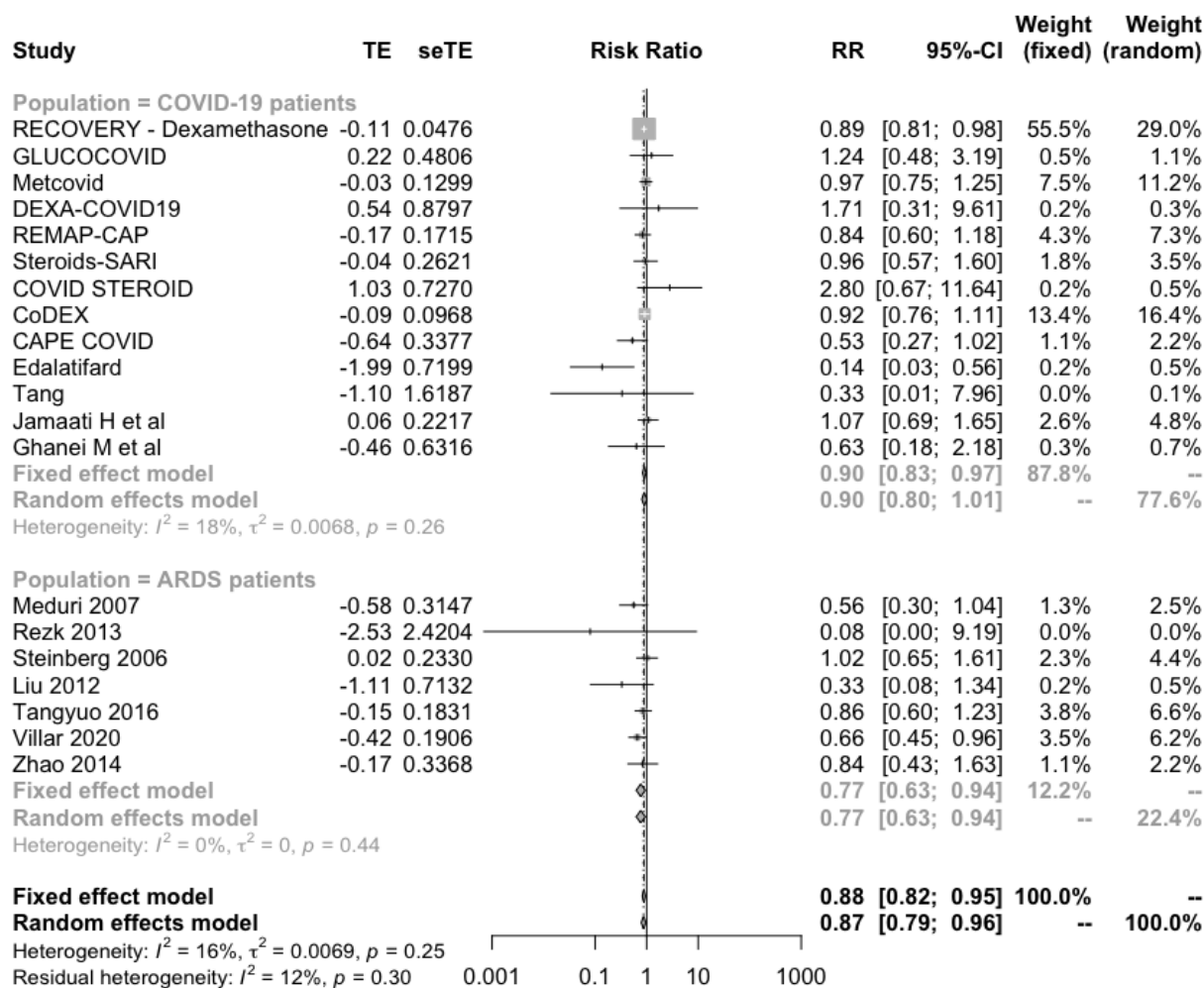


Figure 4. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

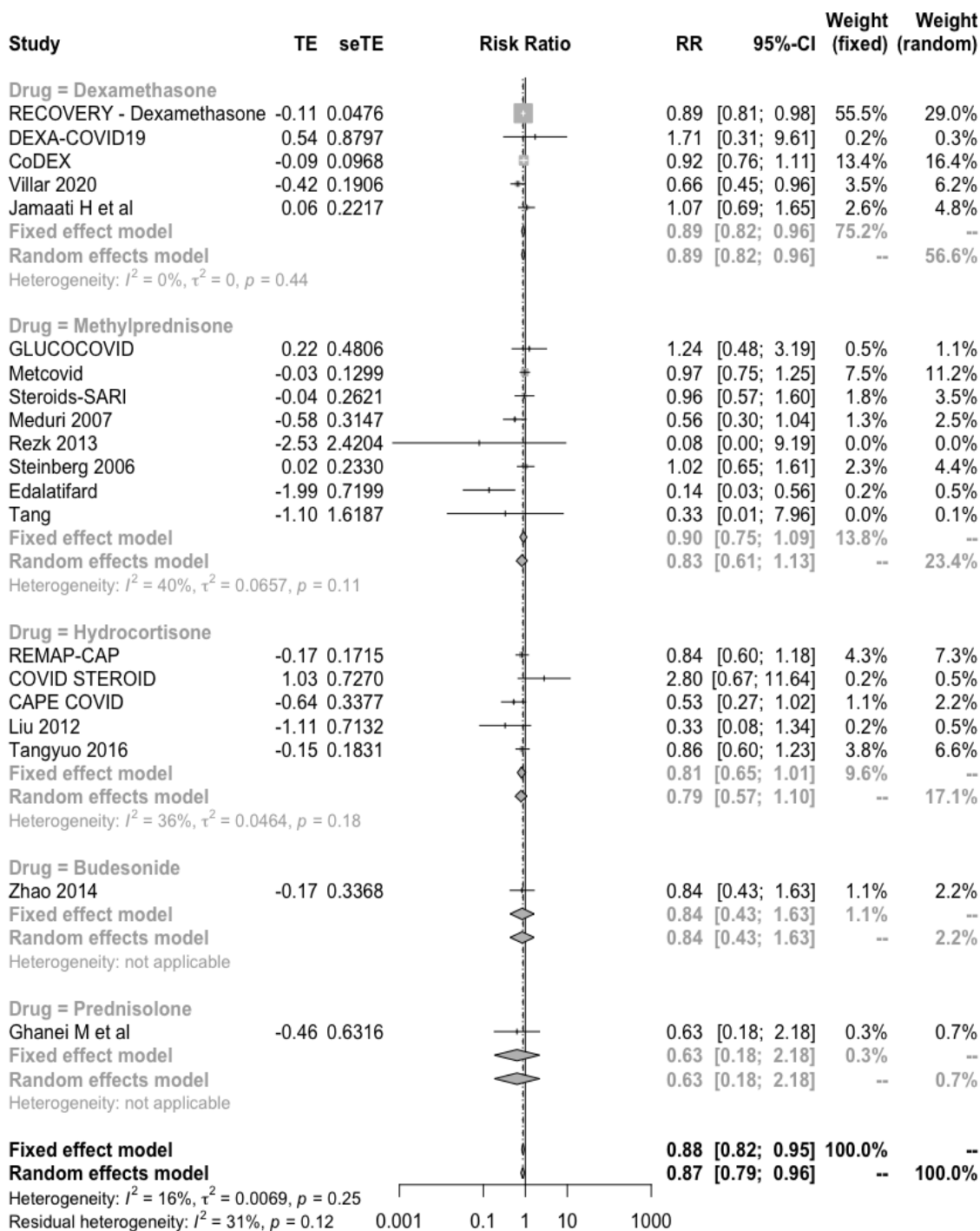
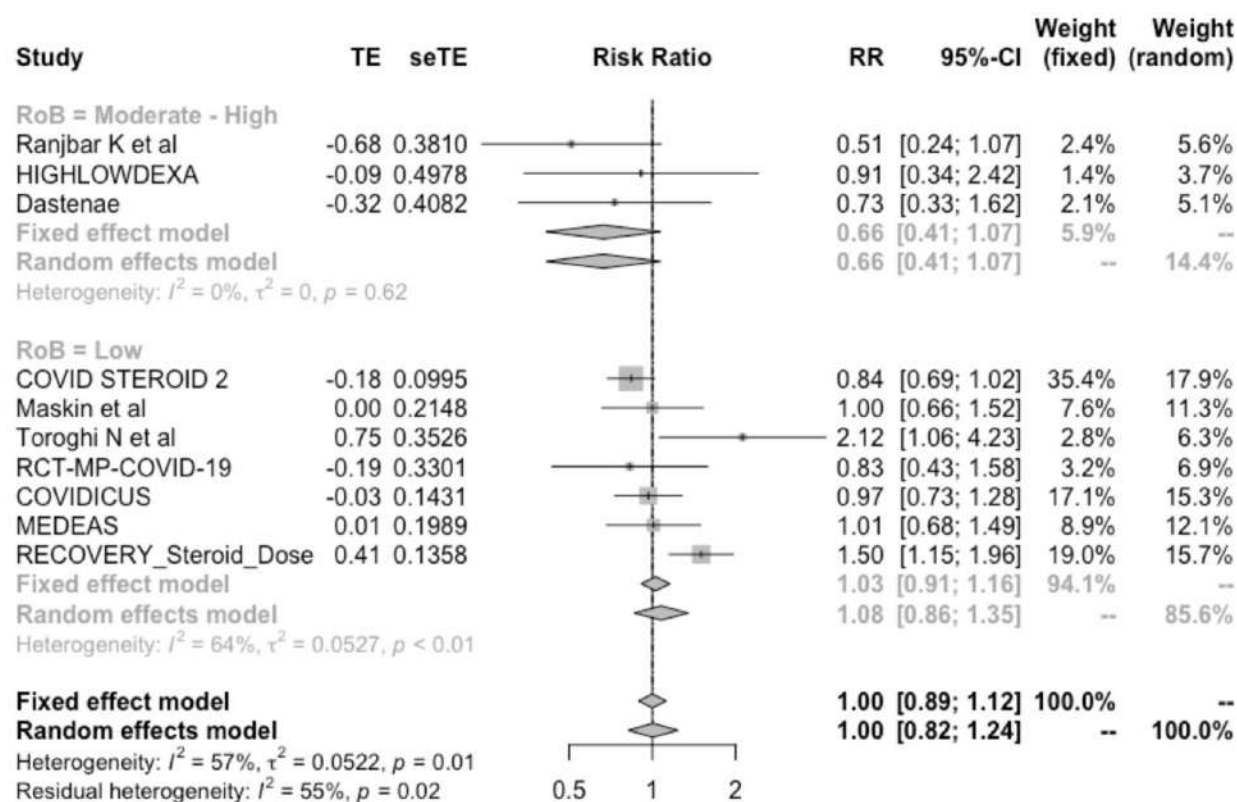


Figure 5. All-cause mortality in RCTs comparing high-dose corticosteroids (i.e., dexamethasone 12 mg a day) with standard-dose corticosteroids (i.e., dexamethasone 6 mg a day) in patients with COVID-19



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

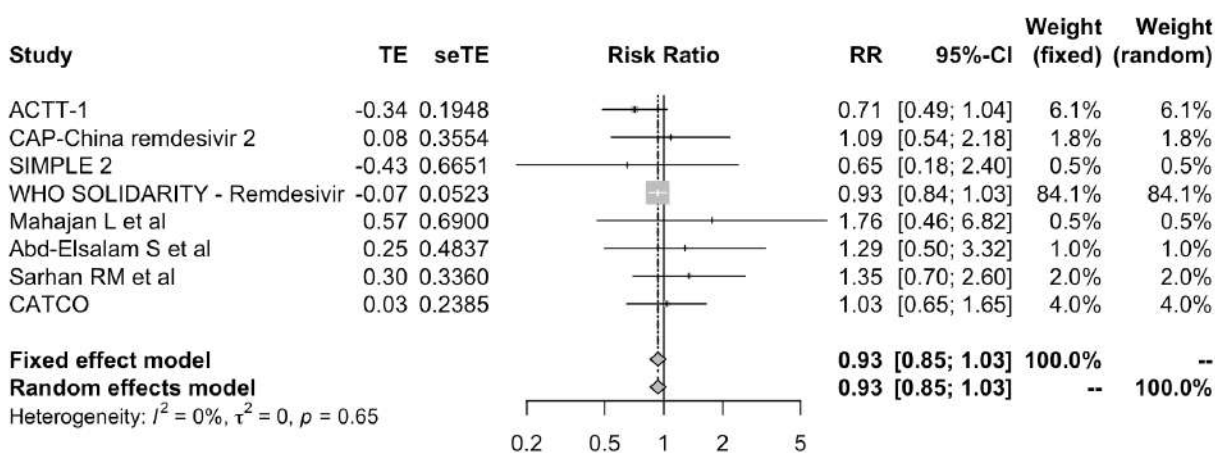


Figure 7. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

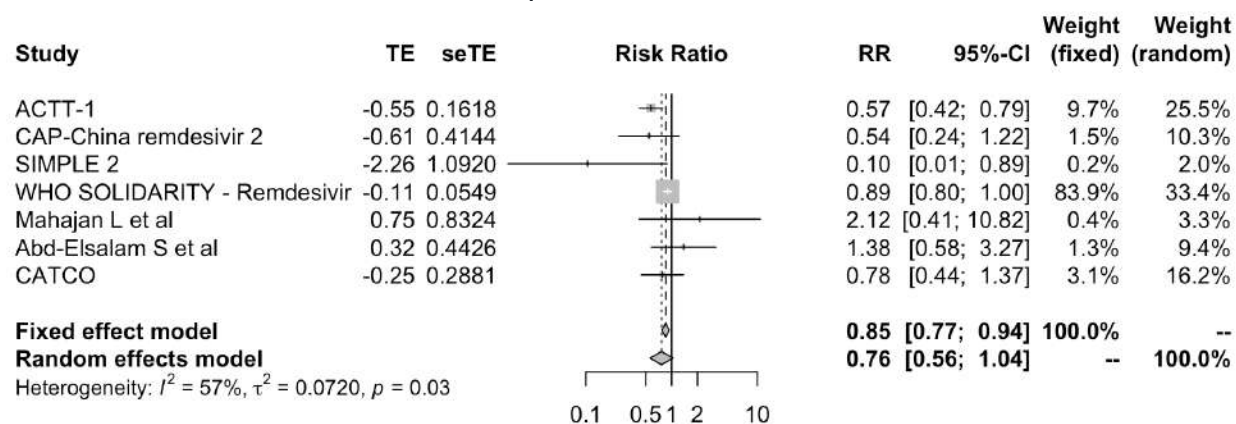
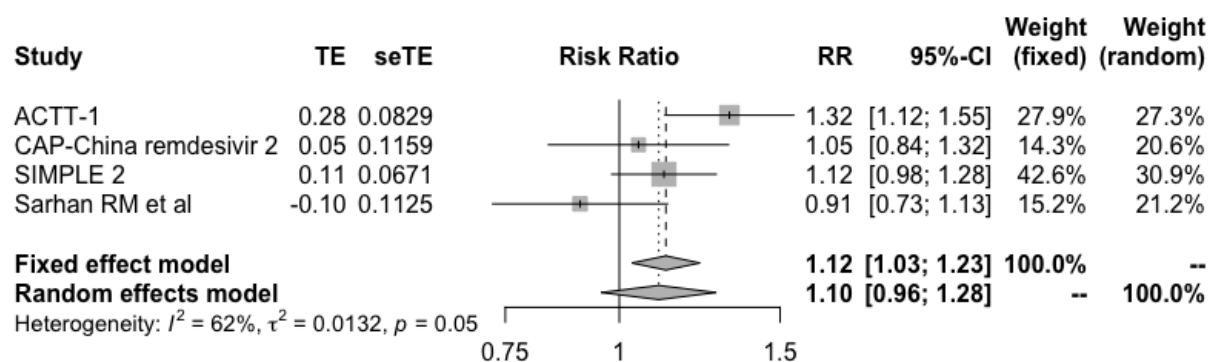


Figure 8. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 67 RCTs including 28,706 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 increases 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 0.84 (95%CI 0.72 to 0.97); RD -2.7% (95%CI -4.9% to -0.5%); 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 0.92 (95%CI 0.68 to 1.23); RD -0.8% (95%CI -3.2% to 2.8%); Low certainty ⊕⊕○○
- Hydroxychloroquine or chloroquine may not have an important effect on hospitalizations in patients with mild COVID-19, RR 0.83 (95%CI 0.63 to 1.1); RD -0.8% (95%CI -1.8% 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

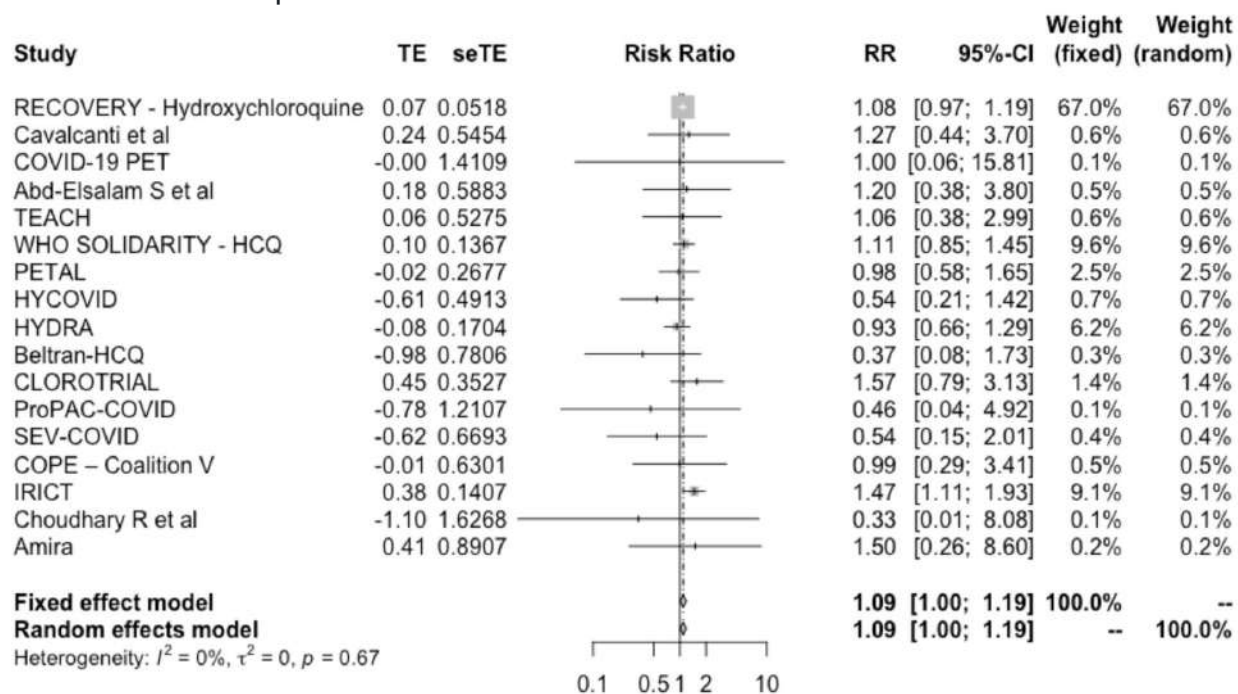
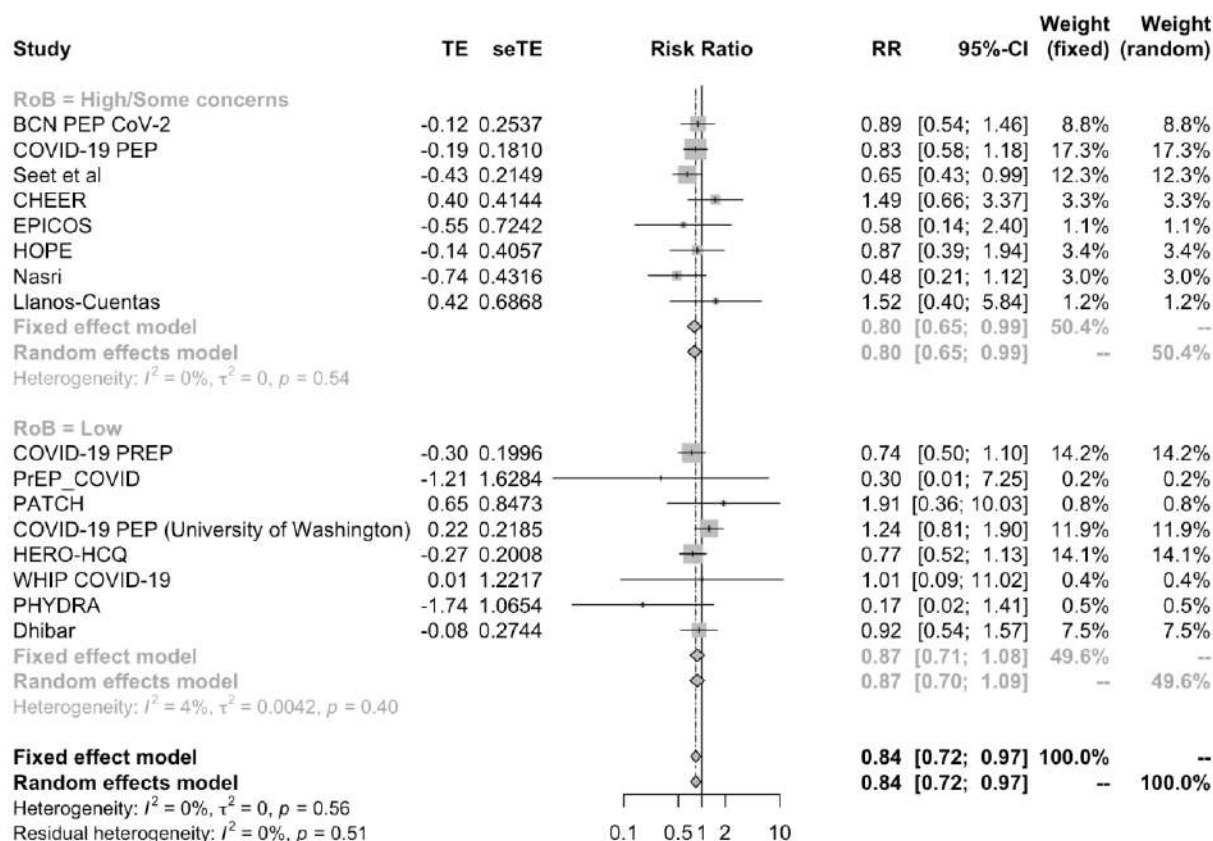


Figure 10. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



In addition, we identified a systematic review¹² 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

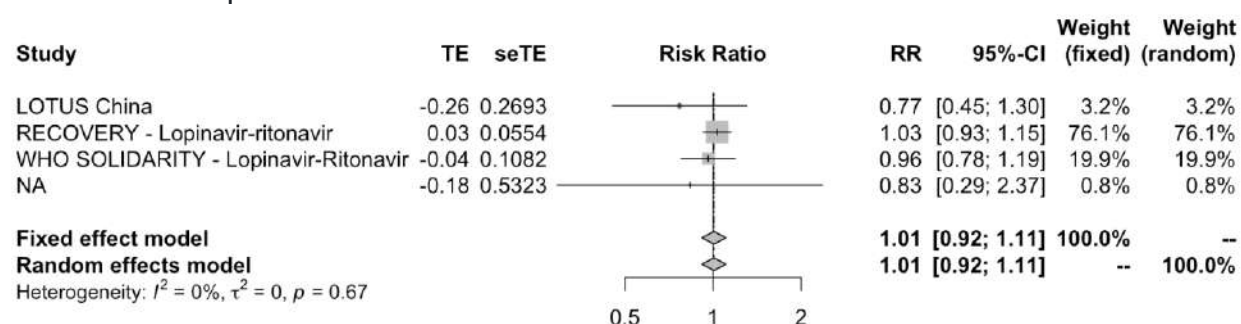
[See Summary of findings Table 4, Appendix 1](#)

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 60 RCTs including 24,818 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 (54/60) 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 does not improve symptom resolution or improvement, RR 0.99 (95% CI 0.96 to 1.02); RD -0.6% (95%CI -2.4% 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 (>10%).

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

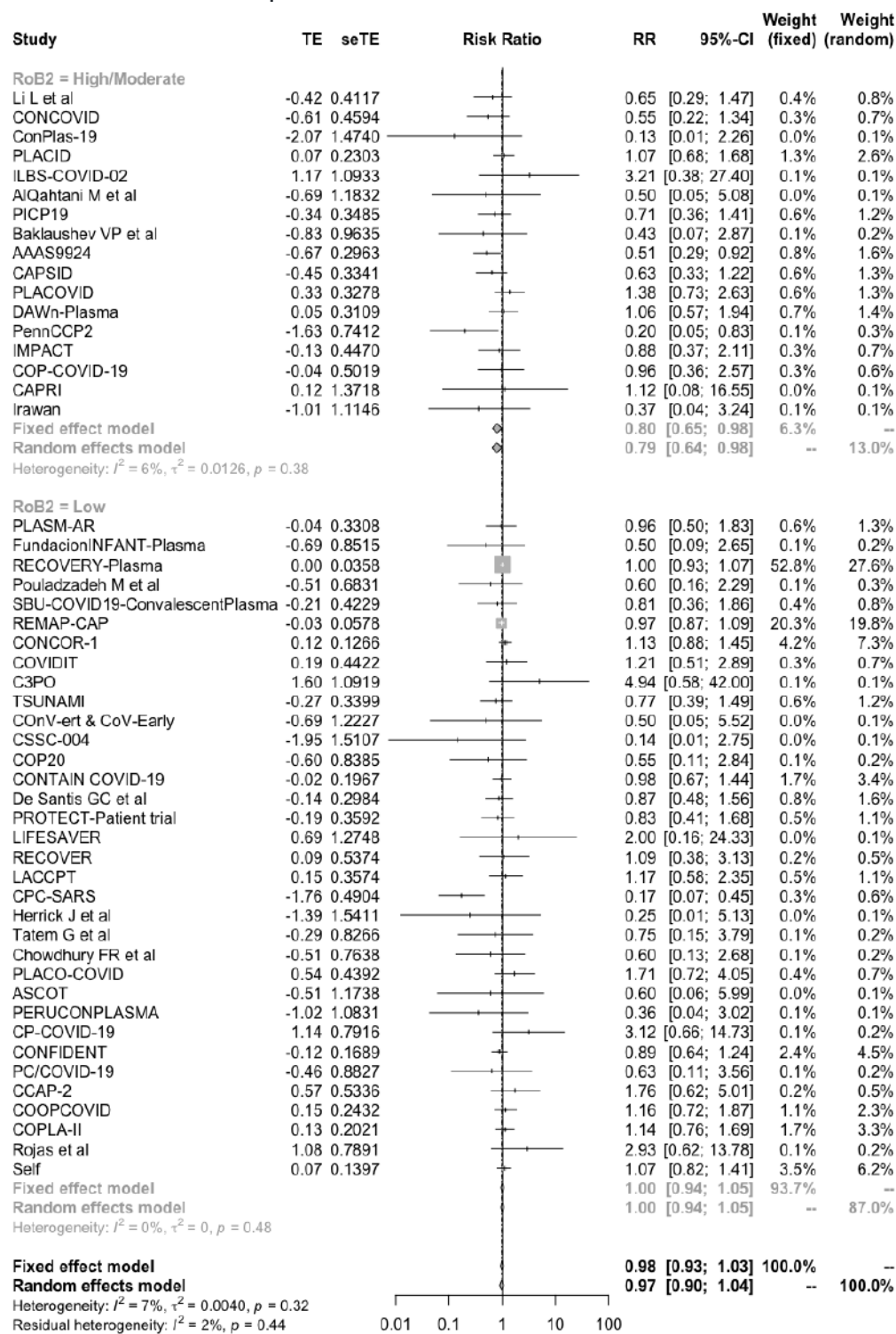
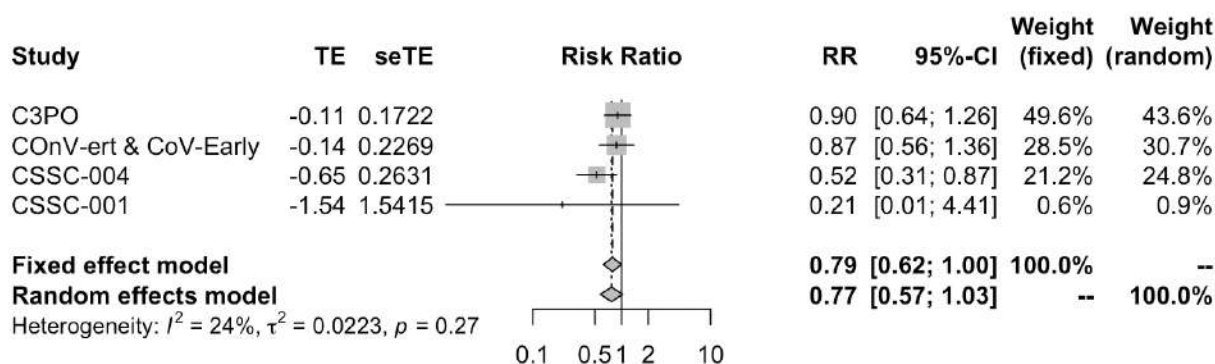


Figure 13. Hospitalizations comparing convalescent plasma with standard of care for treatment of patients with COVID-19



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 0.93); 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

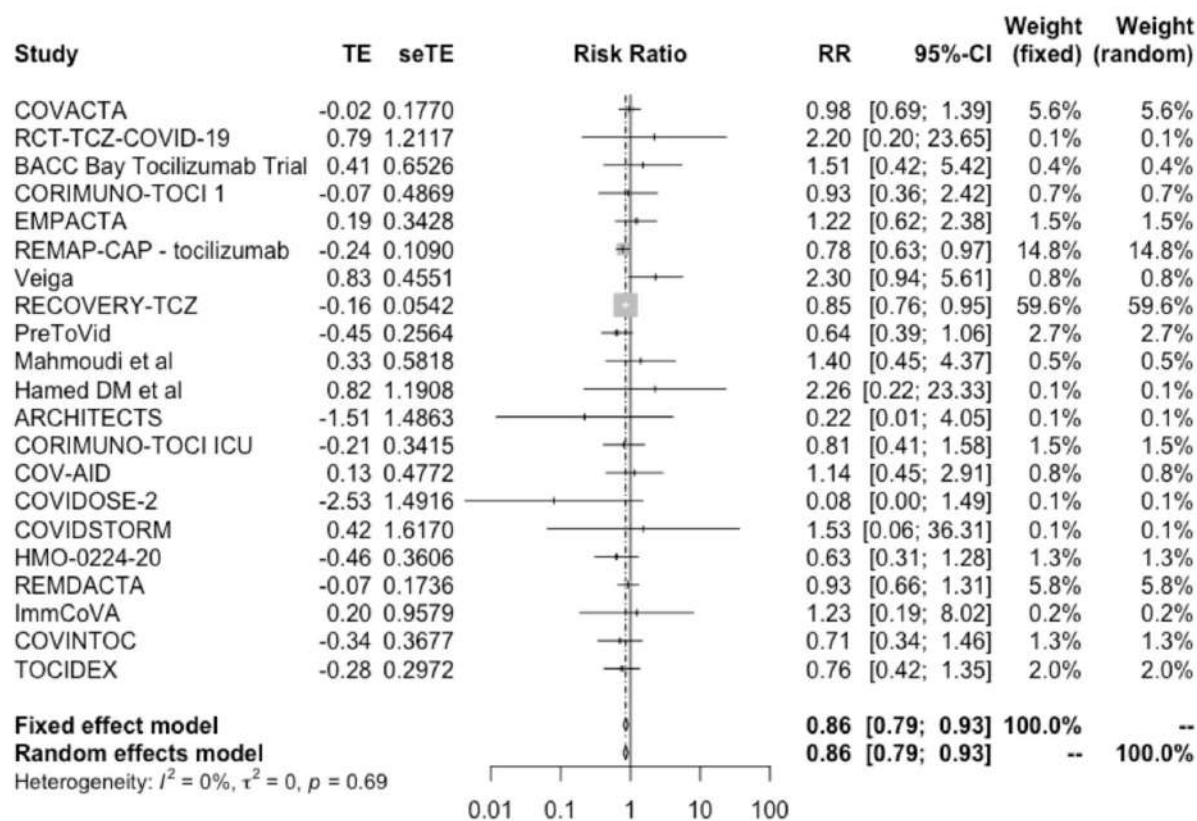
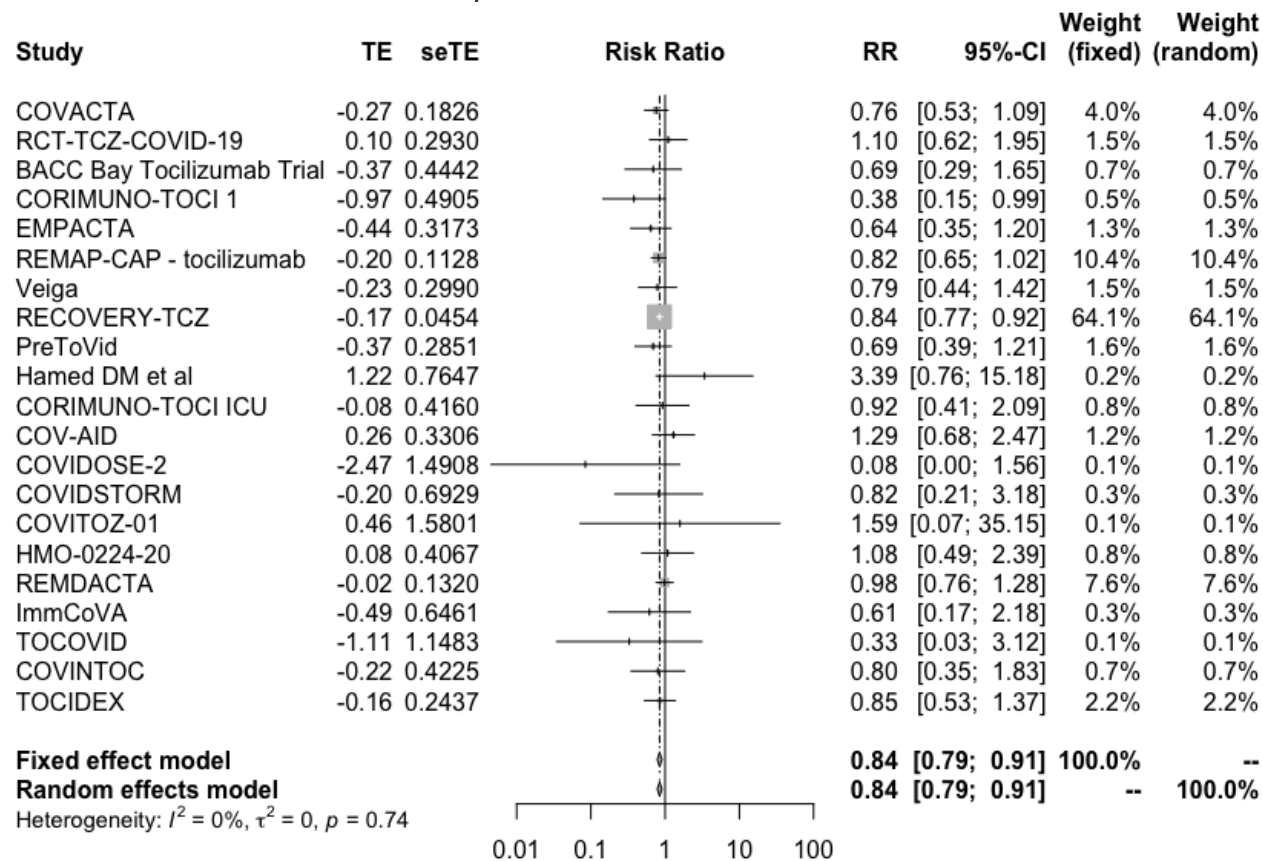


Figure 15. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



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

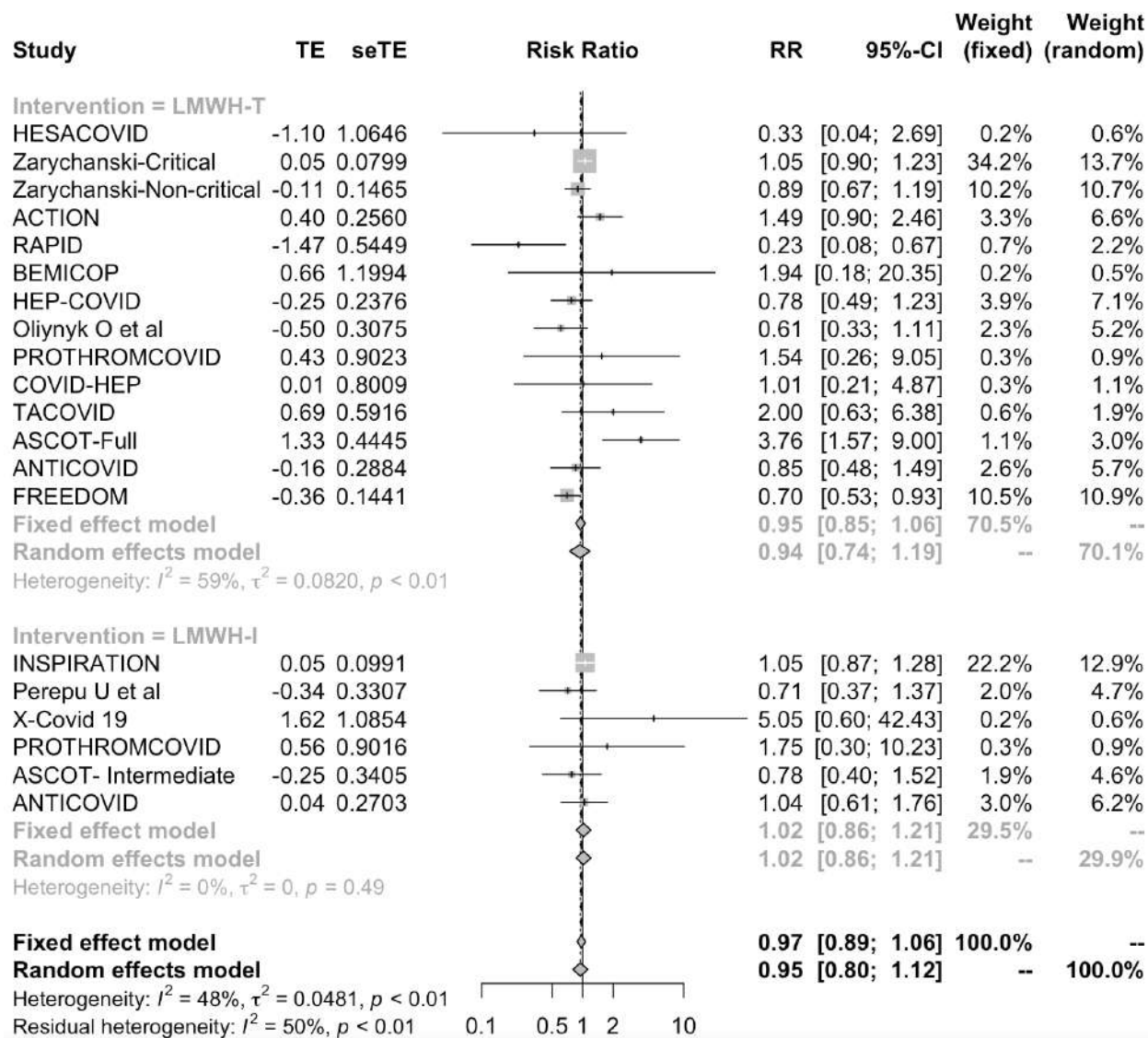
[See Summary of findings Table 7, Appendix 1](#)

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 28 RCTs including 15,863 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 and one study that assessed inhaled unfractionated heparin 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 0.95 (95%CI 0.8 to 1.12); RD -0.8% (95%CI -3.2% to 1.9%); Moderate certainty ⊕⊕⊕○ (Figure 16)
- 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 -1.9%); High certainty ⊕⊕⊕⊕
- In moderate to critical patients, anticoagulants in intermediate dose or full dose increase major bleeding in comparison with prophylactic dose, RR 1.66 (95%CI 1.2 to 2.3); RD 1.3% (95%CI 0.4% 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 1.09 (95%CI 0.81 to 1.47); RD 0.4% (95%CI -0.9% to 2.3%); Moderate certainty ⊕⊕⊕○
- In mild ambulatory patients it is uncertain if anticoagulants in prophylactic dose increase or decrease mortality, venous thromboembolic events and clinically important bleeding; 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



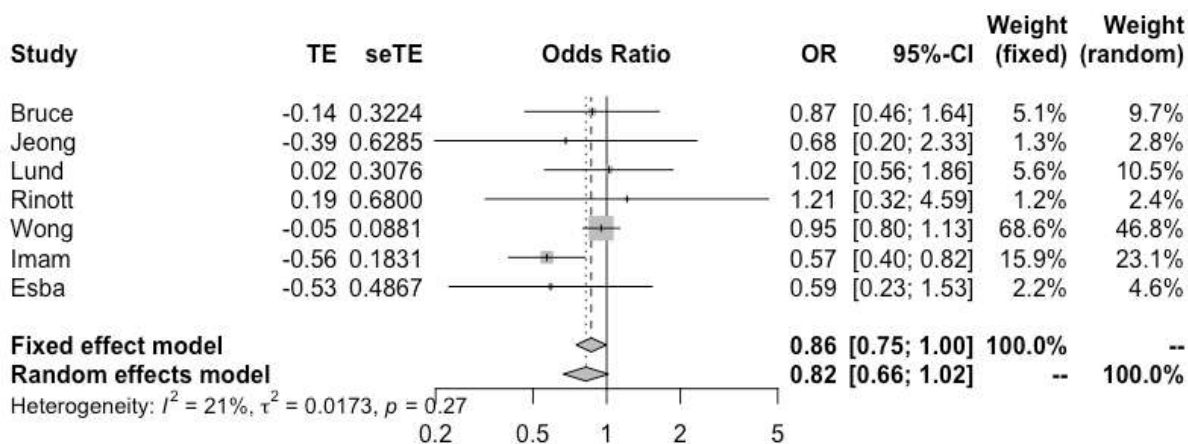
NSAIDs

[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



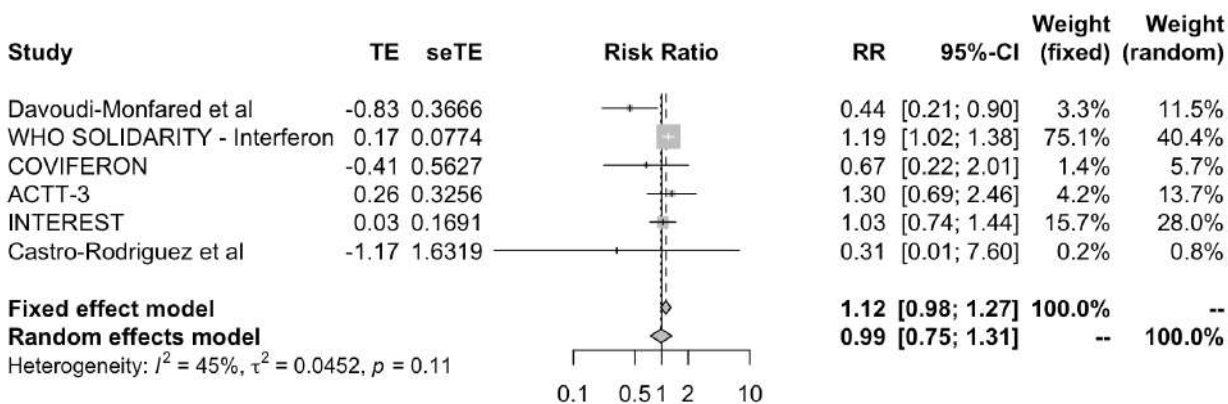
Interferon Beta-1a

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 ⊕⊕⊕○

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



Bamlanivimab +/- etesevimab (monoclonal antibody)

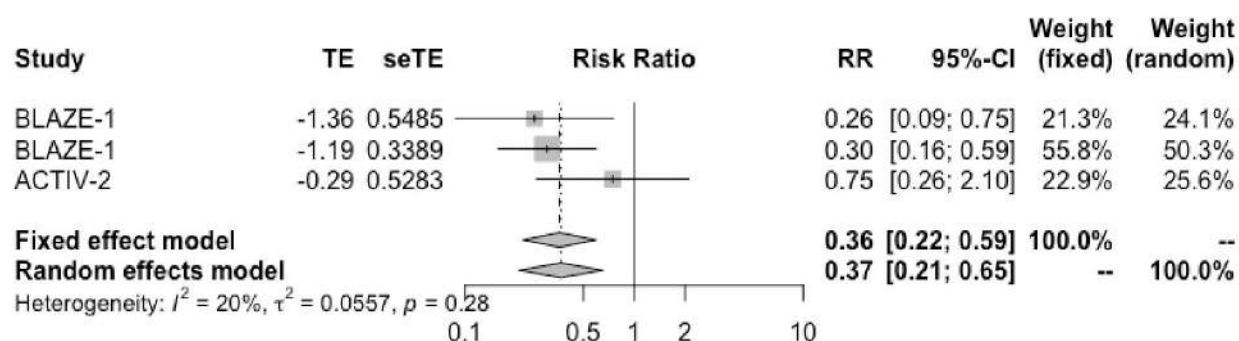
See Summary of findings Table 10, Appendix 1

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

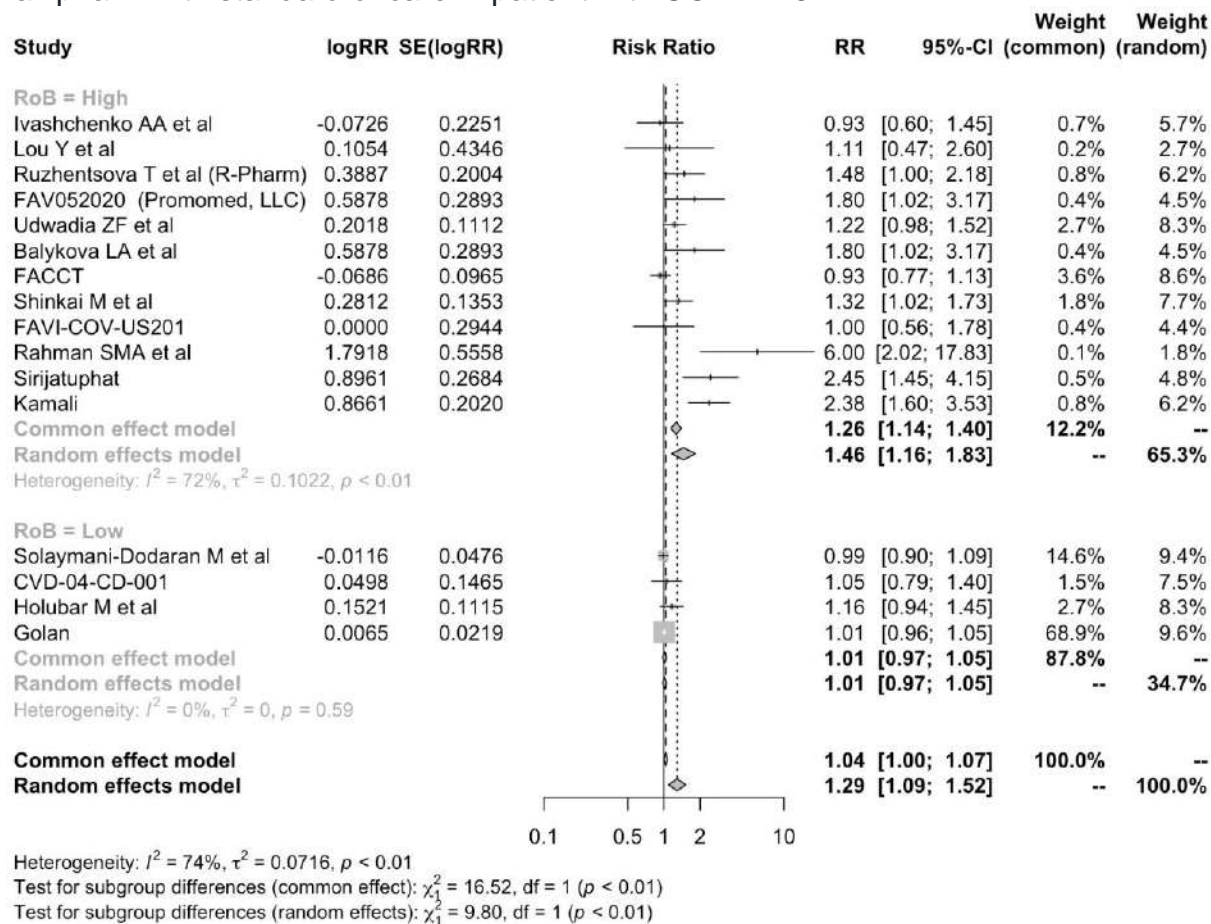
[See Summary of findings Table 11, Appendix 1](#)

We identified 31 RCTs including 5,798 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 1.09 (95%CI 0.76 to 1.54); RD 1.4% (95%CI -3.8% to 8.6%); Low certainty ⊕⊕○○ (based on low risk of bias studies)
- Favipiravir may increase mechanical ventilation requirements; RR 1.24 (95%CI 0.9 to 1.71); RD 4.2% (95%CI -1.7% to 12.3%); 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 increase hospitalizations in patients with non-severe disease; RR 1.46 (95%CI 0.82 to 2.62); RD 2.2% (95%CI -0.9% to 7.8%); 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 50 RCTs including 14,532 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 clinically important outcomes and some 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 1.25); RD -0% (95%CI -3.2% to 4%); 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 1.03 (95%CI 0.99 to 1.07); RD 1.8% (95%CI -0.6% to 4.2%); High certainty ⊕⊕⊕⊕ (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 probably does not increase severe adverse events, RR 1.1 (95%CI 0.73 to 1.65); RD 1% (95%CI -2.8% to 6.6%); Moderate certainty ⊕⊕⊕○
- Ivermectin does not have an important effect on hospitalizations in patients with recent onset non-severe disease, RR 0.91 (95%CI 0.75 to 1.11); RD -0.4% (95%CI -1.2% to 0.5%); High certainty ⊕⊕⊕⊕ (Figure 22)

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

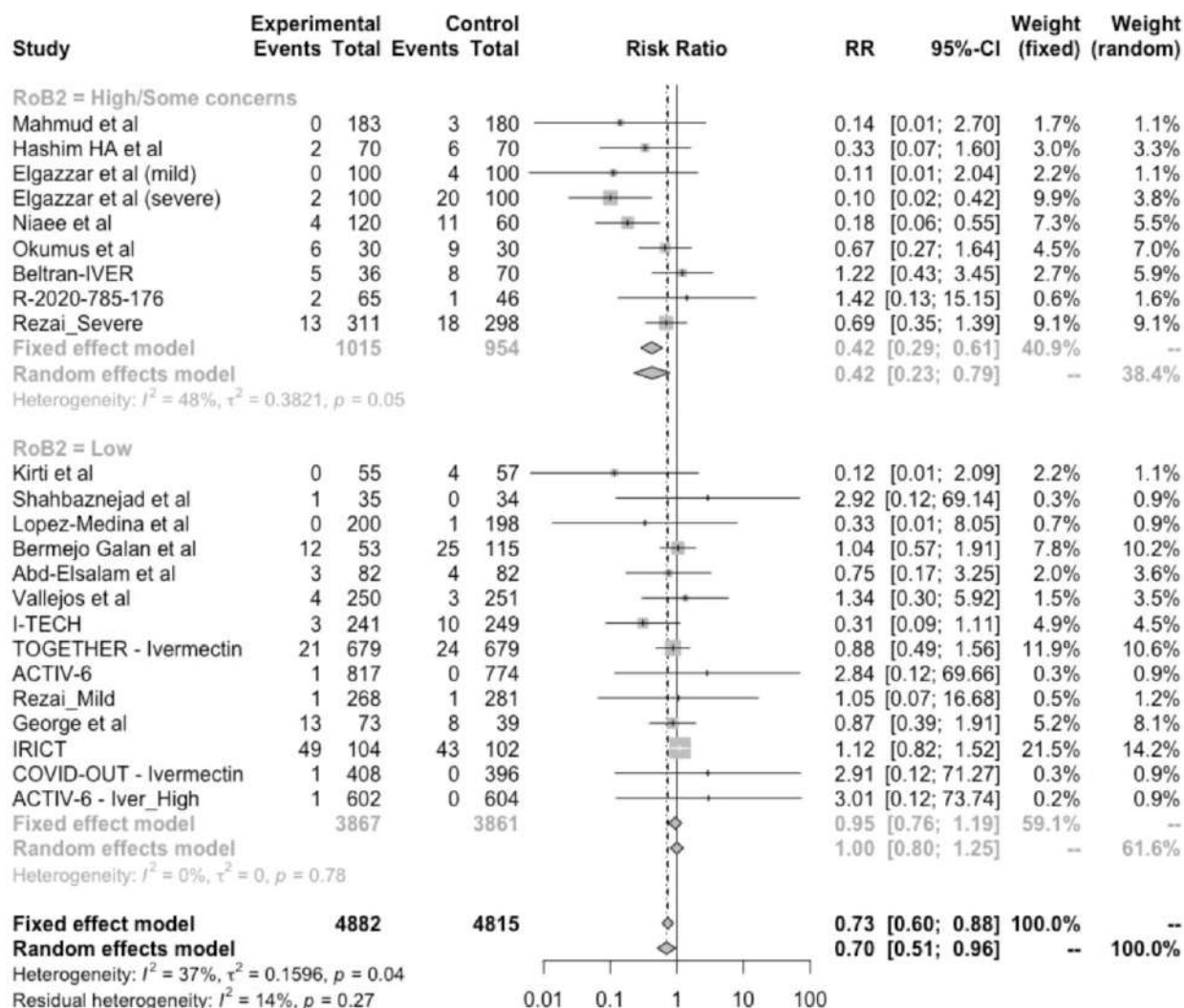
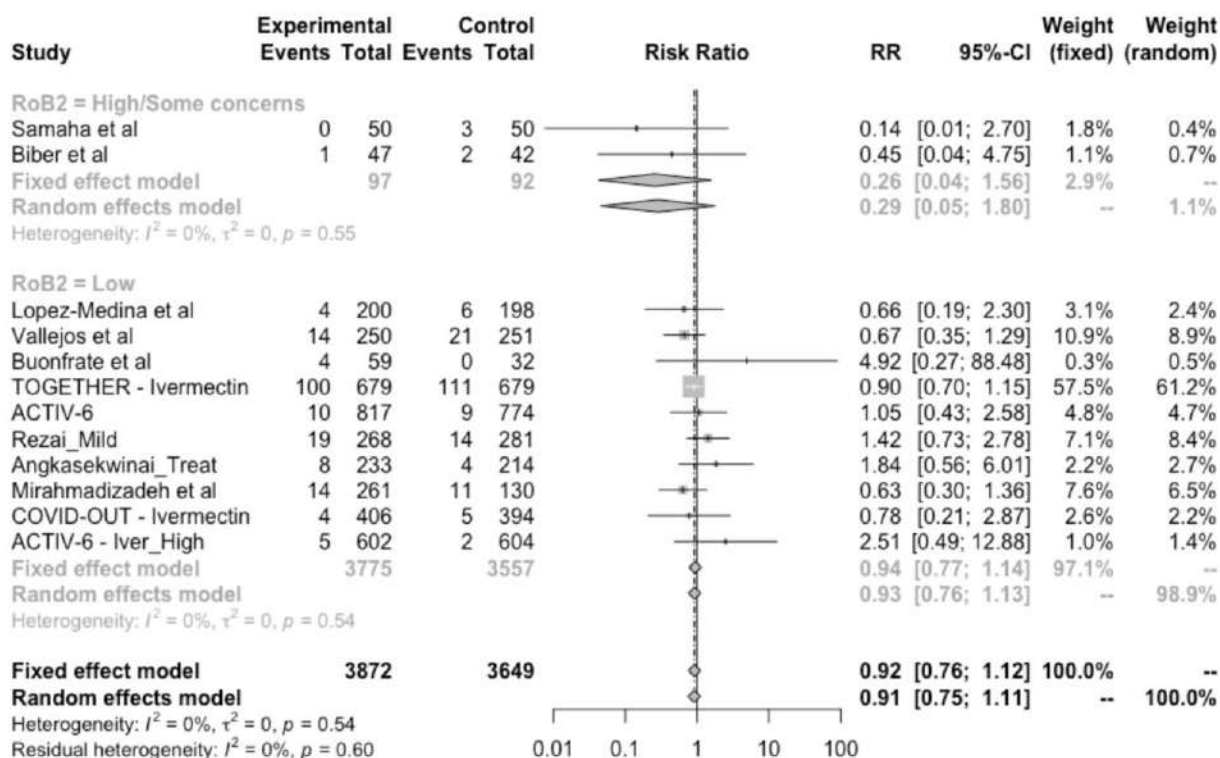


Figure 22. Hospitalizations in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



Baricitinib

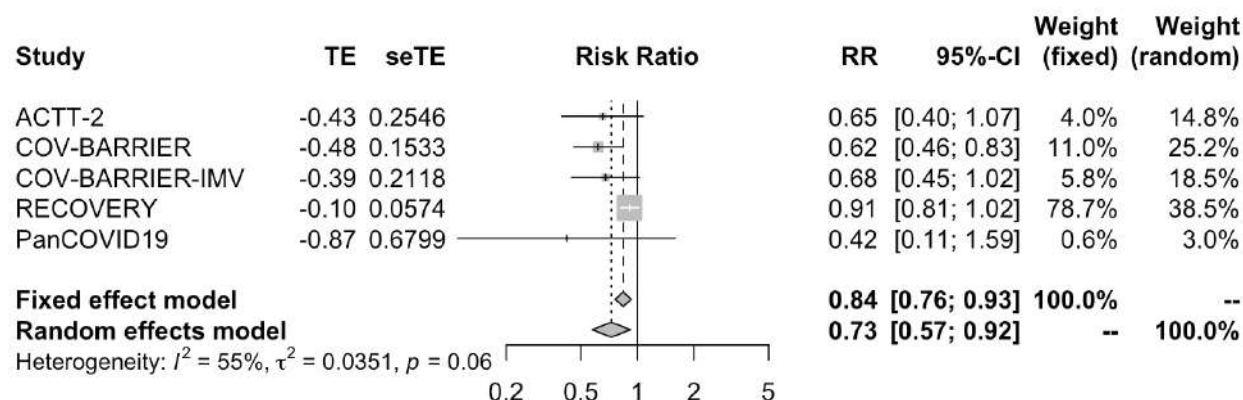
[See Summary of findings Table 13, Appendix 1](#)

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

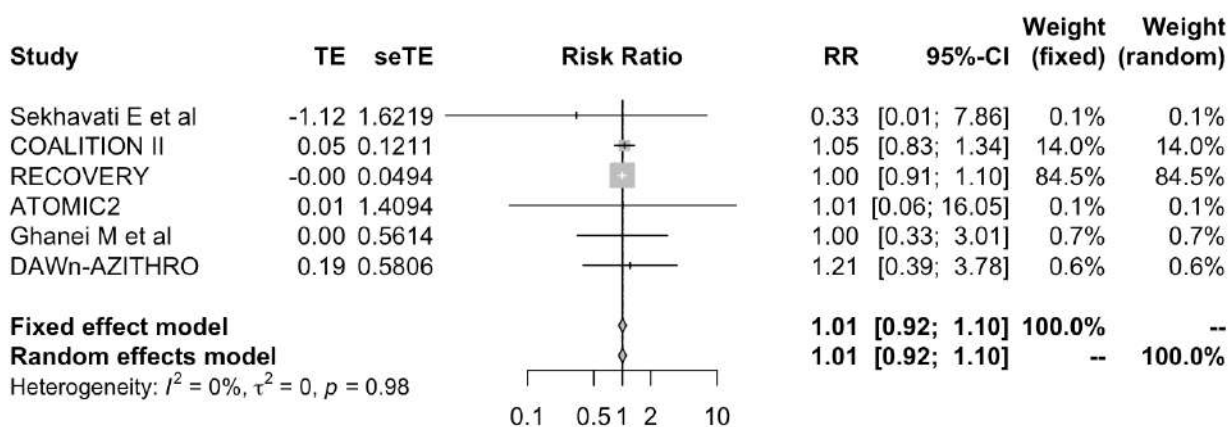
See Summary of findings Table 14, Appendix 1

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

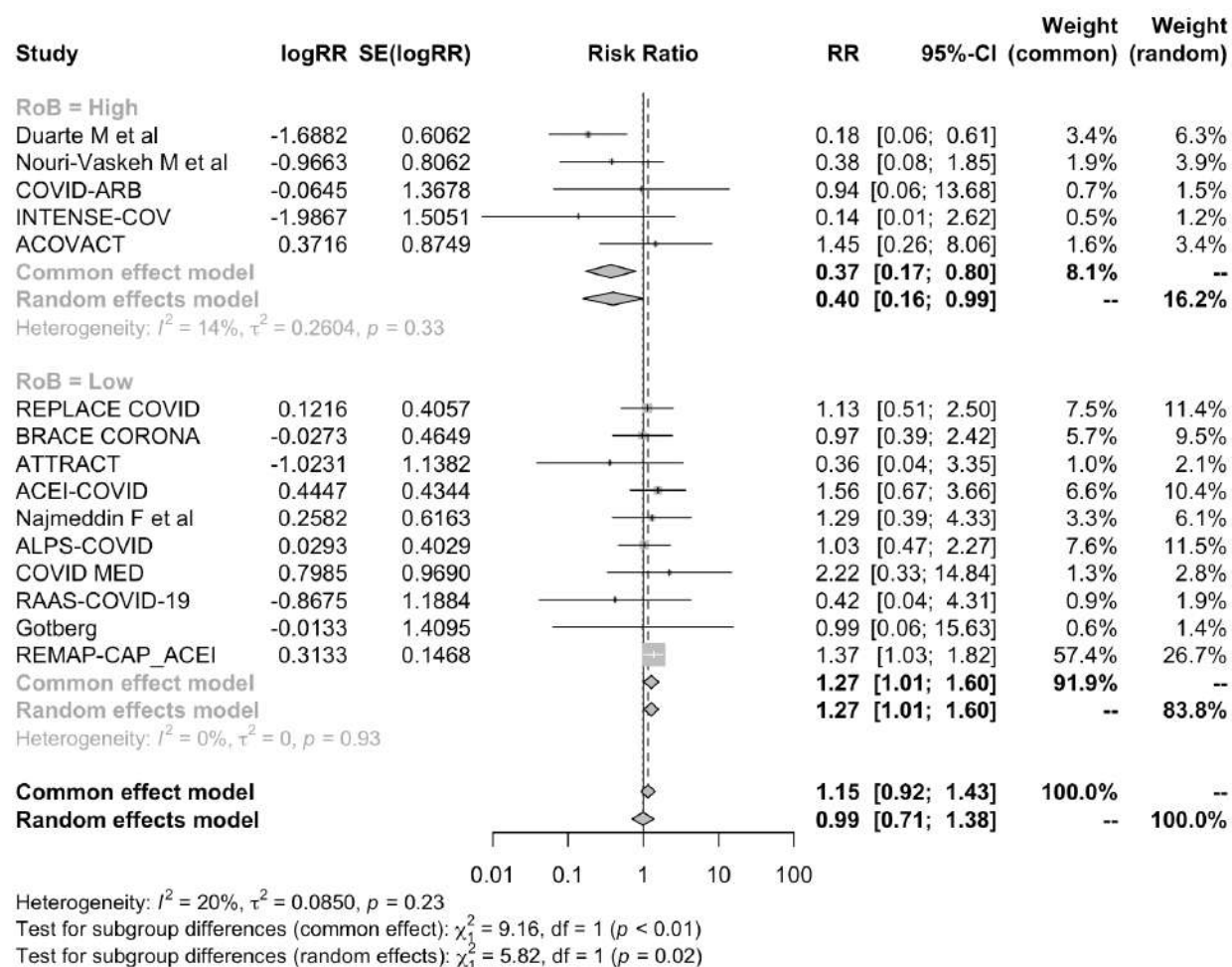


ACEI/ARB initiation or continuation

We identified 16 RCTs including 3,046 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 1.27 (95%CI 1.01 to 1.6); RD 4.3% (95%CI 0.2% to 9.6%); High 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 1.3); RD -0.2% (95%CI -4.3% to 5.2%); Low certainty ⊕⊕○○

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



Colchicine

[See Summary of findings Table 15, Appendix 1](#)

We identified 17 RCTs including 22,638 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 0.85 (95%CI 0.68 to 1.05); RD -1.5% (95%CI -3.3% to 0.5%); High certainty ⊕⊕⊕⊕
- It is uncertain if colchicine increases the risk of pulmonary embolism, RR 2.82 (95%CI 0.79 to 10.8); RD 0.2% (95%CI 0.02% to 0.8%); Very low certainty ⊕○○○
- Colchicine has no important effect on hospitalizations in patients with recent onset disease, RR 0.88 (95%CI 0.73 to 1.07); RD -0.6% (95%CI -1.3% to 0.3%); High certainty ⊕⊕⊕⊕

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

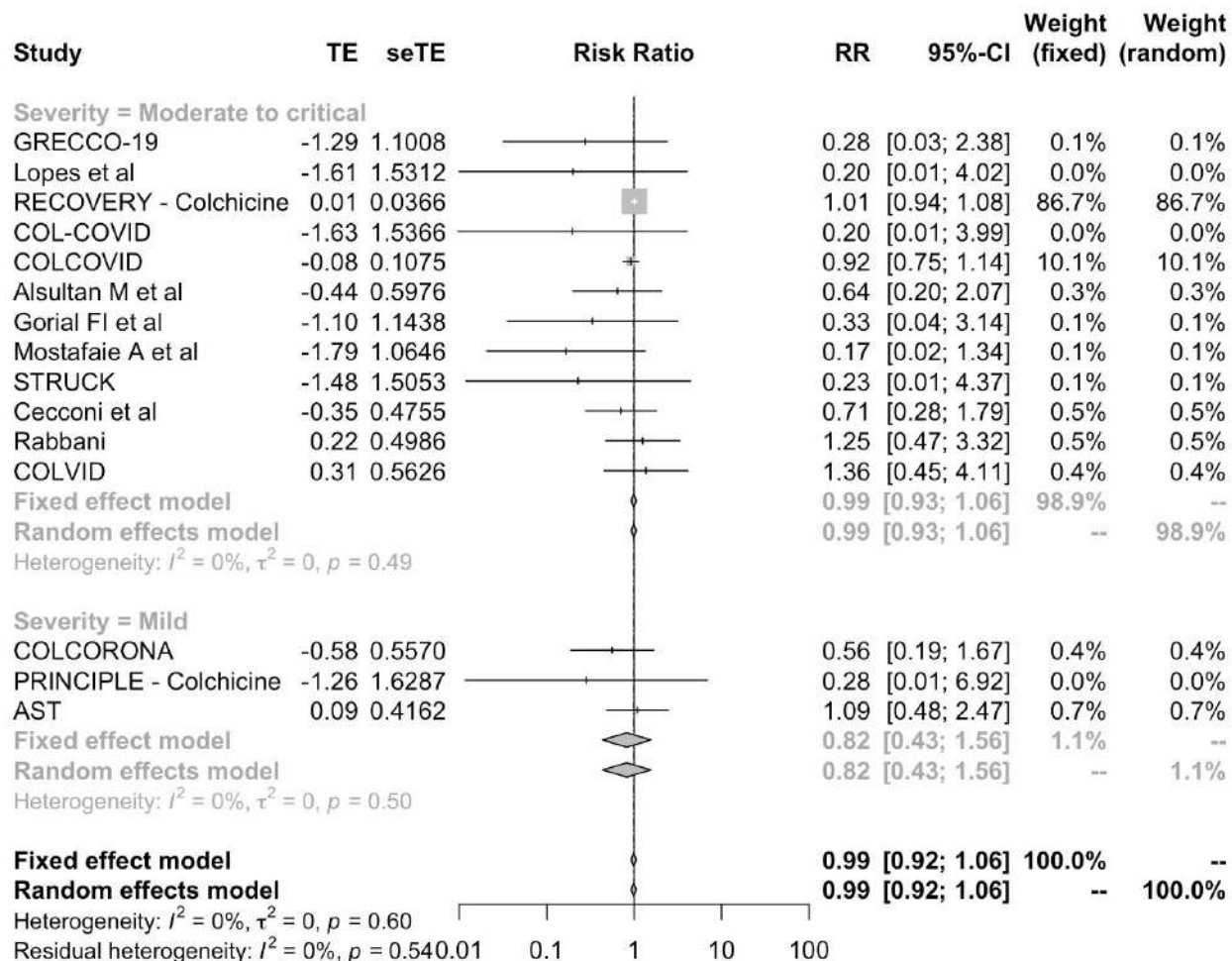
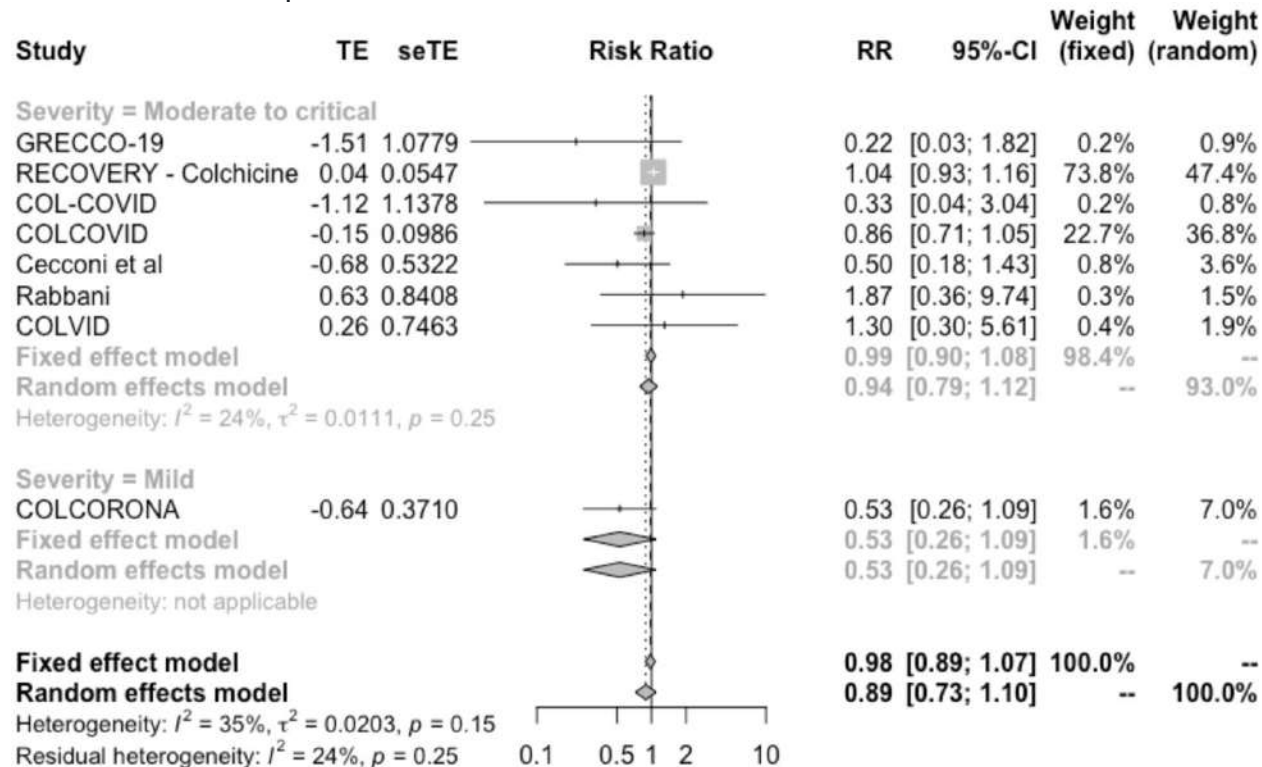


Figure 27. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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

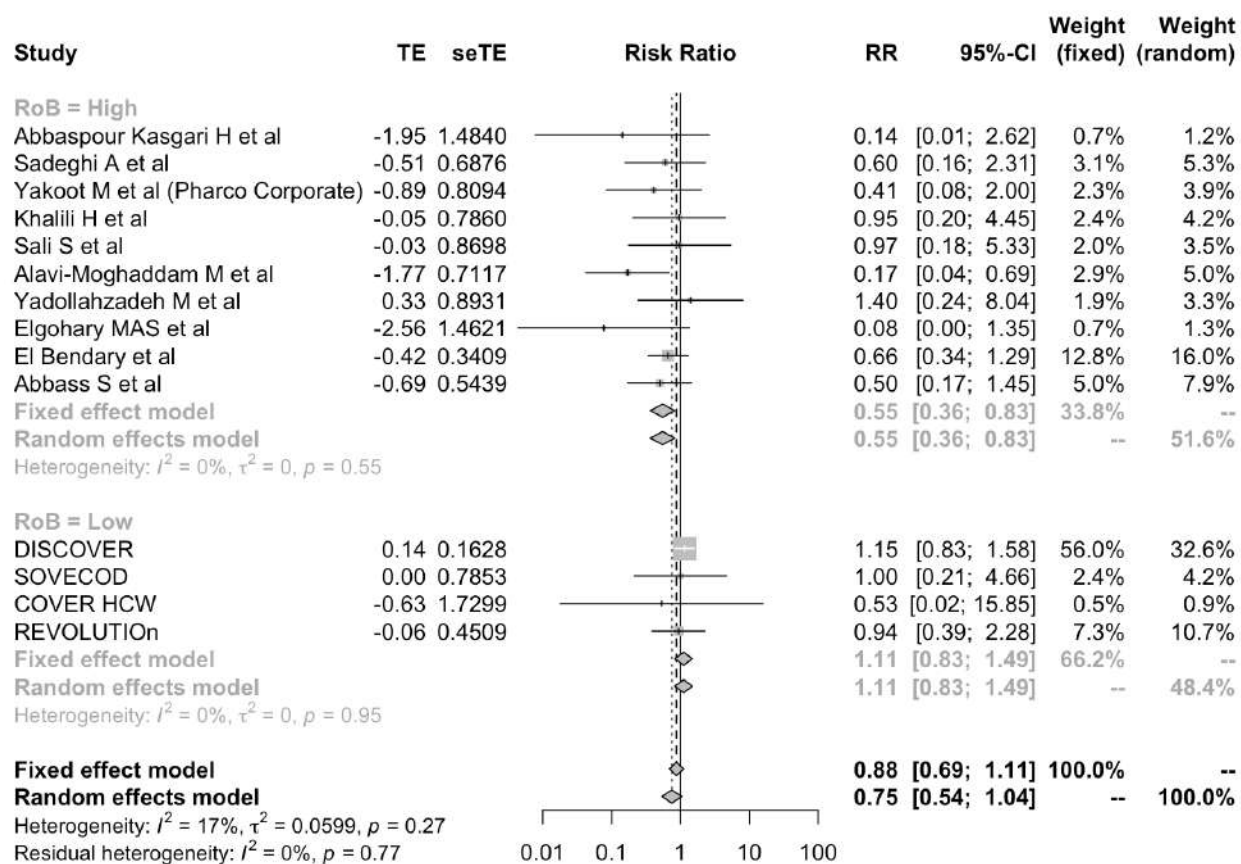
See Summary of findings Table 16, Appendix 1

We identified 17 RCTs including 3,184 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, eight 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 1.11 (95%CI 0.83 to 1.49); 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 0.85 (95%CI 0.31 to 2.34); RD -1.5% (95%CI -7% to 13.7%); 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

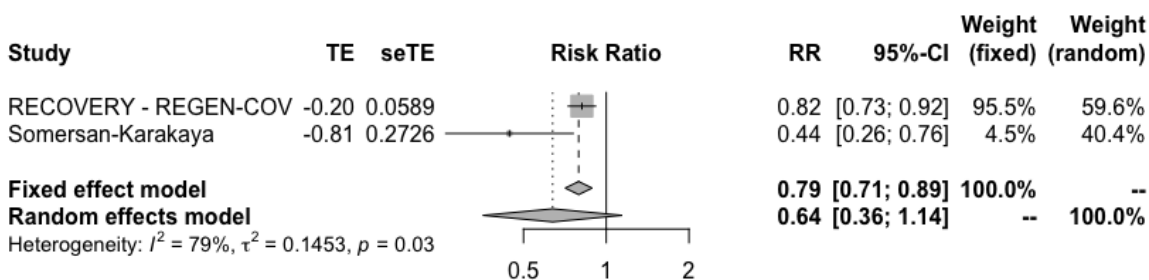
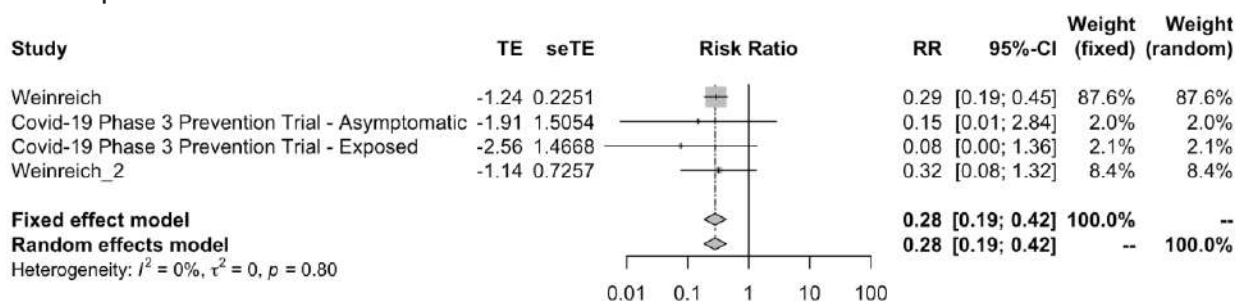


Figure 30. Hospitalization in randomized studies comparing REGEN-COV vs standard of care in patients with COVID-19



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

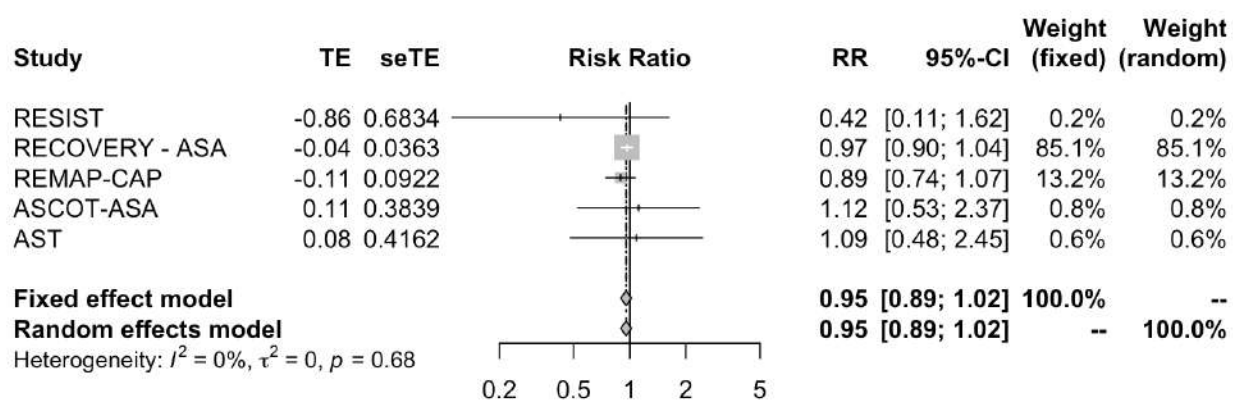
[See Summary of findings Table 18, Appendix 1](#)

We identified six RCTs including 21,454 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 ⊕⊕⊕○
- Aspirin probably does not have an important effect on hospitalizations, RR 0.8 (95%CI 0.57 to 1.11); RD -1% (95%CI -2.1% to 0.5%); Moderate certainty ⊕⊕⊕○. The observed effect would probably be considered important in patients with very high hospitalization risk (>10%).
- Aspirin probably may not increase adverse events, RR 1.1 (95%CI 0.71 to 1.73); RD 1% (95%CI -2.9% to 7.4%); Low certainty ⊕⊕○○

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



Sotrovimab

[See Summary of findings Table 19, 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). One study suggested no important differences in the risk of hospitalization or death between intramuscular sotrovimab and intravenous sotrovimab (RR 0.36, 95%CI 0.14 to 0.98; RD -1.1%, 95%CI -3.3% to 1.2%). However certainty of the evidence was low.

Mesenchymal stem-cells

[See Summary of findings Table 35, Appendix 1](#)

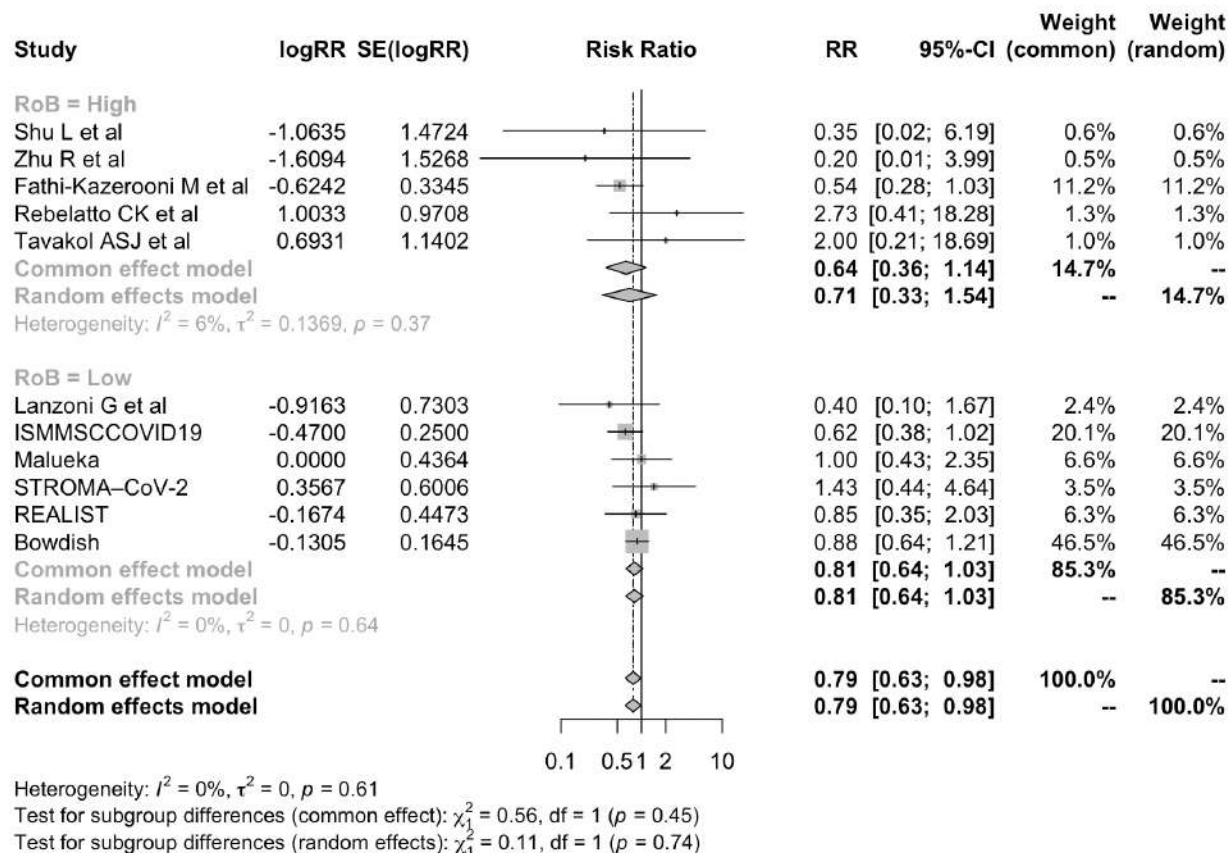
We identified thirteen RCTs including 706 patients with severe to critical COVID-19, in which mesenchymal stem-cells were compared against standard of care. Our results showed:

- Mesenchymal stem-cell transplantation probably reduces mortality, RR 0.82 (95%CI 0.64 to 1.03); RD -2.9% (95%CI -5.8% to 0.5%); Moderate certainty ⊕⊕⊕○ (Figure 32) (Low risk of bias studies)
- Mesenchymal stem-cell transplantation may not increase severe adverse events, RR 0.95 (95%CI 0.78 to 1.15); RD -0.5% (95%CI -2.2% to 1.5%); Low certainty ⊕⊕○○

Adverse events: RR 0.95 (95%CI 0.78 to 1.15); RD -0.5% (95%CI -2.2% to 1.5%); Low certainty ⊕⊕○○

Hospitalization: No information

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

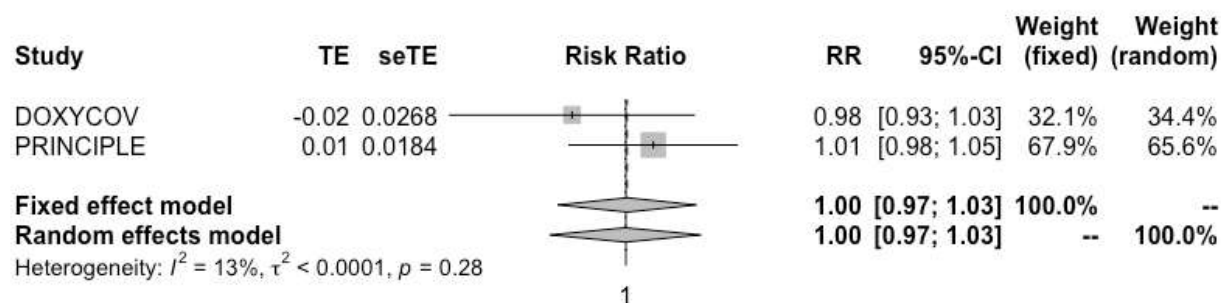


Doxycycline

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



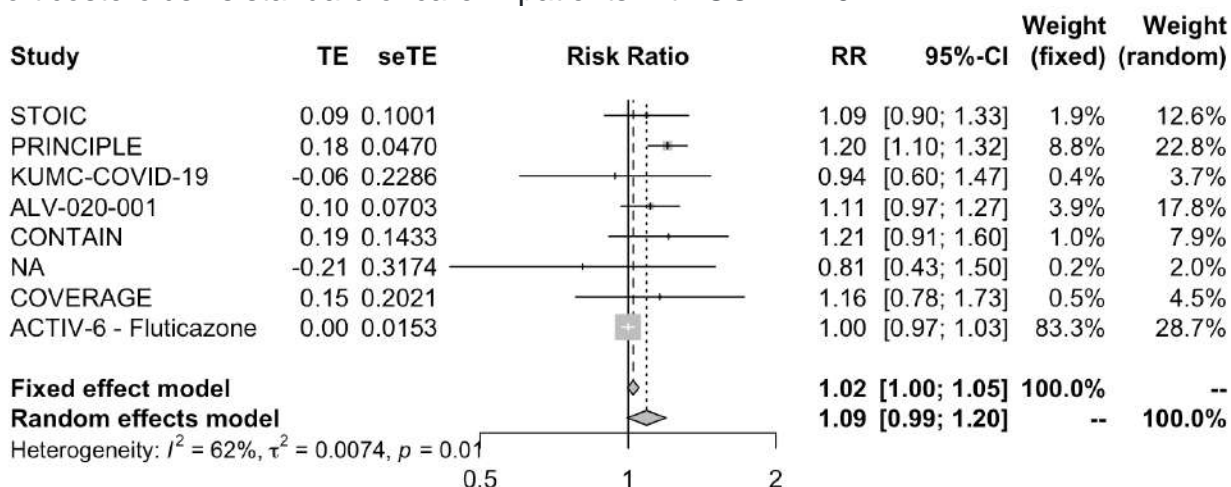
Inhaled corticosteroids

[See Summary of findings Table 20, Appendix 1](#)

We identified ten RCTs including 4,407 patients with mild COVID-19, in which inhaled corticosteroids were compared against standard of care. Our results showed:

- It is uncertain if inhaled corticosteroids reduce or increase mortality, RR 0.9 (95%CI 0.49 to 1.68); RD -1.6% (95%CI -8.2% to 10.9%); Very low certainty ⊕○○○
- It is uncertain if inhaled corticosteroids reduce or increase mechanical ventilation, RR 0.96 (95%CI 0.49 to 1.88); RD -0.7% (95%CI -8.8% to 15.2%); 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



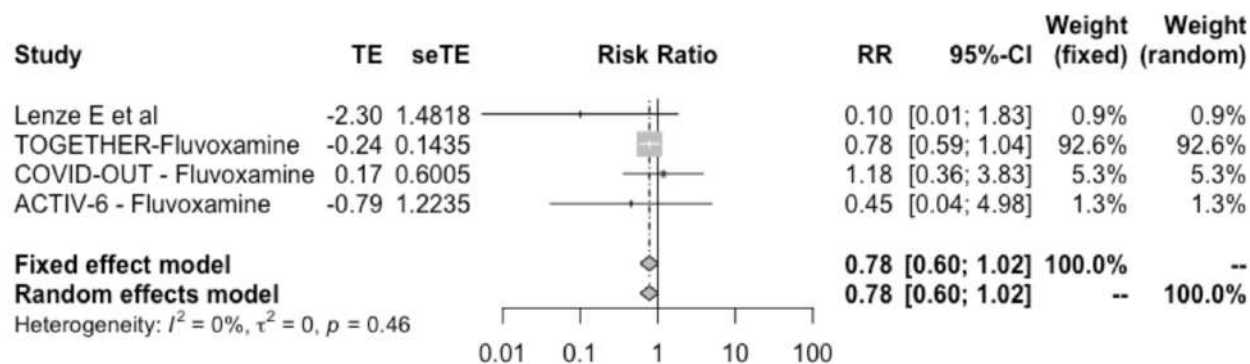
Fluvoxamine

[See Summary of findings Table 21, Appendix 1](#)

We identified six RCTs including 3,695 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 (>10%).
- 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



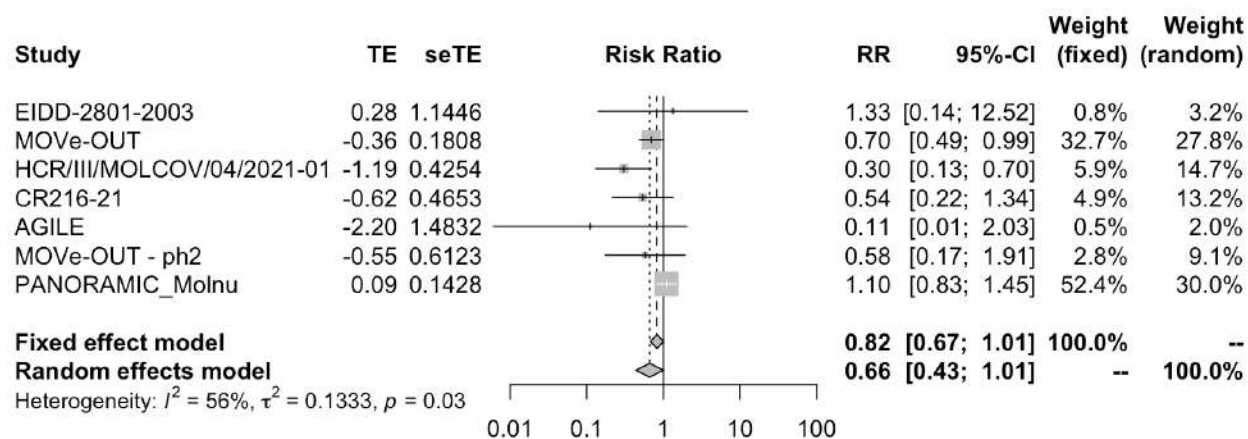
Molnupiravir

[See Summary of findings Table 22, 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). The observed effect would probably be considered important in patients with very high hospitalization risk (>10%).
- 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-ritonavir

[See Summary of findings Table 23, Appendix 1](#)

We identified two RCT including 2,349 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 0.44 (95%CI 0.16 to 1.21); RD -9% (95%CI -13.4% to 3.4%); Very low certainty ⊕○○○
- It is uncertain if nirmatrelvir-ritonavir reduces or increase mechanical ventilation requirements, RR 1.67 (95%CI 0.62 to 4.45); RD 11.5% (95%CI -6.5% to 59.8%); 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 0.53 (95%CI 0.33 to 0.87); RD -4.8% (95%CI -6.8% to -1.3%); Moderate certainty ⊕⊕⊕○

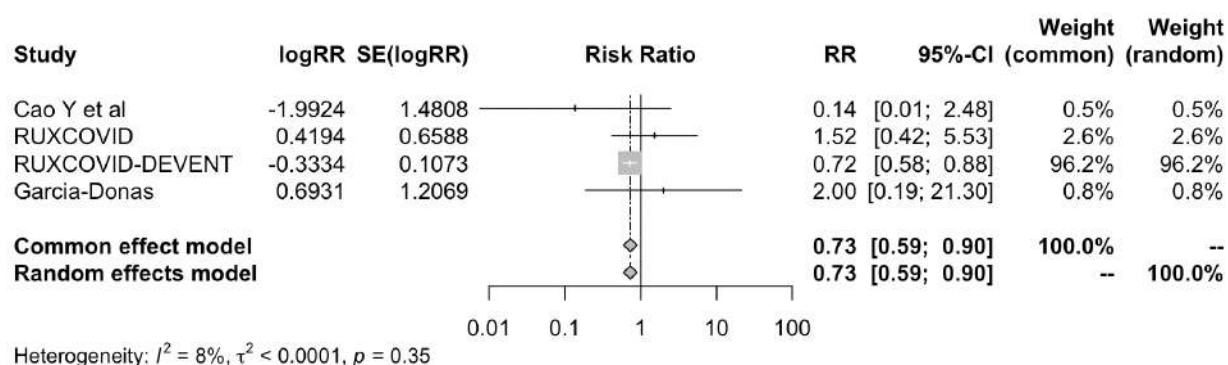
Ruxolitinib

[See Summary of findings Table 24, Appendix 1](#)

We identified Four RCTs including 777 patients with COVID-19, in which ruxolitinib was compared against standard of care. RUXOCVID-DEVENT was the biggest trial including 211 patients with critical COVID-19. Our results showed:

- Ruxolitinib may reduce mortality, RR 0.73 (95%CI 0.59 to 0.9); RD -4.3% (95%CI -6.6% to -1.6%); Low certainty ⊕⊕○○ (Figure 37)
- It is uncertain if ruxolitinib increases or decreases 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 (95%CI 0.94 to 1.07); RD 0% (95%CI -3.6% to 4.2%); Moderate certainty ⊕⊕⊕○
- It is uncertain if ruxolitinib increases 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 25, 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

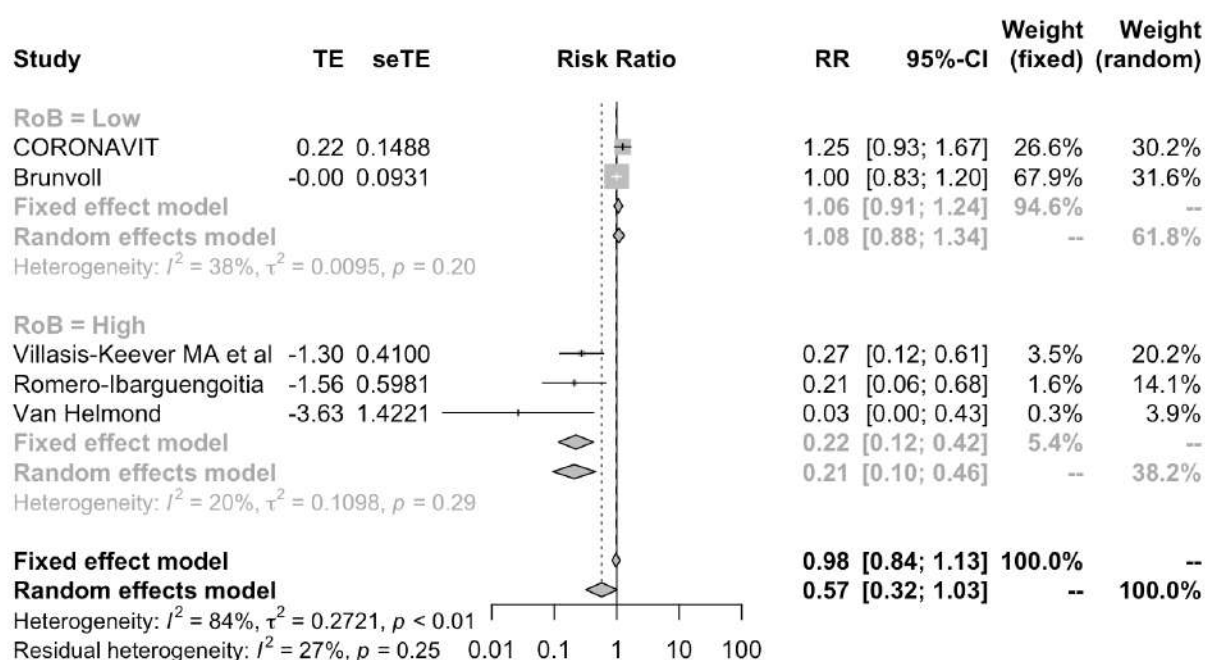
[See Summary of findings Table 26, Appendix 1](#)

We identified 24 RCTs including 44,533 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 1.08 (95%CI 0.79 to 1.48); RD 1.3% (95%CI -3.4% to 7.7%); 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.

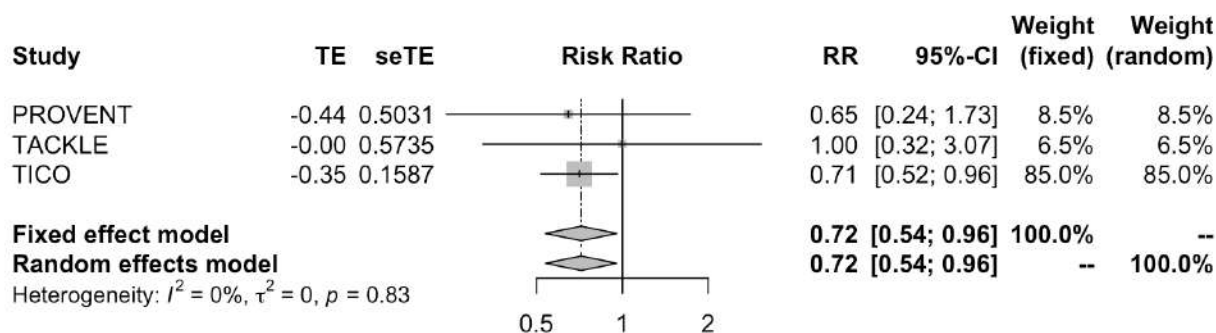
Tixagevimab–Cilgavimab

See Summary of findings Table 27, Appendix 1

We identified four RCT including 7,819 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 0.98 (95%CI 0.73 to 1.31); RD -0.2% (95%CI -2.8% to 3.2%); Low certainty ⊕⊕○○
- Tixagevimab–cilgavimab probably reduces hospitalizations, RR 0.42 (95%CI 0.26 to 0.69); RD -2.8% (95%CI -3.6% to -1.5%); Moderate certainty ⊕⊕⊕○

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



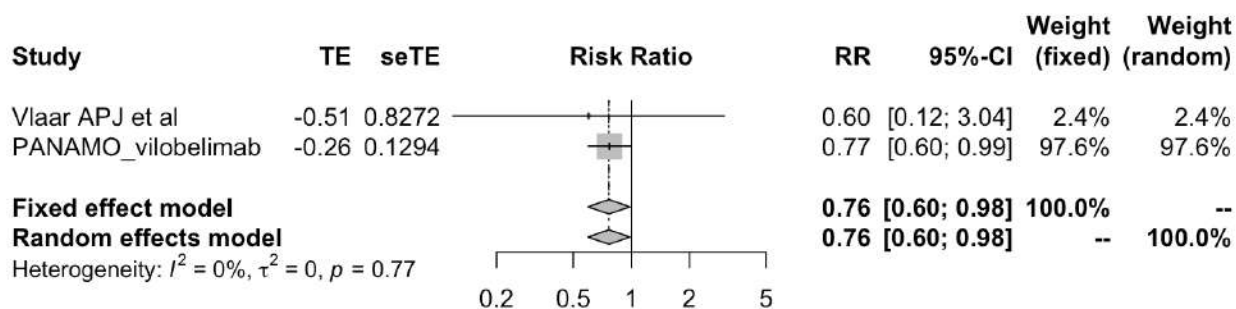
Vilobelimab

[See Summary of findings Table 28, 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



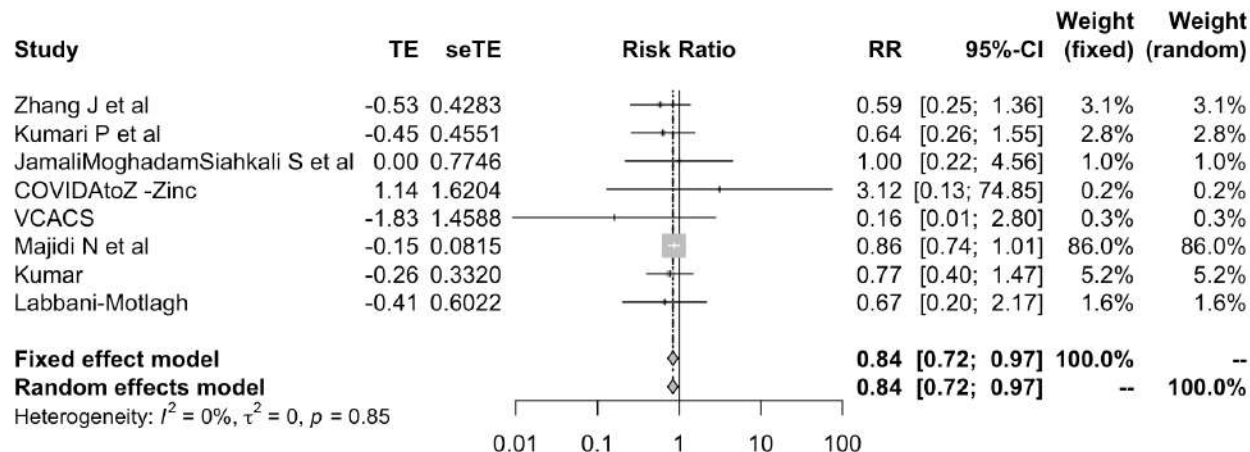
Vitamin C

[See Summary of findings Table 29, Appendix 1](#)

We identified eleven 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 0.97); RD -2.6% (95%CI -4.5% to -0.5%); 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



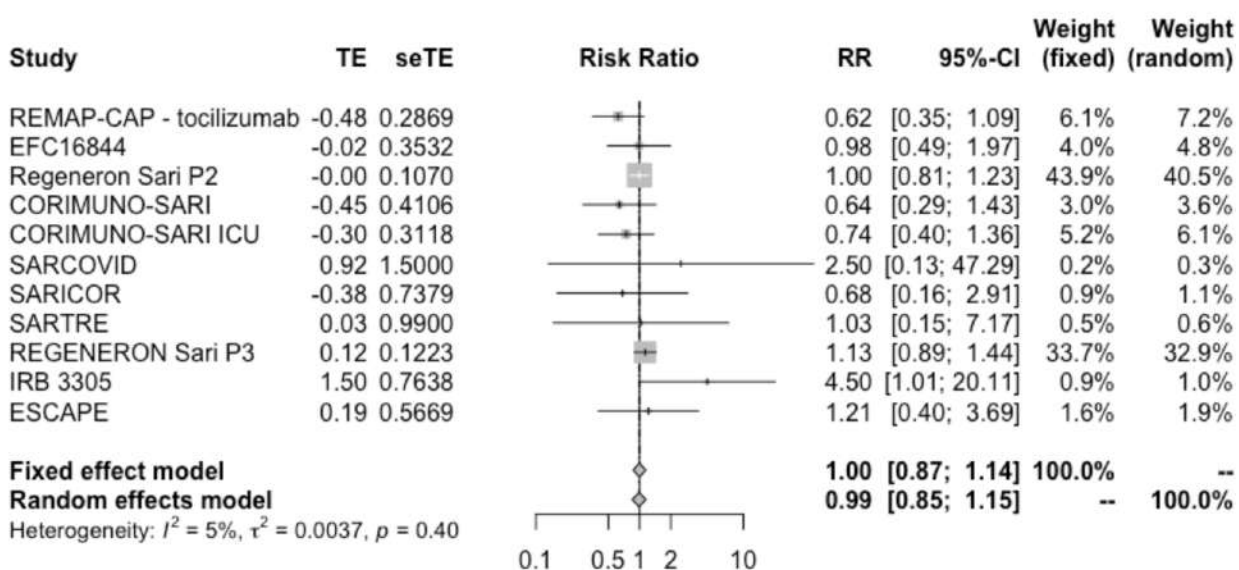
Sarilumab

[See Summary of findings Table 30, 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 31, 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 ⊕○○○

Peg-Interferon lambda

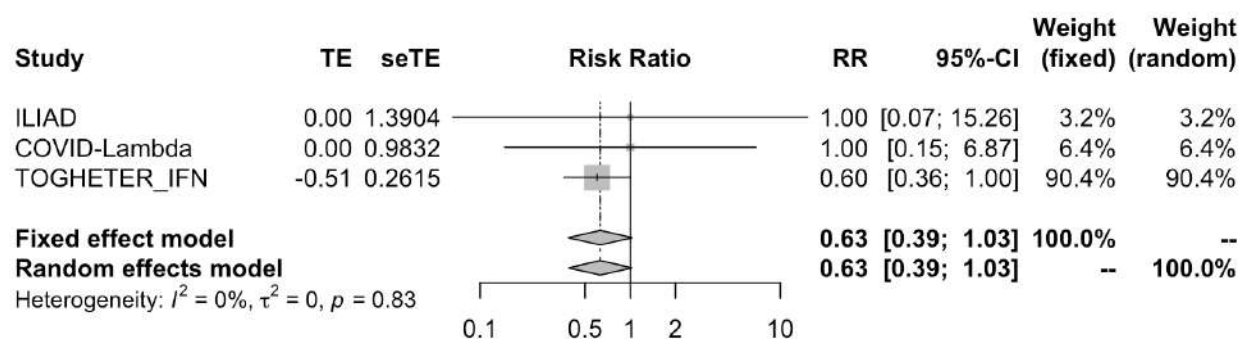
[See Summary of findings Table 32, Appendix 1](#)

We identified six RCT including 2162 individuals with COVID-19 in which Peg-Interferon lambda was compared against SOC. Our results showed:

- It is uncertain if Peg-Interferon lambda reduces or increases mortality, RR 0.73 (95%CI 0.21 to 2.58); RD -4.3% (95%CI -12.7% to 25.2%); Very low certainty ⊕○○○
- It is uncertain if Peg-Interferon lambda reduces or increases mechanical ventilation, RR 0.71 (95%CI 0.23 to 2.23); RD -5% (95%CI -13.3% to 21.3%); Very low certainty ⊕○○○

- Peg-Interferon lambda may not have an important effect on hospitalizations in patients with recent onset disease, RR 0.63 (95%CI 0.39 to 1.03); RD -1.8% (95%CI -2.9% to 0.1%); Low certainty ⊕○○○ (Figure 43). The observed effect would probably be considered important in patients with very high hospitalization risk (>10%).
- Peg-Interferon lambda may not increase severe adverse events, RR 0.76 (95%CI 0.5 to 1.16); RD -2.4% (95%CI -5.1% to 1.6%); Low certainty ⊕○○○.

Figure 43. Hospitalizations in randomized studies comparing Peg-Interferon lambda vs standard of care in patients with COVID-19



Empaglifozin

[See Summary of findings Table 33, Appendix 1](#)

We identified one RCT including 4271 individuals with COVID-19 in which empaglifozin was compared against SOC. Our results showed:

- Empaglifozin probably does not reduce mortality, RR 0.96 (95%CI 0.83 to 1.12); RD 0.6% (95%CI -2.7% to 1.9%); Moderate certainty ⊕⊕⊕○
- Empaglifozin probably does not reduce mechanical ventilation, RR 1.01 (95%CI 0.8 to 1.27); RD 0.1% (95%CI -3.5% to 4.7%); Moderate certainty ⊕⊕⊕○

- Empaglifozin probably does not increase symptom resolution, RR 1.02 (95%CI 1 to 1.05); RD 1.3% (95%CI -0.6% to 3.3%); Moderate certainty ⊕⊕⊕○

Amubarvimab + romlusevimab

See Summary of findings Table 34, Appendix 1

We identified one RCT including 807 individuals with recent onset COVID-19 in which amubarvimab + romlusevimab was compared against SOC. Our results showed:

- It is uncertain if amubarvimab + romlusevimab reduces or increases mortality, RR 0.06 (95%CI 0.004 to 1.05); RD -15% (95%CI -15.9% to 0.8%); Very low certainty ⊕○○○
- Amubarvimab + romlusevimab probably reduces hospitalizations, RR 0.21 (95%CI 0.10 to 0.43); RD -3.8% (95%CI -4.3% to -2.8%); Moderate certainty ⊕⊕⊕○
- Amubarvimab + romlusevimab probably does not increase severe adverse events, RR 0.21 (95%CI 0.10 to 0.43); RD -3.8% (95%CI -4.3% to -2.8%); Moderate 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
Acebilustat 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					

<p>Levitt et al;¹⁶ peer reviewed; 2023</p>	<p>Patients with mild to moderate COVID-19 infection. 60 assigned to acebilustat 100 mg a day for 28 days and 60 assigned to SOC</p>	<p>Mean age 41 ± 13.5, male 35%, obesity 20.8%</p>	<p>Vaccinated 91.7%</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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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 ; ¹⁷ 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.	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

Adintrevimab

Adintrevimab may reduce hospitalizations and may not increase severe adverse events. 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 (standard of care) and GRADE certainty of the evidence
RCT					
STAMP trial ; ¹⁸ Ison et al; peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 169 assigned to Adintrevimab 300 mg once and 167 assigned to SOC	Median age 57, male 65.2%, diabetes 13.1%, COPD 8.9%, CHD 14.6%, CKD 0.6%, cerebrovascular disease 3.9%, immunosuppression 2.7%, obesity 57.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.44 (95%CI 0.24 to 0.82); RD -5.7% (95%CI -7.8% to -1.8%); Low certainty ⊕⊕○○</p> <p>Hospitalization: RR 0.34 (95%CI 0.16 to 0.75); RD -3.2% (95%CI -4% to -1.2%); Low certainty ⊕⊕○○</p>

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 ; ¹⁹ 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	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>

Amantadine

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					
Barczyk et al. ²⁰ peer reviewed; 2023	Patients with moderate to severe COVID-19 infection. 95 assigned to amantadine 100 mg a day for 10 days and 91 assigned to SOC	Mean age 58, male 73%, hypertension 43.5%, diabetes 23.1%, COPD 11.8%, CHD 7%, obesity 30.1%	Remdesivir 51%, convalescent plasma 0.5%;	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>

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					

<p>ReCOVery-SIRIO trial;²¹ Navarese et al; peer reviewed; 2022</p>	<p>Patients with moderate to severe COVID-19 infection. 71 assigned to amiodarone 200 to 400 mg a day and 72 assigned to SOC</p>	<p>Median age 61.3 , male 62.3%, diabetes 23.7%, COPD 6.5%, cancer 7%,</p>	<p>Remdesivir 1.9%, hydroxychloroquine 2.3%, azithromycin 6%, convalescent plasma 1.9%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Siami et al.;²² peer reviewed; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 60 assigned to ammonium chloride 125 mg and 60 assigned to SOC</p>	<p>NR</p>	<p>Corticosteroids 100%,</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Blinding and concealment probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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					

<p>AP-014 trial;²³ Roshon et al; peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 64 ± 15, male 62.5%</p>	<p>Corticosteroids 78%, remdesivir 40%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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Amubarvimab + romlusevimab

Amubarvimab + romlusevimab probably reduces hospitalizations 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 (standard of care) and GRADE certainty of the evidence
RCT					

<p>ACTIV-2 trial;²⁴ Evering et al; peer reviewed; 2023</p>	<p>Patients with mild to moderate COVID-19 infection. 397 assigned to amubarvimab + romlusevimab 1000/1000 mg once and 410 assigned to SOC</p>	<p>Median age 49, male 49.3%, hypertension 35.7%, diabetes 13.6%, COPD 10.8%, CHD 2.8%, CKD 0.3%, immunosuppression 2.3%, cancer 0.8%, obesity 26.1%</p>	<p>Vaccinated 8.2%</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.24 (95%CI 0.12 to 0.47); RD - 7.7% (95%CI - 8.9% to -5.4%); Moderate certainty ⊕⊕⊕○</p> <p>Hospitalization: RR 0.21 (95%CI 0.10 to 0.43); RD - 3.8% (95%CI - 4.3% to -2.8%); Moderate certainty ⊕⊕⊕○</p>
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Anakinra

Anakinra may not increase severe adverse events. However the certainty of the evidence was low because of risk of bias and imprecision. 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 (standard of care) and GRADE certainty of the evidence
RCT					

<p>CORIMUNO-ANA-1 trial;²⁵ Bureau et al; Peer reviewed; 2020</p>	<p>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</p>	<p>Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD 31.6%, cancer 9.6%,</p>	<p>Corticosteroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%, tocilizumab 0.8%, azithromycin 24.6%,</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
<p>SAVE-MORE trial;²⁶ Kyriazopoulou et al; preprint; 2021</p>	<p>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</p>	<p>Mean age 61.9 ± 12.1, male 57.9%, diabetes 15.8%, COPD 4%, asthma %, CHD 3%, CKD 1.7%</p>	<p>Corticosteroids 86.2%, remdesivir 71.9%, azithromycin 18.7%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 1.03 (95%CI 0.82 to 1.28); RD 0.3% (95%CI -1.8% to 2.9%); Low certainty ⊕⊕○○</p>
<p>COV-AID-3 trial;²⁷ Declercq et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 112 assigned to anakinra 100 mg a day for 28 days and 230 assigned to SOC</p>	<p>Mean age 65.5, male 77.4%, hypertension 46.4%, diabetes 27.7%, COPD %, CHD 20.5%, CKD 10.8%</p>	<p>Corticosteroids 62.3%, remdesivir 5%, hydroxychloroquine 11.7%,</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Hospitalization: No information</p>
<p>Kharazmi et al;²⁸ peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 54.1, male 63.3%, hypertension 33.3%, diabetes 36.6%, CHD 26.6%</p>	<p>Corticosteroids 63.3%, remdesivir 20%, lopinavir-ritonavir 63.3%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	

<p>Zeyad et al.²⁹ preprint; 2022</p>	<p>Patients with severe to critical COVID-19 infection. 40 assigned to anakinra 200 mg a day for 3 days and 40 assigned to SOC</p>	<p>Mean age 49.9 ± 11.7, male 82.5%, diabetes 43.8%, COPD 1.3%, CHD 8.8%, CKD 1.3%</p>	<p>Corticosteroids 100%, remdesivir 83.8%, azithromycin 78.8%, convalescent plasma 67.5%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>
<p>ANACONDA trial;³⁰ Audemard-Verger et al; peer reviewed; 2022</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 63.4%, hydroxychloroquine 1.5%, azithromycin 12.6%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>
<p>ANA-COVID-GEAS trial;³¹ Fanlo et al; peer reviewed; 2023</p>	<p>Patients with severe COVID-19 infection. 89 assigned to anakinra 400 mg a day for up to 15 days and 87 assigned to SOC</p>	<p>Mean age 60.5 ± 11.5, male 69.9%, hypertension 39.8%, diabetes 14.2%, COPD 8%, asthma 10.2%, CHD 17%, CKD 6.3%, cancer 6.8%,</p>	<p>Corticosteroids 57.4%, remdesivir 18.2%, hydroxychloroquine 5.7%, lopinavir-ritonavir 4.5%, azithromycin 11.2%</p>	<p>Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)

Continuing or initiating ACEIs or ARBs in patients with COVID-19 increases mortality and may not reduce mechanical ventilation.

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 ; ³² 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 1.27 (95%CI 1.01 to 1.6); RD 4.3% (95%CI 0.2% to 9.6%); High certainty ⊕⊕⊕⊕ Invasive mechanical ventilation: RR 0.99 (95%CI 0.75 to 1.3); RD -0.2% (95%CI -4.3% to 5.2%); Low certainty ⊕⊕○○
BRACE CORONA trial ; ³³ 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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty

<p>ACEI-COVID trial;³⁴ Bauer et al; peer reviewed; 2021</p>	<p>Patients with mild to severe COVID-19 infection. 100 assigned to continuation of ACEI/ARB and 104 assigned to discontinuation of ACEI/ARB</p>	<p>Mean age 72 ± 11, male 63%, hypertension 98%, diabetes 33%, CHD 22%</p>	<p>Remdesivir 6.8%</p>	<p>Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>⊕○○○</p>
<p>ATTRACT trial;³⁵ Tornling et al; peer reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200 mg a day for 7 days and 55 assigned to SOC</p>	<p>Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%</p>	<p>Corticosteroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events</p>	
<p>Nouri-Vaskeh et al;³⁶ Peer reviewed; 2020</p>	<p>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</p>	<p>Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	
<p>SURG-2020-28683 trial;³⁷ Puskarich et al; Preprint; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 58 assigned to losartan 25 mg a day for 10 days and 59 assigned to SOC</p>	<p>Age (35-54) 46%, male 51.4%, hypertension 7.7%, diabetes 6%, COPD %, asthma 10.2%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events</p>	

<p>COVID-ARB trial;³⁸ Geriak et al; peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 16 assigned to losartan 25 mg a day for 10 days and 15 assigned to SOC</p>	<p>Median age 53, male %, hypertension 38.7%, diabetes 25.8%, CHD 3.2%, obesity 41.9%</p>	<p>Corticosteroids 22.6%, remdesivir 29%, hydroxychloroquine 9.7%, , azithromycin 16.1%, convalescent plasma 6.5%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>
<p>Duarte et al;³⁹ peer reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19 infection. 71 assigned to telmisartan 80 mg twice daily and 70 assigned to SOC</p>	<p>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%</p>	<p>Corticosteroids 50.6%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>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.</p>
<p>Najmeddin et al;⁴⁰ peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 28 assigned to continuation of ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB</p>	<p>Mean age 66.3 ± 9.9, male 46.9%, diabetes 50%, COPD 1.6%, CHD 25%, CKD 1.6%, cancer 4.7%,</p>	<p>Corticosteroids 42.2%, remdesivir 10.9%, , azithromycin 9.4%,</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events</p> <p>Notes: 10.9% lost to follow-up</p>
<p>ALPS-COVID trial;⁴¹ Puskarich et al; peer reviewed; 2021</p>	<p>Patients with moderate COVID-19 infection. 101 assigned to ACEI/ARB losartan 100 mg a day and 104 assigned to SOC</p>	<p>Mean age 55, male 60%, hypertension 42%, diabetes 22.9%, COPD 11.7%, asthma 13.2%, CHD 7.8%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>

<p>COVID MED trial;⁴² Freilich et al; preprint; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 9 assigned to losartan 25 mg and 5 assigned to SOC</p>	<p>Mean age 63, male 64.2%, diabetes 7.1%, COPD 42.9%, asthma %, CHD 42.9%, CKD 0%, immunosuppression 35.7%, obesity 14.2%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	
<p>RAAS-COVID-19 trial;⁴³ Sharma et al; peer reviewed; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 25 assigned to continuation of ACEI/ARB and 21 assigned to discontinuation of ACEI/ARB</p>	<p>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%,</p>	<p>Corticosteroids 47.8%,</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>INTENSE-COV trial;⁴⁴ Bonnet et al; preprint; 2022</p>	<p>Patients with mild to moderate COVID-19 infection. 100 assigned to Telmisartan 10 mg a day for 10 days and 96 assigned to SOC</p>	<p>Mean age 37, male %, hypertension 5.1%, diabetes 2.6%, COPD %, asthma 3.6%, CHD 0.5%, CKD 0%, cancer 0.5%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	

Gotberg et al ; ⁴⁵ 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.
REMAP-CAP trial ; ⁴⁶ Lawler et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 448 assigned to ACEI/ARB (i.e ramipril or losartan) and 231 assigned to SOC	Median age 55, male 64.9%, diabetes 14%, COPD 20.6%, CHD 3.4%, CKD 1.7%, immunosuppression therapy 5.9%	Corticosteroids 98.7%, remdesivir 15.8%, tocilizumab 77.2%, Baricitinib 2.5%, Antiviral monoclonal antibody 0.7%	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.
ACOVACT trial ; ⁴⁷ Rathkolb et al; preprint; 2023	Patients with moderate to severe COVID-19 infection. 30 assigned to continuation of ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB	Mean age 60.8, male 62.7%, hypertension 100%, diabetes 37.3%, asthma 8.5%, CHD 11.9%, CKD 8.5%, obesity 44.1%	Corticosteroids 74.6%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.

Anticoagulants

There are specific recommendations on the use of antithrombotic agents⁸ 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. In mild ambulatory patients, anticoagulants in prophylactic dose, may not importantly improve time to symptom resolution and probably does not reduce hospitalizations.

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 ; ⁴⁸ 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 0.95 (95%CI 0.8 to 1.12); RD -0.8% (95%CI -3.2% to 1.9%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
REMAP-CAP, ACTIV-4a, ATTACC trial ; ⁴⁹ Zarychanski et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 534 assigned low molecular weight 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)	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, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	Symptomatic infection (prophylaxis studies): No information Venous thromboembolic events: RR 0.56 (95%CI 0.44 to 0.72); RD -3.1% (95%CI -3.9% to -1.9%); High ⊕⊕⊕⊕
INSPIRATION trial ; ⁵⁰ 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	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.	Major bleeding: RR 1.66 (95%CI 1.2 to 2.3); RD 1.3% (95%CI 0.4% to 2.5%); High ⊕⊕⊕⊕ Hospitalization: No information

	prophylactic dose (i.e., enoxaparin 40 mg a day)				
Perepu et al , ⁵¹ 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 , ⁵² 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 low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	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 Notes: Open-label study but outcome assessors were blinded.	
ACTION trial , ⁵³ 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	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.	

	heparin prophylactic dose				
RAPID trial ; ⁵⁴ 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 ; ⁵⁵ Spyropoulos et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 129 assigned to enoxaparin 1 mg/kg 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	Mean age 66.7 ± 14, male 53.8%, hypertension 59.9%, diabetes 37.3%, COPD 6.7%, CHD 8.7%, CKD 3.6%, cerebrovascular disease 3.2%, cancer 2%	Corticosteroids 81%, remdesivir 70.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events	
BEMICOP trial ; ⁵⁶ Marcos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 33 assigned to bempiparin 115 IU/kg once daily and 32 assigned to low molecular weight heparin	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	

	prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose			inappropriate.	
Oliylyk et al ; ⁵⁷ 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 ; ⁵⁸ Morici et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91 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	Mean age 59 ± 21, male 62.8%, hypertension 36.1%, diabetes 13.7%, COPD 5.5%, CKD 1.6%, cerebrovascular disease 2.7%	Corticosteroids 45.9%, remdesivir 21.8%, tocilizumab 1.1%	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.	
PROTHROMCO VID trial ; ⁵⁹ 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	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	

	and 106 assigned to tinzaparin 4500 IU once daily			have introduced bias to symptoms and adverse events outcomes results.
COVID-HEP trial ; ⁶⁰ 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 ; ⁶¹ 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 ; ⁶² 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 ; ⁶³ 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	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

	enoxaparin 40 mg twice a day or similar and 596 assigned to enoxaparin 40 mg a day or similar			study which might have introduced bias to symptoms and adverse events outcomes results.	
ANTICOVID trial ; ⁶⁴ Labbé et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 110 assigned to enoxaparin 1 mg /kg twice a day or similar, 110 assigned to enoxaparin 1 mg /kg once a day or similar and 114 assigned to enoxaparin 40 mg a day or similar	Median age 58.3 ± 13.1, male 67.7%, hypertension 31.4%, diabetes 18.2%, COPD 3.6%, CHD 4.2%, CKD 2.1%, cancer 7.5%	Corticosteroids 92.2%, remdesivir 0.6%, hydroxychloroquine 0.6%, tocilizumab 25.1%,	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.	
FREEDOM trial ; ⁶⁵ Stone et al; peer reviewed; 2023	Patients with moderate to severe COVID-19 infection. 2257 assigned to LMWH-T and 1141 assigned to LMWH-P	Mean age 52, male 59.7%, hypertension 32%, diabetes 20%, COPD 2.9%, asthma 4.6%, CHD %, CKD 2%, cerebrovascular disease 1%, immunosuppressive therapy %, cancer %, obesity %	Corticosteroids 22%, remdesivir 10%, hydroxychloroquine 1.7%, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma 0.3%; 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.	
ACTIV-4B trial ; ⁶⁶ 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: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information
Gates MRI RESPOND-1 trial ; ⁶⁷ 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	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	Symptom resolution or improvement: RR 1.08 (95%CI 0.92 to 1.27); RD 4.8%

	assigned to SOC				(95%CI -4.8% to 16.4%); Low ⊕⊕○○
OVID trial ; ⁶⁸ Barco et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 234 assigned to LMWH-P enoxaparin 40 mg a day for 14 days and 238 assigned to SOC	Mean age 56.5 ± , male 54%, hypertension 24.4%, diabetes 8%, COPD 2%, asthma %, CHD %, CKD %, cerebrovascular disease %, immunosuppressive therapy %, cancer %, obesity %	Corticosteroids 1.7%, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 0.6%	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.	Symptomatic infection (prophylaxis studies): No information Venous thromboembolic events (intermediate dose): Very low certainty ⊕○○○
ETHIC trial ; ⁶⁹ 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.	Clinically important bleeding: Very low certainty ⊕○○○ Hospitalization: RR 1.09 (95%CI 0.81 to 1.47); RD 0.4% (95%CI -0.9% to 2.3%); Moderate ⊕⊕⊕○
COPE Coalition trial ; ⁷⁰ Avazum et al; preprint; 2023	Patients with mild to moderate COVID-19 infection. 327 assigned to rivaroxaban 10 mg a day and 330 assigned to SOC	Mean age 60.5, male 44.4%, hypertension 79.3%, diabetes 35.7%, asthma 11%, CKD 0.5%, cerebrovascular disease 1.5%, cancer 5.5%, obesity 59.6%	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.	
Amira et al ; ⁷¹ peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 50 assigned to enoxaparin 40 mg a day for 14 days and 50 assigned to SOC	Mean age 54.6, male 50%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment	

				of allocation probably inappropriate.	
DeNucci et al. ⁷² peer reviewed; 2023	Patients with moderate to severe COVID-19 infection. 38 assigned to inhaled unfractionated heparin 5000 IU 4 times a day and 37 assigned to SOC	Mean age 52 ± 12.4, 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.	
PREVENT-HD trial ; ⁷³ Piazza et al; peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 641 assigned to rivaroxaban 10 mg a day for 35 days and 643 assigned to SOC	Mean age 56 ± 13.2, male 39%, diabetes 21.3%, CHD 5.4%, cerebrovascular disease 1.4%, cancer 12.5%, obesity 41.4%	Monoclonal antibodies 1.8%; Vaccinated 2.1%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

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. ⁷⁴ 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 , potassium 100	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 improvement: No information

	micrograms, sodium selenate 82.5 micrograms) twice a day for 10 days and 93 assigned to SOC				<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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Apremilast

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
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RCT

<p>I-SPY COVID trial;⁷⁵ Files et al; peer reviewed; 2023</p>	<p>Patients with severe to critical COVID-19 infection. 67 assigned to apremilast 60 mg a day for 14 days and 143 assigned to SOC</p>	<p>Mean age 67 ± 14, male 62.4%, hypertension 61.9%, diabetes 33.3%, COPD 20.5%, CKD 14.8%,</p>	<p>Corticosteroids 100%, remdesivir 100%,</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection</p>
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					<p>(prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
<p>Aprepitant</p> <p>Uncertainty in potential benefits and harms. Further research is needed.</p>					
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 ; ⁷⁶ 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	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁷⁷ 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 ; ⁷⁸ 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 ; ⁷⁹ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ⁸⁰ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Aspirin

Aspirin probably does not reduce mortality or mechanical ventilation and probably does not increase symptom resolution or improvement. In mild patients It probably does not have an important effect on hospitalizations.

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 ; ⁸¹ 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 ⊕⊕⊕○
RECOVERY - ASA trial ; ⁸² 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.	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 studies): No information
ACTIV-4B trial ; ⁶⁶ Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 144 assigned to aspirin 81 mg 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	Adverse events: RR 1.1 (95%CI 0.71 to 1.73); RD 1% (95%CI -2.9% to 7.4%); Low certainty ⊕⊕○○
REMAP-CAP - ASA trial ; ⁸³ Bradbury et al; peer reviewed;	Patients with severe to critical COVID-19 infection. 565	Median age 57, male 65%, hypertension %, diabetes 22.7%, CHD 4.2%, CKD	Corticosteroids 98.1%, remdesivir 22%, tocilizumab 42.9%	Low for mortality and mechanical ventilation; High for symptom resolution,	

2021	assigned to aspirin 75 to 100 mg a day for 14 days and 529 assigned to SOC	3.4%		infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Hospitalization: RR 0.8 (95%CI 0.57 to 1.11); RD -1% (95%CI -2.1% to 0.5%); Moderate certainty ⊕⊕⊕○
ASCOT trial ; ⁶³ 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 %, immunosuppressive 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.	
AST trial ; ⁸⁴ Eikelboom et al; peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 1945 assigned to aspirin 100 mg a day for 28 days and 1936 assigned to SOC	Mean age 45, male 60.6%, hypertension 22%, diabetes 13%, COPD 7.5%, CHD 5%, cerebrovascular disease 0.2%	Vaccinated 27.6%	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.	

Aspirin + Dipyridamole

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					
Singla et al. ⁸⁵	Patients with	Median age 57, male	NR	Low for mortality and	Mortality: Very

peer reviewed; 2023	severe to critical COVID-19 infection. 49 assigned to aspirin + dipyridamole 50/400 mg a day for 14 days and 49 assigned to SOC	46.9%, obesity 41.8%		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.	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
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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
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RCT

Nekoukar et al. ⁸⁶ peer reviewed; 2021	Patients with severe COVID-19 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	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 Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○
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REVOLUTION trial ; ⁸⁷ Maia et al; peer reviewed; 2023	Patients with severe COVID-19 infection. 63 assigned to atazanavir 2 capsules once followed by 1 capsule a day for 10 days and 56 assigned to SOC	Mean age 54.2 ± 14, male 68%, hypertension 41.6%, diabetes 23%, COPD 2%, asthma %, CHD 1%, CKD 1%, cancer 2%, obesity 24%	Corticosteroids 83%, tocilizumab 1%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Atovacune

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
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RCT

STU-2020-0707 trial ; ⁸⁸ Jain et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 41 assigned to atovacune 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
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					<p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Auxora

Auxora may not increase severe adverse events. The effects of auxora 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
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RCT

<p>CARDEA trial;⁸⁹ Bruen et al; Preprint; 2020</p>	<p>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</p>	<p>Mean age 60, male 67.4%, hypertension 62.8%, diabetes 41.8%</p>	<p>Steroids 100%, remdesivir 77.6%, tocilizumab 2.8%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: RR 0.68 (95%CI 0.39 to 1.17); RD -5.1% (95%CI -9.8% to 2.7%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕○○○</p>
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					<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.69 (95%CI 0.48 to 1); RD - 3.2% (95%CI - 5.3% to 0%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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 ; ⁹⁰ 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	<p>Mortality: RR 1.68 (95%CI 0.87 to 3.26); RD 10.9% (95%CI -2.1% to 36.2%); Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No</p>

					<p>information</p> <p>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 ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>COVID-AIV trial:⁹¹ Jihad et al; preprint (now retracted); 2021</p>	<p>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</p>	<p>Mean age 61 ± NR, male 69%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Blinding and concealment probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
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					Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

Singh et al. ⁹² 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
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					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 ⁹³ 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 ⊕⊕○○

					<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>CARVIN trial;⁹⁴ Klusmann et al; preprint; 2021</p>	<p>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</p>	NR	NR	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
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					<p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

Sekhavati et al ⁹⁵ 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.	<p>Mortality: RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕○</p> <p>Invasive mechanical ventilation: RR 0.92 (95%CI 0.77 to 1.1); RD -1.4% (95%CI -4% to 1.7%); Moderate certainty ⊕⊕⊕○</p>
Guvenmez et al ⁹⁶ peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and	<p>Symptom</p>

	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			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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 ⊕⊕⊕⊕
COALITION II trial ; ⁹⁷ 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.	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 ⊕⊕○○
RECOVERY trial ; ⁹⁸ 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 ; ⁹⁹ 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.	

<p>PRINCIPLE trial;¹⁰⁰ Butler et al; peer reviewed; 2021</p>	<p>Patients with mild to severe COVID-19 infection. 500 assigned to azithromycin 500 mg a day for 3 days and 629 assigned to SOC</p>	<p>Mean age 60.7 ± 7.8, male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,</p>	<p>NR</p>	<p>Some concerns for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.</p>	
<p>ATOMIC2 trial;¹⁰¹ Hinks et al; preprint; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 145 assigned to azithromycin 500 mg a day for 14 days and 147 assigned to SOC</p>	<p>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%,</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>ACTION trial;¹⁰² Oldenburg et al; peer reviewed; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 131 assigned to azithromycin 1.2 g once and 70 assigned to SOC</p>	<p>Median age 43, male 44%, hypertension 12.2%, diabetes 3.8%, COPD 1.5%, asthma 12%, CKD 1%, cerebrovascular disease 1%, cancer 0.4%,</p>	<p>NR</p>	<p>Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Significant loss to follow-up.</p>	
<p>Ghanei et al;¹⁰³ peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 110 assigned to lopinavir-ritonavir 200/50 mg twice a day for 7 days and 110 assigned to azithromycin</p>	<p>Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,</p>	<p>Convalescent plasma 1.8%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment</p>	

	500 mg once followed by 250 mg a day for 5 days			of allocation probably inappropriate.	
DAWn-AZITHRO trial ; ¹⁰⁴ Gyselink et al; peer reviewed; 2021	Patients with severe 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.	

Azvadine

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 ; ¹⁰⁵ peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 10 assigned to azvadine 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
Bacteriophage (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					
Samaee et al. ¹⁰⁶ peer reviewed; 2023	Patients with moderate to critical COVID-19 infection. 30 assigned to bacteriophage (inh) 10 ml twice a day and 30 assigned to SOC	Mean age 63, male 51.7%, hypertension 20%, diabetes 40%, COPD 2%, asthma 0%, CHD 23.5%, cancer 3%	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:

					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 ; ¹⁰⁷ 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 ; ¹⁰⁸ 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 ; ¹⁰⁹ 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 on 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 ⊕⊕○○
Gottlieb et al ; ¹¹⁰ 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	Adverse events: RR 1.12 (95%CI 0.75 to 1.66); RD 1.2% (95%CI -2.5% to -6.7%); Low certainty ⊕⊕○○
BLAZE-2 trial ; ¹¹¹ Cohen et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 484 assigned to	Median age 53	NR	Low for mortality and mechanical ventilation; Low for symptom resolution,	Hospitalization:

	bamlanivimab 4200 mg once and 482 assigned to SOC			infection, and adverse events	RR 0.37 (95%CI 0.21 to 0.65); RD -3% (95%CI -3.8% to -1.7%); Moderate certainty ⊕⊕⊕○
BLAZE-1 trial ; ¹¹² 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 ; ¹¹³ 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 ; ¹¹⁴ 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%, immunosuppressive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
ACTIV-2 trial ; ¹¹⁵ 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 ; ¹¹⁶ Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-	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	

	COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion			events	
MANTICO trial ; ¹¹⁷ 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 ; ¹¹⁸ 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 + etesevimab 1400 mg mg once	Median age 35 ± , male 44.5%	Vaccinated 20.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

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 ; ¹¹⁹ 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 ⊕⊕⊕○
COV-BARRIER trial ; ¹²⁰ 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	Symptom resolution or improvement: RR 1.27 (95%CI 1.13 to 1.42); RD 16.4% (95%CI 7.9% to 25.5%); Moderate certainty ⊕⊕⊕○
COV-BARRIER-IMV trial ; ¹²¹ 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	Symptomatic infection (prophylaxis studies): No information
RECOVERY trial ; ¹²² 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	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%; Vaccinated 42%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events	Adverse events: RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty

	SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	⊕⊕⊕○ Hospitalization: No information
ACTT-4 trial ; ¹²³ 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 ; ¹²⁴ 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 ; ¹²⁵ Montejano et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 145 assigned to baricitinib 2 to 4 mg a day for 14 days and 142 assigned to SOC	Median age 67, male 65.5%, hypertension 57.5%, diabetes 29.6%, obesity 18.8%	Corticosteroids 100%, remdesivir 15.3%, 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.	

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 ; ¹²⁶ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 , ¹¹⁸ Dogan et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 252 assigned to bebtelovimab 175 +/- bamlanivimab/etes evimab 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:	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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 ; ¹²⁷ 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
Pushkala et al ; ¹²⁸ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Bicarbonate (inhaled or nasal)

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. ¹²⁹ 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
El-Badrawy et al. ¹³⁰ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
Wang et al. ¹³¹ peer reviewed; 2023	Patients with mild COVID-19 infection. 23 assigned to bicarbonate (nasal) 2 times a day and 32 assigned to SOC	Mean age 66.7, male 47.3%, hypertension 41.8%, diabetes 21.8%, COPD 1.8%, cerebrovascular disease 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.	

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. ¹³² 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 ; ¹³³ 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	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ¹³⁴ 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 ⊕○○○
Ansarin et al ; ¹³⁵ 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.	Symptomatic infection (prophylaxis studies): RR 0.38 (95%CI 0.13 to 1.09); RD -10.8% (95%CI -15.1% to 1.6%); Low certainty ⊕⊕○○
Mikhaylov et al ; ¹³⁶ 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	Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○

				outcomes results.	
Tolouian et al. ¹³⁷ 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. ¹³⁸ 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 ; ¹³⁹ 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.	
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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
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RCT

Elamir et al ; ¹⁴⁰ 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 inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p>
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					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 ; ¹⁴¹ 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 ; ¹⁴² 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 ⊕⊕○○
CANDLE trial ; ¹⁴³ Kinoshita et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 78 assigned to	Mean age 55.9 ± 18.4, male 50.3%, hypertension 28.4%, diabetes 17.4%, COPD 16.1%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse	Symptomatic infection (prophylaxis studies): No

	camostat mesilate 2400 mg a day for 14 days and 77 assigned to SOC	asthma %, CHD 5.2%, CKD 5.8%, obesity 9.7%		events	information Adverse events: Very low certainty ⊕○○○
Terada et al ; ¹⁴⁴ 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.	Hospitalization: Very low certainty ⊕○○○
Tobback et al ; ¹⁴⁵ 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 ; ¹⁴⁶ 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 ; ¹⁴⁷ Cremer et al;	Patients with moderate to severe	Mean age 68.8 ± 13.2, male 73.3%,	Steroids 46.7%, remdesivir 46.7%,	Low for mortality and mechanical	Symptom resolution or

peer reviewed; 2021	COVID-19 infection. 29 assigned to canakinumab 300 to 600 mg once and 16 assigned to SOC	hypertension 71.1%, diabetes 46.7%, COPD 17.8% CHD 22.2%, CKD 33.3%, cerebrovascular disease 4.4%	convalescent plasma 9%	ventilation; low for symptom resolution, infection, and adverse events	<p>improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

CANDIDATE trial ; ¹⁴⁸ 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 SOC	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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
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					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 ; ¹⁴⁹ 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 ⊕○○○
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Celecoxib/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 (standard of care) and GRADE certainty of the evidence
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RCT

I-SPY COVID trial ; ⁷⁵ Files et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 30 assigned to celecoxib/famotidine 400/80 mg a day for 7 days and 37 assigned to SOC	Mean age 60, male 71.6%, hypertension 49.2%, diabetes 40.3%, COPD 8.9%, CKD 9%,	Corticosteroids 100%, remdesivir 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:
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					No information
Cenicriviroc 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					
I-SPY COVID trial ; ⁷⁵ Files et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 92 assigned to cenicriviroc 300 mg a day for 14 to 28 days and 169 assigned to SOC	Mean age 67 ± 14, male 63.9%, hypertension 64.7%, diabetes 36.3%, COPD 21.5%, CKD 14.2%	Corticosteroids 100%, remdesivir 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
CERC-002 (monoclonal antibody) 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 (standard of care) and GRADE certainty of the evidence
RCT					
Perlin et al. ¹⁵⁰ 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 follow-up.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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. ¹⁵¹ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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 ; ¹⁵² 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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 ; ¹⁵³ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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 ; ⁹⁹ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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. ¹⁵⁴ 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%, immunosuppressive therapy 7.2%, cancer 8.6%, obesity 11.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: No information</p> <p>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 ⊕⊕○○</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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 ; ¹⁵⁵ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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 ; ¹⁵⁶ 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 trial ; ¹⁵⁷ Altay et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 229 assigned to cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 75 assigned to SOC	Mean age 36.3 , male 57.6%, hypertension 9.2%, diabetes 6.2%	Hydroxychloroquine 81.9%	High for mortality and 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 ⊕○○○
Hu et al ; ¹⁵⁸ 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.	Hospitalization: No information
Colchicine					
Colchicine probably does not reduce mortality and mechanical ventilation requirements or improve time to symptom resolution. In mild ambulatory patients it does not have an important effect on hospitalizations.					
Study; publication	Patients and interventions	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard

status	analyzed				of care (standard of care) and GRADE certainty of the evidence
RCT					
GRECCO-19 trial ; ¹⁵⁹ Defftereos 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 standard of care	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 adverse events outcomes results.	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 0.98 (95%CI 0.89 to 1.02); RD -0.3% (95%CI -1.9% to 1.4%); Moderate certainty ⊕⊕⊕○
Lopes et al ; ¹⁶⁰ 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
Salehzadeh et al ; ¹⁶¹ 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.	Adverse events: RR 0.85 (95%CI 0.68 to 1.05); RD -1.5% (95%CI -3.3% to 0.5%); High certainty ⊕⊕⊕⊕
Tardif et al ; ¹⁶² peer-reviewed; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe	Mean age 54.3, male 46%, hypertension 36.3%, diabetes 19.9%, COPD	NR	Low for mortality and mechanical ventilation; Low for symptom resolution,	Pulmonary embolism: RR 5.55 (95%CI 1.23 to 25); RD 0.4%

	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	26.5%, CHD 5.4%, obesity 45.7%		infection, and adverse events	(95%CI 0.02% to 2.2%); Low certainty ⊕⊕○○ Hospitalization: RR 0.88 (95%CI 0.73 to 1.07); RD - 0.6% (95%CI - 1.3% to 0.3%); High certainty ⊕⊕⊕⊕
RECOVERY - Colchicine trial ; ¹⁶³ 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 ; ¹⁶⁴ 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%, immunosuppressive 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 ; ¹⁶⁵ 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.	

<p>COLCOVID trial;¹⁶⁶ Diaz et al; peer reviewed; 2021</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 91.5%, hydroxychloroquine 0.3%, lopinavir-ritonavir 0.2%, convalescent plasma 7.3%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>Alsultan et al;¹⁶⁷ peer reviewed; 2021</p>	<p>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 and 21 assigned to SOC</p>	<p>Age 60 to 80 65.3, male 38.8%, diabetes 53.1%, CKD 8.2%, cerebrovascular disease 4.1%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Pourdowlat et al;¹⁶⁸ peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 55, male 56.4%, hypertension 12.7%, diabetes 14.5%, COPD %, asthma 3.6%, CHD 5.4%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Gorial et al;¹⁶⁹ peer reviewed; 2021</p>	<p>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</p>	<p>Median age 49, male 53.1%, hypertension 41.2%, diabetes 20.6%, COPD %, asthma 1.2%, cancer 2.5%, obesity 35%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Mostafaie et al; NCT04392141, other; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 60</p>	<p>Mean age 53.5 ± 15.1, male 54.2%, hypertension 26.7%, diabetes 7.5%,</p>	<p>NR</p>	<p>NA</p>	

	assigned to colchicine and 60 assigned to SOC	cancer 5.8%,			
STRUCK trial ; ¹⁷⁰ 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 ; ¹⁷¹ peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 119 assigned to colchicine 1 mg once followed by 0.5 mg a day for 5 days and 120 assigned to SOC	Mean age 65.1 ± 16, male 59%, hypertension 40%, diabetes 16%, COPD 4%, asthma 5%, CHD 7%	Corticosteroids 98%, remdesivir 15.5%, hydroxychloroquine 0%, lopinavir-ritonavir 0.8%,	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.
Rabbani et al ; ¹⁷² 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 ; ¹⁷³ 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.	
AST trial ; ⁸⁴ Eikelboom et al; peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 1939 assigned to colchicine 0.6 mg a day for 3 days followed by 1.2 mg a day for 25 days and 1942 assigned to SOC	Mean age 45, male 60.5%, hypertension 22%, diabetes 13%, COPD 8%, CHD 5%, cerebrovascular disease 0.2%	Vaccinated 27.6%	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.	

Colchicine + statin

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
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RCT

Gaitan-Duarte et al ; ¹⁷⁴ 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 ⊕○○○
COLSTAT trial ; ¹⁷⁵ Shah et	Patients with moderate to severe	Mean age 60.5, male 56%, hypertension	Corticosteroids 92%, remdesivir	High for mortality and mechanical	Symptom resolution or improvement: No information

al; peer reviewed; 2023	COVID-19 infection. 125 assigned to Colchicine + rosuvastatin 0.6/40 mg a day for 30 days and 125 assigned to SOC	65%, diabetes 42.4%, COPD 14.4%, CHD 19.2%, CKD 29%, cerebrovascular disease 10.8%	87.2%, tocilizumab 18.4%, Vaccinated 4.4%, Baricitinib 1.6%	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
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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 ; ¹⁷⁶ 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
CONCOVID trial ; Gharbharan et	Patients with moderate to critical	Median age 62 ± 18, male 72%,	NR	Low for mortality and invasive mechanical	

al; ¹⁷⁷ preprint; 2020	COVID-19 infection. 43 assigned to convalescent plasma 300 ml once or twice and 43 assigned to standard of care	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%		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.	certainty ⊕⊕⊕⊕ Symptom resolution or improvement: RR 0.99 (95% CI 0.96 to 1.02); RD -0.6% (95%CI -2.4% to 1.2%); High certainty ⊕⊕⊕⊕
Avendaño-Solá et al; ¹⁷⁸ 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.	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 ⊕⊕⊕○
PLACID trial; ¹⁷⁹ 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 standard of care	Median age 52 ± 18, male 76.3%, hypertension 37.3%, diabetes 43.1%, chronic lung disease 3.2%, coronary heart disease 6.9%, chronic kidney disease 3.7%, cerebrovascular disease 0.9%, cancer 0.2%, obesity 7.1%	Corticosteroids 64.4%, remdesivir 4.3%, hydroxychloroquine 67.7%, lopinavir-ritonavir 14.2%, tocilizumab 9%, azithromycin 63.8%	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.	
PLASM-AR trial; ¹⁸⁰ 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 ; ¹⁸¹ 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 ; ¹⁸² 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 ; ¹⁸³ 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 ; ¹⁸⁴ 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 ; ¹⁸⁵ 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 ; ¹⁸⁶ 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 ; ¹⁸⁷ 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 ; ¹⁸⁸ 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 ; ¹⁸⁹ 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 ; ¹⁹⁰ 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 ; ¹⁹¹ 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 ; ¹⁹² Koerper et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to CP	Mean age 60 ± 13, male 73.3%, hypertension 56.2%, diabetes 31.4%, COPD 16.2%, CHD	Corticosteroids 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and

	850 ml in three infusions and 52 assigned to SOC	21.9%, cancer 4.7%, obesity 54.2%		adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP trial ; ¹⁹³ 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 ; ¹⁹⁴ Bégin et al; preprint; 2021	Patients with severe COVID-19 infection. 614 assigned to CP 500 ml and 307 assigned to SOC	Mean age 67.5 ± 15.6, male 59.1%, diabetes 35%, COPD 24.1%, CHD 62%	Corticosteroids 80.4%, azithromycin 44.3%	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.	
PLACOVID trial ; ¹⁹⁵ 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.	

<p>COVIDIT trial;¹⁹⁶ Kirenga et al; peer reviewed; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 69 assigned to CP 150 -300 ml twice and 67 assigned to SOC</p>	<p>Mean age 50 ± 23.5, male 71.3%, hypertension 36%, diabetes 32%, asthma 3.7%, obesity 33.3%</p>	<p>Corticosteroids 58.8%,</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>C3PO trial;¹⁹⁷ Korley et al; peer reviewed; 2021</p>	<p>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</p>	<p>Median age 54 ± 21, male 46%, hypertension 42.3%, diabetes 27.8%, COPD 6.1%, CHD 10%, CKD 5.3%, cancer 0.8%, obesity %</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	
<p>DAWn-Plasma trial;¹⁹⁸ Devos et al; peer reviewed; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 320 assigned to CP 200 to 250 ml once or twice and 163 assigned to SOC</p>	<p>Mean age 62 ± 14, male 68.7%, hypertension %, diabetes 29.6%, COPD 9.4%, asthma 10.1%, CHD 14.1%, CKD 13.4%,</p>	<p>Corticosteroids 66.4%, remdesivir 14.8%, hydroxychloroquine 1.4%, lopinavir-ritonavir 0.4%, tocilizumab 0.6%,</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>PennCCP2 trial;¹⁹⁹ Bar et al; peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 40 assigned to CP two units and 39 assigned to SOC</p>	<p>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%</p>	<p>Corticosteroids 83.5%, remdesivir 81%, hydroxychloroquine 2.5%,</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>TSUNAMI trial;²⁰⁰ Manichetti et al;</p>	<p>Patients with moderate to severe</p>	<p>Median age 64 ± 20, male 64.3%,</p>	<p>NR</p>	<p>Low for mortality and mechanical</p>	

peer reviewed; 2021	COVID-19 infection. 231 assigned to CP 200 ml a day for 1 to 3 days and 239 assigned to SOC	hypertension 37.8%, diabetes 19.2%, COPD 5.7%, CKD 4.7%, cancer 3.6%		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-ert & CoV- Early trial ; ²⁰¹ 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 ; ²⁰² 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%, cerebrovascular disease 0.2%, cancer 0.5%, obesity 17.3%	Vaccinated 17.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
COP20 trial ; ²⁰³ 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 ; ²⁰⁴ Ortigoza et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 463 assigned to CP 250 ml once and 463	Median age 63, male 59.1%, hypertension 60.7%, diabetes 35.3%, COPD %, asthma 11.7%, CHD	Corticosteroids 76.6%, remdesivir 57.1%, hydroxychloroquine 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse

	assigned to SOC	42.9%, CKD 10.5%, cancer 11.3%,		events	
IMPACT trial ; ²⁰⁵ 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 ; ²⁰⁶ 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 ; ²⁰⁷ 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 ; ²⁰⁸ 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 ; ²⁰⁸ other;	Patients with severe to critical	NR	NR	Low for mortality and mechanical	

2021	COVID-19 infection. 43 assigned to CP and 47 assigned to SOC			ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review
LACCPT trial ; ²⁰⁸ 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 ; ²⁰⁹ Fernández-Sánchez et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 29 assigned to CP 300 ml twice and 10 assigned to SOC	Mean age 55.9 ± 9.6, male 76.9%, hypertension 51.3%, diabetes 35.9%, COPD 2.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
Herrick J et al ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ 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 ; ²⁰⁸ other; 2021	Patients with severe to critical COVID-19 infection. 49 assigned to CP and 51 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	
CONFIDENT trial ; ²⁰⁸ 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 ; ²⁰⁸ other; 2021	Patients with severe to critical COVID-19	NR	NR	Low for mortality and mechanical ventilation; low for	

	infection. 38 assigned to CP and 36 assigned to SOC			symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review
COP-COVID-19 trial ; ²⁰⁸ 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 ; ²¹⁰ peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 98 assigned to CP 600 ml once and 46 assigned to SOC	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
COOPCOVID trial ; ²¹¹ 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 ; ²¹² 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 ; ²¹³ 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 ; ²¹⁴ 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%, immunosuppressive 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 ; ²¹⁵ 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-Leonart et al ; ²¹⁶ 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 ; ²¹⁷ 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:	
Irawan et al ; ²¹⁸ peer reviewed; 2023	Patients with moderate COVID-19 infection. 21 assigned to CP 400 ml once and 23 assigned to SOC	Mean age 56.5, male 63.6%, hypertension 40.9%, diabetes 25%, asthma 2.3%, CHD 9%, cancer 6.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Saito et al ; ²¹⁹ peer reviewed; 2023	Patients with moderate COVID-19 infection. 10 assigned to CP and 11 assigned to SOC	Mean age 62, male 81%, hypertension 66.6%, diabetes 23.8%, COPD 5%, cerebrovascular disease 14.3%,	Corticosteroids 42.9%, remdesivir 71.4%, tocilizumab 5%, Baricitinib 5%	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.	
Balcells et al ; ²²⁰ peer reviewed; 2020	Patients with moderate to severe COVID-19. 28	Mean age 65.8 ± 65, male 50%, hypertension 67.2%,	Corticosteroids 51.7%, hydroxychloroquine	Low for mortality and invasive mechanical ventilation; high for	Mortality: Very low certainty ⊕○○○

	assigned to convalescent plasma at enrolment, 200 mg twice and 30 assigned to convalescent plasma when clinical deterioration was observed (43.3% received CP in this arm)	diabetes 36.2%, chronic lung disease %, asthma 5.1%, coronary heart disease %, chronic kidney disease 8.6%, cerebrovascular disease 5.1%, immunosuppression 12%, cancer 7%, obesity 12%	12%, lopinavir-ritonavir 1.7%, tocilizumab 3.4%	symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	<p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Non-RCT

Joyner et al ; ²²¹ 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	<p>Adverse events: Transfusion related circulatory overload 0.18%; Transfusion related lung injury 0.10%; Severe allergic transfusion reaction 0.10%</p>
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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					
<p>CRITICAL trial;²²² Leucker et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 22 assigned to crizanlizumab 5 mg/kg once and 20 assigned to SOC</p>	<p>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%,</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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; ²²³ 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:	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Curcumin + Quercetin +/- Vitamin D

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					
Khan et al ; ²²⁴ 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 ⊕○○○
Ujjan et al ; ²²⁵ peer reviewed; 2023	Patients with mild COVID-19 infection. 25 assigned to curcumin + quercetin 168/260 mg twice a day for 14 days and 25 assigned to SOC	Median age 37, male 64%, hypertension 18%, diabetes 14%, asthma 8%,	Vaccinated 96%	High for mortality and 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

Dapagliflozin

Dapagliflozin may reduce mortality but probably does 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 and GRADE certainty of the evidence
RCT					
DARE-19 trial ; ²²⁶ 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	<p>Mortality: RR 0.76 (95%CI 0.51 to 1.12); RD -3.8% (95%CI -7.8% to 1.9%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ²²⁷ 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

Degalactosylated bovine glycoprotein

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					
Inui et al ; ²²⁸ preprint; 2023	Patients with moderate to severe COVID-19 infection. 132 assigned to degalactosylated bovine glycoprotein and 72 assigned to SOC	Mean age 63.6, male 35.4%, hypertension 72.5%, diabetes 23.5%	Corticosteroids 58.5%, remdesivir 4.4%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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 ; ²²⁹ Nickols et al;	Patients with moderate to severe	Mean age 68.5 ± 8.4, male 100%,	NR	Low for mortality and mechanical	Mortality: Very low certainty

peer reviewed; 2021	COVID-19 infection. 62 assigned to degarelix 240 mg once and 34 assigned to SOC	hypertension 78.1%, diabetes 51%, COPD 15.6%, asthma 12.5%, CHD 28.1%		ventilation; low for symptom resolution, infection and adverse events	<p>⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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. ²³⁰ 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
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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. ²³¹ preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 116 assigned to DSMO	Mean age 37.2 ± 8.7	NR	Low for mortality and mechanical ventilation; high for symptom resolution,	Mortality: No information Invasive

	three applications a day for one month and 116 assigned to SOC			infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: No information Hospitalization: No information
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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 ; ²³² 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: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
I-SPY COVID trial ; ⁷⁴ Files et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 39 assigned to dornase alfa (inh) 5	Mean age 61, male 63%, hypertension 53.5%, diabetes 32.3%, COPD 14.9%, CKD 8.7%,	Corticosteroids 100%, remdesivir 100%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	Symptomatic infection (prophylaxis)

	to 10 mg a day and 88 assigned to SOC			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: No information
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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
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RCT

Madioko et al. ²³³ 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
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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 ; ²³⁴ 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 SOC	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 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: RR 1 (95%CI 0.97 to 1.03); RD 0% (95%CI -1.8% to 1.8%); High certainty ⊕⊕⊕⊕
PRINCIPLE trial ; ²³⁵ 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	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○
DOXPREVENT ICU trial ; ²³⁶ 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.	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 ⊕⊕○○
Stambouli et al ; ²³⁷ peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 56 assigned to doxycycline 100 mg	Mean age 38.4 ± 10.7, male 61%, hypertension 4.1%, diabetes 2.3%, COPD 0.6%, asthma	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse	

	a day for 6 weeks and 57 assigned to SOC	1.2%,		events	
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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
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RCT

SafeDrop trial ; ²³⁸ 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
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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 ; ²³⁹ 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 of allocation probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
EAT-DUTA AndroCoV trial ; ²⁴⁰ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○
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 ; ²⁴¹ peer reviewed; 2022	Patients with severe COVID-19 infection. 19 assigned to	Mean age 60.5, male 47.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution,	Mortality: Very low certainty ⊕○○○

	edaravone 30 mg a day for 3 days and 19 assigned to SOC			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: No information Hospitalization: No information
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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 ; ²⁴² Delgado-Enciso et al; preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to	Mean age 47 ± 14.6, male 53.5%, hypertension 18.9%, diabetes 11.9%	Corticosteroids 3.65%, hydroxychloroquine 7.5%, ivermectin	High for mortality and invasive mechanical ventilation; high for symptom resolution,	Mortality: Very low certainty ⊕○○○

	electrolyzed saline nebulizations 4 times a day for 10 days and 39 assigned to standard of care		9.4%, ATB 30.6%	infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
ICU-VR trial: Gutiérrez-García et al ; ²⁴³ 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.	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: No information Hospitalization: Very low certainty ⊕○○○

Empaglifozin

Empaglifozin probably does not reduce mortality or mechanical ventilation and probably it does not increase 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					
RECOVERY trial ; ²⁴⁴ Horby et al; preprint; 2023	Patients with severe to critical COVID-19	Mean age 61.5, male 62.4%, diabetes 16%, COPD 24.5%,	Corticosteroids 90%, remdesivir 25.6%, tocilizumab	Low for mortality and mechanical ventilation; Some	Mortality: RR 0.96 (95%CI 0.83 to 1.12); RD 0.6%

	infection. 2113 assigned to empaglifozin 10 mg a day for 28 days and 2158 assigned to SOC	CKD 3.5%	23.5%, Baricitinib 26.5%, Sotrovimab 9%, Molnupiravir 6.5%, Nirmatrelvir-ritonavir 1%; Vaccinated 67%,	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 -2.7% to 1.9%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 1.01 (95%CI 0.8 to 1.27); RD 0.1% (95%CI -3.5% to 4.7%); Moderate certainty ⊕⊕⊕○ Symptom resolution or improvement: : RR 1.02 (95%CI 1 to 1.05); RD 1.3% (95%CI -0.6% to 3.3%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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 ; ²⁴⁵ Matli et al; peer	Patients with mild to severe COVID-19 infection. 17	Mean age 56.6, male 81.8%, hypertension 27%, diabetes	Corticosteroids 91.9%, remdesivir 59.5%, tocilizumab	High for mortality and mechanical ventilation; high for	Mortality: Very low certainty ⊕○○○

reviewed; 2022	assigned to nicorandil 20 mg a day, L-arginine 3 gr a day, folate 5 mg a day, nebivolol 2.5 to 5 mg a day, and atorvastatin 40 mg a day for 14 days, and 20 assigned to SOC	21.6%, asthma 10.8%, CHD 5.4%, CKD 2.7%, cancer 2.7%,	8.1%	symptom resolution, infection, and adverse events Notes: 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
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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 ; ²⁴⁶ Preprint;	Patients with moderate to severe	NR	NR	High for mortality and mechanical	Mortality: No information

2020	COVID-19. assigned to enisamium 500 mg 4 times a day for 7 days or SOC. Number of patients in each arm not reported.			ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	<p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Mukae et al.;²⁴⁷ peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 38.9, male 61.7%,</p>	<p>Vaccinated 80.8%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Ensovibep

Ensovibep may not improve time to symptom resolution. The effects of ensovibep 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
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RCT

<p>ACTIV-3/TICO trial;²⁴⁸ Barkauskas et al; peer reviewed; 2022</p>	<p>Patients with moderate to severe COVID-19 infection. 247 assigned to ensovibep 600 mg once and 238 assigned to SOC</p>	<p>Median age 57 ± , male 56.7%, hypertension 39.4%, diabetes 23.5%, COPD 6.2%, asthma 9.3%, CHD %, CKD 9.5%, cerebrovascular disease %, immunosuppressive therapy 6.2%, cancer %, obesity 13.4%</p>	<p>Corticosteroids 72.9%, remdesivir 68.7%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 31.6%</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>COVIDENZA trial;²⁴⁹ Welen et al; peer reviewed; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 30 assigned to enzalutamide 160 mg a day for 5 days and 12 assigned to SOC</p>	<p>Median age 64.9, hypertension 45.2%, diabetes 19%, asthma 14.3%, CHD 9.5%, cancer 11.9%,</p>	<p>Corticosteroids 85.7%, remdesivir 28.6%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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Non-RCT

Amoushahi et al ; ²⁵⁰ 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 ⊕○○○
Castro-Balado et al ; ²⁵¹ peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 38 assigned to ethanol (inhaled) and 37 assigned to SOC	Mean age 83 ± 8.2, male 32%, hypertension 69.3%, diabetes 26.7%, COPD %, CHD 24%, obesity 13.3%	Corticosteroids 50.6%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	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
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Non-RCT

Non-RCT					
Samimagham et al. ²⁵² 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
Brennan et al. ²⁵³ 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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
Pahwani et al. ²⁵⁴ 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.	Adverse events: No information Hospitalization: No information

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
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RCT

Chen et al ; preprint; ²⁵⁵ 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 1.09 (95%CI 0.76 to 1.54); RD 1.4% (95%CI -3.8% to 8.6%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 1.24 (95%CI 0.9 to 1.71); RD 4.2% (95%CI -1.7% to 12.3%); Low certainty ⊕⊕○○
Ivashchenko et al ; ²⁵⁶ 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.	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 ⊕⊕⊕⊕
Lou et al ; ¹⁰⁷ 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.	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 ⊕○○○
Doi et al ; ²⁵⁷ 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	Hospitalization: RR 1.46 (95%CI 0.82 to 2.62); RD 2.2% (95%CI -0.9% to 7.8%); Low certainty ⊕⊕○○

	1800 mg on day 6 followed by 800 mg twice daily for 10 days			probably inappropriate.	
Dabbous et al ; ²⁵⁸ 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 ; ²⁵⁹ 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 ; ²⁶⁰ 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 ; ²⁶¹ 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 ; ²⁶² 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 ; ²⁶³ peer-reviewed; 2020	Patients with moderate to severe COVID-19. 100 assigned to favipiravir 3200 mg 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 ; ²⁶⁴ 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 ; ²⁶⁵ 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 ; ²⁶⁶ 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 ; ²⁶⁷ 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 ; ²⁶⁸ 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 ; ²⁶⁹ 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 ; ²⁷⁰ 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	

<p>Malaysian Favipiravir Study trial;²⁷¹ Chuah et al; peer reviewed; 2021</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 24.6%, tocilizumab 2%, vaccinated 0.4%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>FAVI-COV-US201 trial;²⁷² Finberg et al; peer reviewed; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 25 assigned to favipiravir 3600 mg once followed by 2000 mg a day for 14 days and 25 assigned to SOC</p>	<p>Mean age 57.2 ± 13.14, male 60%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>Avi-Mild trial;²⁷³ Bosaeed et al; peer reviewed; 2021</p>	<p>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</p>	<p>Median age 37, male 67%, hypertension 6%, diabetes 10.8%, COPD %, asthma 3.4%, CHD 0.4%, obesity 16.8%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>Hassaniazad et al;²⁷⁴ peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 53.7 ± 13.5, male 57.1%, hypertension 27%, diabetes 20.6%, COPD 1.6%, CHD 14.2%, obesity 7.9%</p>	<p>Interferon beta 100%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	

FLARE trial ; ²⁷⁵ 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 ; ²⁷⁶ 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 ; ²⁷⁷ 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 ; ²⁷⁸ 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 ; ²⁷⁹ 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 ; ²⁸⁰ 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 ; ²⁸¹ 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.	
Vaezi et al ; ²⁸² peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 38 assigned to favipiravir 1600 mg a day for 5 days and 39 assigned to SOC	Mean age 41, male 55.8%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Kamali et al ; ²⁸³ peer reviewed;	Patients with severe COVID-19	Mean age 53.4, male 56.7%	NR	High for mortality and mechanical	

2023	infection. 50 assigned to favipiravir 600 mg a day for 7 days and 47 assigned to SOC			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; ²⁸⁴ 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 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					
FERMIN trial ; ²⁸⁵ 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:	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.76 (95%CI 0.53 to 1.08); RD -2.5% (95%CI -4.8% to 0.8%); Low certainty ⊕⊕○○</p>

					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 ; ²⁸⁶ 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

Fluoxetine					
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					
Sedighi et al. ²⁸⁷ peer reviewed; 2023	Patients with moderate COVID-19 infection. 34 assigned to fluoxetine 10 mg a day for 4 days followed by 20 mg a day for 28 days and 33 assigned to SOC	Mean age 52.6 ± 11, male 51.4%, hypertension 25%, diabetes 29.2%, CHD 5.6%, CKD 0%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ²⁸⁸ peer-reviewed; 2020	Patients with mild 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	Median age 45.5 ± 20.5, male 28.2%, hypertension 19.7%, diabetes 11%, asthma 17.1%, obesity 56.6%	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 ⊕○○○
TOGETHER-Fluvoxamine trial ; ²⁸⁹ 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:	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
Seo et al ; ²⁹⁰ 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.	Adverse events: RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕○○
COVID-OUT trial ; ²⁹¹ 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	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	Hospitalization: RR 0.78 (95%CI 0.6 to 1.02); RD -1.1% (95%CI -1.9% to 0.1%); Moderate certainty ⊕⊕⊕○

	assigned to SOC				
ACTIV-6 trial ; ²⁹² 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	
Tanaffos et al ; ²⁹³ peer reviewed; 2023	Patients with moderate to severe COVID-19 infection. 38 assigned to Fluvoxamine 25 to 300 mg and 40 assigned to SOC	Mean age 57.4 ± 13, male 56.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Fluvoxamine + corticosteroids (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					
TOGETHER trial ; ²⁹⁴ Reis et al; peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 738 assigned to Fluvoxamine + budesonide (inhaled) 200mg + 1600 µg a day for 10 days and 738 assigned to SOC	Median age 51, male 39.2%, hypertension 44.4%, diabetes 18.9%, COPD 2.4%, asthma 11.5%, CHD 3.9%, CKD 0.3%, cancer 2.4%, obesity 38.4%	Vaccinated 97.7%	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

					<p>infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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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
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RCT

<p>Strich et al.,²⁹⁵ peer-reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 30 assigned to fostamatinib 300 mg a day for 14 days and 29 assigned to SOC</p>	<p>Mean age 55.6 ± 13.7, male 79.7%, hypertension 54.2%, diabetes 37.3%, asthma 11.9%, CHD 13.6%, obesity 57.6%</p>	<p>Corticosteroids 100%, remdesivir 100%, convalescent plasma 42.4%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
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					<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Soltani et al.²⁹⁶ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 56.7, male 56.1%, hypertension 22.2%, diabetes 16.1%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic</p>
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					<p>infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Galectin 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
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RCT

<p>Sigamani et al;²⁹⁷ peer reviewed; 2023</p>	<p>Patients with mild to moderate COVID-19 infection. 17 assigned to galectin inhibitor 14000 mg a day for 7 days and 17 assigned to SOC</p>	<p>Mean age 39.5 ± , male 70.6%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic</p>
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					infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
Garadacimab 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					
Papi et al. ²⁹⁸ peer reviewed; 2023	Patients with severe COVID-19 infection. 63 assigned to garadacimab 700 mg once and 61 assigned to SOC	Mean age 62.5 ± 13.7, male 59.7%, hypertension 54.8%, diabetes 38.7%, obesity 58.1%	Corticosteroids 41.9%	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
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 ; ²⁹⁹ 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 ; ³⁰⁰ 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 %, immunosuppressive 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	<p>Mortality: RR 1.02 (95%CI 0.67 to 1.56); RD 0.3% (95%CI -5.3% to 6%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>

					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 ; ³⁰¹ 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

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
Hesperidin					
Hesperidin may not improve symptom resolution; however, the certainty of the evidence was low. Further research is needed.					
RCT					
HESPERIDIN trial ; ³⁰² 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events:</p>

					<p>Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
<p>Hemadsorption Uncertainty in potential benefits and harms. Further research is needed.</p>					
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					
<p>CYTOCOV-19 trial;³⁰³ Jarczак et al; preprint; 2021</p>	<p>Patients with critical COVID-19 infection. 12 assigned to hemadsorption and 12 assigned to SOC</p>	<p>Mean age 64.5 , male 75%, hypertension 66.6%, diabetes 33.3%, CHD 4%, CKD 25%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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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
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RCT

CloroCOVID19 trial ; ³⁰⁴ 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 ⊕⊕⊕○
Huang et al ; ³⁰⁵ 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	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	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

	400/100 mg twice a day for 10 days			probably inappropriate.	certainty ⊕⊕⊕○
RECOVERY - Hydroxychloroquine trial ; ³⁰⁶ 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.	Symptomatic infection (prophylaxis studies): RR 0.84 (95%CI 0.72 to 0.97); RD -2.7% (95%CI -4.9% to -0.5%); Moderate certainty ⊕⊕⊕○ Severe Adverse events: RR 0.92 (95%CI 0.68 to 1.23); RD -0.8% (95%CI -3.2% to 2.8%); Low certainty ⊕⊕○○
BCN PEP CoV-2 trial ; ³⁰⁷ 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.	Hospitalization: RR 0.83 (95%CI 0.63 to 1.1); RD -0.8% (95%CI -1.8% to 0.5%); Low certainty ⊕⊕○○
COVID-19 PEP trial ; ³⁰⁸ 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.	

<p>Cavalcanti et al trial;³⁰⁹ Cavalcanti et al; peer-reviewed; 2020</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 1.5%, ACE inhibitors 1.2%, ARBs 17.4%, NSAID 4.4%</p>	<p>Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>
<p>Kamran SM et al trial;³¹⁰ Kamran et al; preprint; 2020</p>	<p>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</p>	<p>Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%</p>	<p>NR</p>	<p>High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>
<p>COVID-19 PET trial;³¹¹ Skipper et al; peer-reviewed; 2020</p>	<p>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</p>	<p>Median age 40 ± 9, male 44%, hypertension 11%, diabetes 4%, chronic lung disease %, asthma 11%,</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events</p>
<p>BCN PEP CoV-2 trial;³¹² Mitja et al; preprint; 2020</p>	<p>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</p>	<p>Mean age 41.6 ± 12.6, male 49%, comorbidities 53.2%</p>	<p>NR</p>	<p>High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>
<p>Tang et al; peer-reviewed;³¹³</p>	<p>Patients with mild to moderate</p>	<p>Mean age 46.1 ± 14.7, male 54.7%,</p>	<p>Corticosteroids 7%, lopinavir-ritonavir</p>	<p>Low for mortality and invasive mechanical</p>

2020	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	hypertension 6%, diabetes 14%, other comorbidities 31%	17%, umifenovir 47%, oseltamivir 11%, entecavir 1%, ATB 39%, ribavirin 47%	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 ; ³¹⁴ preprint; 2020	Patients with moderate COVID-19 infection. 31 assigned to hydroxychloroquine 200 mg twice a day for 5 days and 31 assigned to standard of care	Mean age 44 ± 15.3, male 46.8%,	ATB 100%, IVIG 100%, 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.
Chen et al ; ³¹⁵ 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 ; ³¹⁶ 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.

<p>HC-nCoV trial;³¹⁷ Jun et al; peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%, chronic lung disease 3.3%</p>	<p>Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>
<p>Abd-Elsalam et al;³¹⁸ peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 40.7 ± 19.3, male 58.8%, chronic kidney disease 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%</p>	<p>NR</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>
<p>COVID-19 PREP trial;³¹⁹ Rajasingham et al; peer-reviewed; 2020</p>	<p>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</p>	<p>Median age 41 ± 15, male 49%, hypertension 14%, asthma 10%</p>	<p>NR</p>	<p>Low for infection, and adverse events</p>
<p>TEACH trial;³²⁰ Ulrich et al; peer-reviewed; 2020</p>	<p>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</p>	<p>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%,</p>	<p>Corticosteroids 10.2%, remdesivir 0.8%, lopinavir-ritonavir 0.8%, azithromycin 23.4%, convalescent plasma 13.3%</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>

	standard of care	cerebrovascular disease 6.2%		
PrEP COVID trial ; ³²¹ 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 standard of care	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
PATCH trial ; ³²² 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 ; ³²³ 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 which might have introduced bias to symptoms and adverse events outcomes results.
Davoodi et al ; ²⁸⁴ 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; ³²⁴ 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 ; ³²⁵ 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 ; ³²⁶ 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 ; ³²⁷ 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 ; ³²⁸ 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 ; ³²⁹ peer reviewed; 2020	Patients with mild to moderate COVID-19. 44 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 10 days and 48 assigned to CQ	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 adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HYDRA trial ; ³³⁰ 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 ; ³³¹ 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 ; ³³² peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution,	

	lopinavir-ritonavir 500/100 a day, 123 assigned to hydroxychloroquine 200 mg a day and 119 to SOC			infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
Beltran et al. ³³³ peer reviewed; 2020	Patients with moderate to severe COVID-19. 33 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 5 days 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: Non-blinded study. Concealment of allocation is probably inappropriate.
PATCH 1 trial ³³⁴ 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. ³³⁵ 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. ³³⁶ peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 432 assigned to	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution,

	hydroxychloroquine 400 mg once followed by 200 mg a day for 42 days and 619 assigned to SOC (vitamin C)			infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
TOGETHER trial ; ³³⁷ Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 9 days and 227 assigned to SOC	Mean age 53, 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
CLOROTRIAL trial ; ³³⁸ 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 ; ³³⁹ 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 ; ³⁴⁰ Sivapalan et al; peer	Patients with moderate to severe COVID-19	Median age 65 ± 25, male 56%, hypertension 38%,	Corticosteroids 32%, remdesivir 25%,	Low for mortality and mechanical ventilation; Low for

reviewed; 2021	infection. 61 assigned to hydroxychloroquine + AZT 400 mg plus 500 to 250 mg a day and 56 assigned to SOC	diabetes 24%, COPD 9%, asthma 22%, CHD 7%, CKD 7%		symptom resolution, infection, and adverse events	
HONEST trial ; ³⁴¹ Byakika-Kibwika et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 55 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 5 days and 50 assigned to SOC	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 Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ALBERTA HOPE-Covid19 trial ; ³⁴² 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 ; ³⁴³ 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 ; ³⁴⁴ peer reviewed; 2021	Patients with mild COVID-19 infection. 42 assigned to hydroxychloroquine + azithromycin 400/500 mg a day for 7 days and 42	Mean age 36.5 ± 9.6, male 40.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

	assigned to SOC				
Babalola et al. ³⁴⁵ 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 , ²⁶⁸ 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 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.	
SEV-COVID trial , ³⁴⁶ 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	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	

	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			study. Concealment of allocation probably inappropriate.	
Ahmad et al , ³⁴⁷ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to 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	Mean age 37.6, 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 probably inappropriate.	
WHIP COVID-19 trial , ³⁴⁸ 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 , ³⁴⁹ 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 , ³⁵⁰ Polo et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 231 assigned to hydroxychloroquine 200 mg a day and 223 assigned to	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	

	SOC				
COPE – Coalition V trial ; ³⁵¹ 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 ; ²⁷⁷ peer reviewed; 2021	Patients with moderate COVID-19 infection. 51 assigned to HCQ 800 mg once followed by 400 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.	
Omehecatl trial ; ³⁵² 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 ; ³⁵³ 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.	

<p>IRICT trial;³⁵⁴ Elshafie et al; peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 60, male 54.3%, hypertension 40.7%, diabetes 30.1%, CKD 10.6%, obesity 20.6%</p>	<p>Corticosteroids 100%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>Choudhary et al;³⁵⁵ peer reviewed; 2022</p>	<p>Patients with mild to moderate COVID-19 infection. 99 assigned to HCQ 1400 mg once followed by 600 mg a day for 5 days and 99 assigned to SOC</p>	<p>Mean age 43, male 48%, hypertension 24%, diabetes 3.5%, asthma 7.8%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Dhibar et al;³⁵⁶ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 35 ± 10.4, male 74%, hypertension 3.5%, diabetes 3.7%, asthma 0.1%, CHD 0.3%</p>	<p>Vaccinated 0%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>Nasri et al;³⁵⁷ peer reviewed; 2023</p>	<p>Individuakls exposed to SARS-COV-2. 73 assigned to HCQ 400 mg a day for 12 weeks and 70 assigned to SOC</p>	<p>Mean age 29.7 ± 10.5, male 10.3%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Spivak et al;³⁵⁸ peer reviewed; 2023</p>	<p>Patients with mild COVID-19 infection. 152 assigned to HCQ 800 mg once followed by 400 mg</p>	<p>Mean age 41.9 ± 14.5, male 52%, hypertension 14.2%, diabetes 7.6%, COPD 2.2%, CKD 0.5%,</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events</p>	

	a day for 5 days and 150 assigned to SOC	immunosuppression 1.9%, obesity 2.5%			
Llanos-Cuentas et al. ³⁵⁹ peer reviewed; 2023	Individuals exposed to SARS-COV-2. 34 assigned to HCQ 600 mg once followed by 400 meg a day every other day for 28 days and 31 assigned to SOC	Mean age 39, male 41.2%, hypertension 10.4%, diabetes 1.4%, asthma 14.6%, obesity 10.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Amira et al. ³⁶⁰ peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 50 assigned to HCQ 400 mg a day for 5 days and 50 assigned to SOC	Mean age 50.6, male 52%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	Notes: Non-blinded study. Concealment of allocation probably inappropriate.

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. ³⁶¹ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Notes: Blinding and concealment are probably inappropriate.</p>

Cannellotto et al ; ³⁶² peer reviewed; 2021	Patients with severe COVID-19 infection. 20 assigned to hyperbaric oxygen 5 sessions (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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○
COVID-19-HBO trial ; ³⁶³ Kjellberg et al; preprint; 2021	Patients with severe COVID-19 infection. 15 assigned to hyperbaric oxygen 60 minutes at 2.4 ATA for up to 5 sessions 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.	Hospitalization: No information
Siewiera et al ; ³⁶⁴ 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)

Hyperimmune IVIG may not increase severe adverse events, however its effects on other 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					

Ali et al ; ³⁶⁵ 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 have introduced bias to symptoms and adverse events outcomes results.	Mortality: Very low certainty ⊕○○○
Parikh et al ; ³⁶⁶ 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.	Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
ITAC trial; Polizzotto et al ; ³⁶⁷ 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	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○
COVID-Compromise trial ; ³⁶⁸ 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	Hospitalization: Very low certainty ⊕○○○
Alemany et al ; ³⁶⁹ peer reviewed; 2023	Patients with mild COVID-19 infection. 305 assigned to C-IVIG 1 gr to 2 gr C19-IG20% (SC) and	Mean age 39.7, male 57.3%, hypertension 6.9%, diabetes 5%, COPD 0.4%, asthma 5.6%, CHD 0.9%, CKD 0.9%, obesity	Vaccinated 0%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

	156 assigned to SOC	16.7%			
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 ; ¹²⁹ peer reviewed; 2022	Patients with critical COVID-19 infection. 42 assigned to hypertonic saline (inhaled) twice a day and 52 assigned to SOC	Mean age 65.7 , male 68%, hypertension 60.6%, diabetes 30.9%, CHD 7.4%, cerebrovascular disease 2.1%	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
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					

Prasenoahadi et al ; ³⁷⁰ 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
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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
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RCT

<p>INSPIRE trial,³⁷¹ Coutre et al; peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 22 assigned to ibrutinib 420 mg a day for 14 to 28 days and 24 assigned to SOC</p>	<p>Median age 51.5, male 70%, hypertension 39%, diabetes 43%, COPD 2%, asthma 9%, CHD 2%, CKD 4%, obesity 24%</p>	<p>Corticosteroids 63%, remdesivir 72%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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IC14

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
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RCT

<p>I-SPY COVID trial;⁷⁴ Files et al; peer reviewed; 2023</p>	<p>Patients with severe to critical COVID-19 infection. 67 assigned to IC14 4 mg/kg on day 1, followed by 2 mg/kg on days 2, 3, 4 and 76 assigned to SOC</p>	<p>Mean age 60 ± 17, male 63.6%, hypertension 51%, diabetes 31.5%, COPD 15.4%, CKD 7%,</p>	<p>Corticosteroids 100%, remdesivir 100%,</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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Icatibant

Icatibant may not reduce mortality. 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
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RCT

<p>Mansour et al;³⁷² preprint; 2020</p>	<p>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</p>	<p>Mean age 51.6 ± 11.5, male 53.3%, hypertension 50%, diabetes 46.7%, asthma 3.3%, obesity 43.3%</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: RR 1.02 (95%CI 0.74 to 1.42); RD 0.3% (95%CI -4.2% to 6.7%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p>
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ICAT-COVID trial ; ³⁷³ Malchair et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 37 assigned to 90 mg a day for 3 days and 36 assigned to SOC	Mean age 53, male 67.1%	Vaccinated 32.9%	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: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
I-SPY COVID trial ; ⁷⁴ Files et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 96 assigned to 90 mg a day for 6 days and 183 assigned to SOC	Mean age 65.9 ± 14, male 63.4%, hypertension 63.4%, diabetes 36.6%, COPD 22.9%, CKD 13.6%,	Corticosteroids 100%, remdesivir 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.	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 ; ³⁷⁴ kosmopoulos et	Patients with mild COVID-19 infection. 46 assigned to icosapent ethyl 8 g	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and	Mortality: No information Invasive mechanical

al; peer reviewed; 2021	a day for three days followed 4 g a day for 11 days and 49 assigned to SOC			adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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Imatinib

Imatinib may not increase severe adverse events. The effects of imatinib 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					
COUNTER-COVID trial ³⁷⁵ Aman et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 197 assigned to	Median age 64 ± 17, male 69%, hypertension 37.6%, diabetes 25%, COPD 18.4%,	Corticosteroids 72%, remdesivir 21%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and	Mortality: Very low certainty ⊕○○○ Invasive

	imatinib 800 mg once followed by 400 mg a day for 10 days and 188 assigned to SOC	asthma 18%, CHD 22%, obesity 38%		adverse events	<p>mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 1.05 (95%CI 0.84 to 1.32); RD 0.5% (95%CI -1.6% to 3.3%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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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. ³⁷⁶ preprint; 2021	Patients with moderate COVID-19 infection. 102 assigned to indomethacin	Mean age 47 ± 16, male 56.2%, hypertension 19%, diabetes 29%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive</p>

	75 mg a day and 108 assigned to SOC			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ³⁷⁷ Fisher et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 29 assigned to	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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive</p>

	infliximab and 34 assigned to SOC			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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
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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. ³⁷⁸ peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to	Mean age 53.8 ± 12.5, male 65.1%, comorbidities 80%	Corticosteroids 57.2%	Low for mortality and mechanical ventilation; low for symptom resolution,	Mortality: Very low certainty ⊕○○○

	INM005 4 mg/kg in two doses on days 1 and 3 and 123 assigned to SOC			infection, and adverse events	<p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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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 ; ³⁷⁹ Esquivel-Moynelo et al; preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, antibiotics 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and	<p>Mortality: No information</p> <p>Invasive mechanical</p>

	interferon alpha-2b plus interferon gamma twice a week for two weeks (standard care) and 33 assigned to interferon alpha-2b three times a week (IM)	coronary heart disease 6.3%, any comorbidities 50.8%		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
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Interferon beta-1a

IFN beta-1a probably does not reduce mortality or invasive mechanical ventilation requirements.

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					

<p>Davoudi-Monfared et al;³⁸⁰ preprint; 2020</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: RR 0.99 (95%CI 0.75 to 1.31); RD -0.2% (95%CI -4% to 5%); Moderate certainty ⊕⊕⊕○</p> <p>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 ⊕⊕⊕○</p>
<p>WHO SOLIDARITY trial;³²³ Pan et al; peer reviewed; 2020</p>	<p>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</p>	<p>Age range 50-69 years old 46.3%, male 62.3%, diabetes 25.2%, COPD 5.4%, asthma 4.3%, CHD 22%</p>	<p>Steroids 58.7%, convalescent plasma 2.4%, Anti IL6 3.6%</p>	<p>Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>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 ⊕⊕⊕○</p>
<p>COVIFERON trial;³⁸¹ Darazam et al; Preprint; 2020</p>	<p>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</p>	<p>Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,</p>	<p>Hydroxychloroquine 100%, lopinavir-ritonavir 100%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○</p> <p>Adverse events: RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕○</p>
<p>Darazam et al;³⁸² Preprint; 2020</p>	<p>Patients with severe to critical COVID-19. 85 assigned to interferon beta-1a 88 micrograms on</p>	<p>Mean age 59.8 ± 16.5, male 61.9%, hypertension 37.3%, diabetes 26.8%, COPD 1.2%, asthma 1.8%, CHD 18.7%,</p>	<p>Corticosteroids 1.1%, lopinavir-ritonavir 100%</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p>	<p>Hospitalization: Very low certainty ⊕○○○</p>

	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 ³⁸³ 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 ³⁸⁴ 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 ³⁸⁵ 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.

<p>Monk P et al;³⁸⁶ et al; peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 57.1 ± 13.2, male 59.2%, hypertension 54.7%, diabetes 22.6%, COPD 44.2%, asthma %, coronary heart disease 24.5%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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SPRINTER trial ; ³⁸⁷ Monk et al; peer reviewed; 2023	Patients with severe COVID-19 infection. 309 assigned to Interferon beta-1a_INH nebulized once a day for 15 days and 314 assigned to SOC	Mean age 53, male 66%, hypertension 37.5%, diabetes 17.8%, COPD 6.7%, CKD 3.4%, cerebrovascular disease 2.1%, cancer 5.1%, obesity 23%	Corticosteroids 87%, remdesivir 18.9%; Vaccinated 27%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
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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
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RCT

Rahmani et al ; ³⁸⁸ peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to interferon beta-1b 250 mcg subcutaneously every other day for	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart	Corticosteroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical
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	two consecutive weeks and 33 assigned to standard of care	disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%		Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○
COVIFERON trial ; ³⁸¹ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
UW 20-535 trial ; ³⁸⁹ 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 ; ³⁹⁰ Peer reviewed; 2021	Patients with moderate COVID-19 infection. 18 assigned to interferon gamma	Mean age 63 ± 12, male 44%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and	Mortality: No information Invasive mechanical

	500000 IU a day for 5 days and 18 assigned to SOC			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
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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 ; ³⁹¹ peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2	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	Mortality: Very low certainty ⊕○○○ Invasive

	mg once a day for six days and 40 assigned to standard of care			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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 ; ¹⁷⁰ Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to IL-2 1.5	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse	Mortality: Very low certainty ⊕○○○ Invasive

	million IU per day for seven days and 16 assigned to SOC	5%		events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<p>mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ³⁹² Chahla et al; Preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 117 assigned to ivermectin + iota-	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	Mortality: Very low certainty ⊕○○○

	carrageenan 12 mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC			adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
CARR-COV-02 trial , ³⁹³ 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.	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○

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 , ³⁹⁴ preprint; 2022	Patients with moderate to critical COVID-19 infection. 300	Mean age 54, male 48.8%, hypertension 60.6%, diabetes 13.2%, asthma 24%,	Corticosteroids 12.5%	High for mortality and mechanical ventilation; high for symptom resolution,	Mortality: Very low certainty ⊕○○○

	assigned to isothymol 6 mg until discharge and 300 assigned to SOC	CHD 10.8%, CKD 5%, obesity 16.8%		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).	Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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-C19-02-1-00 trial ³⁹⁵ Kumar et al; preprint; 2020	Patients with severe COVID-19. 20 assigned to itolizumab 1.6	Mean age 49 ± 13, male 86.6%, hypertension 20%,	Nr	High for mortality and mechanical ventilation; high for symptom resolution,	Mortality: Very low certainty ⊕○○○

	mg/kg once followed by 0.8 mg/kg weekly and 10 assigned to standard of care			infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Ivermectin

Ivermectin probably does not reduce mortality nor improves time to symptom resolution and probably does not increase severe adverse events. In patients with recent onset disease ivermectin does not have an important effect on hospitalizations. 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 ; ³⁹⁶ Shouman et al;	Individuals exposed to SARS-CoV-2 infection. 203	Mean age 38.72 ± 15.94, male 51.3%, hypertension 10.2%,	NR	High for mortality and invasive mechanical ventilation; high for	Mortality: RR 1 (95%CI 0.8 to 1.25); RD -0%

peer-reviewed; 2020	assigned to ivermectin 15 to 24 mg and 101 assigned to standard of care	diabetes 8.1%, CKD 1%, asthma 2.7%		symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	(95%CI -3.2% to 4%); 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 ⊕○○○
Chowdhury et al ; ³⁹⁷ preprint; 2020	Patients with mild to moderate COVID-19. 60 assigned to ivermectin plus doxycycline 200 µg/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.	Symptom resolution or improvement: RR 1.03 (95%CI 0.99 to 1.07); RD 1.8% (95%CI -0.6% to 4.2%); High certainty ⊕⊕⊕⊕
Podder et al ; ³⁹⁸ peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 µg/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.	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 1.1 (95%CI 0.73 to 1.65); RD 1% (95%CI -2.8% to 6.6%); Moderate certainty ⊕⊕⊕○
Hashim et al ; ³⁹⁹ preprint; 2020	Patients with mild to critical COVID-19. 70 assigned to ivermectin plus doxycycline 200 µg/kg two or three doses + 100 mg twice a day for 5 to 10 days and 70 assigned to standard of care	Mean age 48.7 ± 8.6, male %	Corticosteroids 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.	Hospitalization: RR 0.91 (95%CI 0.75 to 1.11); RD -0.4% (95%CI -1.2% to 0.5%); High certainty ⊕⊕⊕⊕
Mahmud et al ; ⁴⁰⁰ peer-reviewed;	Patients with mild to moderate	Mean age 39.6 ± 13.2, male 58.8%,	NR	Low for mortality and mechanical	

2020	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			ventilation; low for symptom resolution, infection, and adverse events. Notes: 8% of patients were lost to follow-up.	
Elgazzar et al (mild); ⁴⁰¹ preprint (now retracted); 2020	Patients with mild to moderate COVID-19. 100 assigned to ivermectin 400 µg/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); ⁴⁰¹ preprint (now retracted); 2020	Patients with severe COVID-19. 100 assigned to ivermectin 400 µg/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); ⁴⁰¹ preprint (now retracted); 2020	Individuals exposed to SARS-CoV-2 infection. 100 assigned to ivermectin 400 µg/kg twice (second dose after one week) and 100 assigned to standard of care	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.	
Krolewiecki et al ; ⁴⁰² peer-	Patients with moderate to severe	Mean age 40.2 ± 12, male 55.5%,	NR	Low for mortality and mechanical	

reviewed; 2020	COVID-19. 20 assigned to ivermectin 0.6 mg/kg for 5 days and 12 assigned to standard of care	hypertension 13.3%, diabetes 15.5%, COPD 11.1%		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 , ⁴⁰³ 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 , ⁴⁰⁴ 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 , ⁴⁰⁵ Chaccour et al; peer-reviewed; 2020	Patients mild (early within 3 days of onset) COVID-19. 12 assigned to ivermectin 400 microg/kg and 12 assigned to SOC	Median age 26 ± 36, male 50%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
Cachar et al , ⁴⁰⁶ 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 ; ⁴⁰⁷ 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 ; ⁴⁰⁸ 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 ; ³⁹² 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 ; ⁴⁰⁹ 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. ⁴¹⁰ 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. ⁴¹¹ 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. ⁴¹² 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. ⁴¹³ 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. ⁴¹⁴ 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. ³³³ 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. ⁴¹⁵ 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. ³³⁵ 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. ⁴¹⁶ peer-reviewed (now retracted); 2021	Patients with moderate to critical COVID-19 infection. 27 assigned to	Mean age 49.4 ± 14.6, male 45.2%	Corticosteroids 32.3%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and	

	ivermectin 100 to 400 mcg/kg and 4 assigned to SOC			adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Kishoria et al ; ⁴¹⁷ 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 ; ³³⁶ 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 ; ⁴¹⁸ 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 ; ⁴¹⁹ 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 ; ⁴²⁰ 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 ; ⁴²¹ 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 ; ⁴²² Buonfrate et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 61 assigned to ivermectin 600 to 1200 µg/kg once a day for 5 days and 32 assigned to SOC	Median age 47 ± 27, male 58.1%, diabetes 9.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
Manomaipiboon et al ; ⁴²³ preprint; 2021	Patients with mild COVID-19 infection. 36 assigned to	Mean age 48.6 ± 14.8, male 37.5%, hypertension 40.3%, diabetes 23.6%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution,

	ivermectin 12 mg a day for 5 days and 36 assigned to SOC	CHD 2.8%, CKD 6.9%, cerebrovascular disease 2.8%		infection, and adverse events	
I-TECH trial ; ⁴²⁴ 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 ; ⁴²⁵ 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 ; ⁴²⁶ 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; NCT04673214 ; other; 2021	Patients with mild COVID-19 infection. 65 assigned to ivermectin adjusted to body weight and 46 assigned to SOC	Age (18 – 65 years old) 96.4% , male 47.7%,	NR	NA	
ACTIV-6 trial ; ⁴²⁷ Naggie et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 817 assigned to ivermectin 400 µg/kg for three	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	Remdesivir 0.3%, Vaccinated 48.8%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

	days and 774 assigned to SOC	40.8%		
Rezai Mild trial ; ⁴²⁸ 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 ; ⁴²⁸ 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.
Angkasekwina treatment trial ; ⁴²⁹ 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:
Angkasekwina prevention trial ; ⁴²⁹ peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 259 assigned to ivermectin 400–600 µg/kg/d and 277 assigned to SOC	Mean age 37.6 ± 12, male 42.2%, hypertension 8.8%, diabetes 4.7%, COPD 0.2%, CHD 1.1%, cerebrovascular disease 0.4%, cancer 1.3%	Vaccinated 84.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:
Mirahmadizadeh et al ; ⁴³⁰ 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:

<p>George et al;⁴³¹ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 41.2 ± , male 70.5%, cancer 75.9%</p>	<p>Corticosteroids 62.5%, remdesivir 18.7%</p>	<p>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.</p>	
<p>PLATCOV - Iver trial;⁴³² Schilling et al; peer reviewed; 2022</p>	<p>Patients with mild to moderate COVID-19 infection. 45 assigned to ivermectin 600µg/kg daily for seven days and 41 assigned to SOC</p>	<p>Mean age 28, male 45.5%</p>	<p>NR</p>	<p>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.</p>	
<p>IRICT trial;³⁵⁴ Elshafie et al; peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 59.4 ± , male 53.4%, hypertension 38.3%, diabetes 27.7%, CKD 9.2%, obesity 19.9%</p>	<p>Corticosteroids 100%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>Nimitvilai et al;⁴³³ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 40, male 45.1%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	

<p>COVID-OUT trial;²⁹¹ Bramante et al; peer reviewed; 2022</p>	<p>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</p>	<p>Median age 45.5, male 45.3%, hypertension 22.8%, diabetes 1.6%, obesity 47.4%</p>	<p>Corticosteroids 1.5%, monoclonal antibodies 4.2%; vaccinated 55.6%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>ACTIV-6 - Iver High dose trial;⁴³⁴ Naggie et al; peer reviewed; 2023</p>	<p>Patients with mild to moderate COVID-19 infection. 602 assigned to Ivermectin 600 µg/kg a day for 6 days and 604 assigned to SOC</p>	<p>Mean age 47.5, male 40.5%, hypertension 26.8%, diabetes 9.2%, COPD 2.2%, asthma 14.4%, CHD 4%, CKD 0.9%, cancer 2%, obesity 38%</p>	<p>Vaccinated 84.1%</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events</p>	

Ivermectin (inhaled)

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
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status	analyzed				of care and GRADE certainty of the evidence
RCT					
Aref et al. ; ⁴³⁵ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
Intravenous immunoglobulin (IVIG) 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					
Sakoulas et al. ⁴³⁶ 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 ⊕○○○
Gharebaghi et al. ⁴³⁷ 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.	Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
Tabarsi et al. ⁴³⁸ 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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
Raman et al. ⁴³⁹ 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	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	

	SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
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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
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RCT

STRUCK trial ; ¹⁷⁰ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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KB109 (microbiome modifier)

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 , ⁴⁴⁰ 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 ; ⁴⁴¹ peer reviewed; 2023	Patients with severe COVID-19 infection. 85 assigned to L-arginine 1.66 g twice a day during hospitalization and 85 assigned to SOC	Mean age 61.5, male 70%, hypertension 42.2%, diabetes 11.4%, CHD 16.2%, obesity 10.2%	Corticosteroids 89.6%, remdesivir 42.1%; Vaccinated 46.4%	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
Muralidharan et al ; ⁴⁴² 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	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

***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 ; ⁴⁴³ Endam et al; preprint; 2021	Patients with mild recently diagnosed COVID-19 infection. 12 assigned to <i>Lactococcus lactis</i> (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 ; ⁴⁴⁴ 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: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○
LF-COVID trial ; ⁴⁴⁵ 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	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○
LAC trial ; ⁴⁴⁶ Matino et al; peer reviewed; 2023	Patients with moderate to severe COVID-19 infection. 113 assigned to lactoferrin 800 mg a day for 30 days and 105 assigned to SOC	Mean age 65.5, male 64.7%, obesity 29.8%	Corticosteroids 44.9%, hydroxychloroquine 0.9%, azithromycin 28.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	Adverse events: No information Hospitalization: No information

Leflunomide

Leflunomide may increase severe adverse events, 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					
Hu et al. ⁴⁴⁷ 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: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information
Wang et al. ⁴⁴⁸ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: RR 1.95 (95%CI 1.3 to 2.92); RD - 9.7% (95%CI 3% to 19.6%); Low certainty ⊕⊕○○
DEFEAT-COVID trial. ⁴⁴⁹ Kralj-Hans et al; ; 2023	Patients with severe to critical COVID-19 infection. 104 assigned to Leflunomide 100 mg a day for 3 days followed by 20 mg a day for 7 days and 110 assigned to SOC	Mean age 55.8, male 67%, diabetes 22%, COPD 12%, CHD 39%, immunosuppression therapy 7%, cancer 3%, obesity 4%	Corticosteroids 95%, hydroxychloroquine 47%, tocilizumab 2.3%,	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

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.

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 ; ⁴⁵⁰ 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	<p>Mortality: RR 0.72 (95%CI 0.44 to 1.19); RD -4.5% (95%CI -9% to 3%); Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: RR 0.71 (95%CI 0.48 to 1.04); RD -5% (95%CI -9% to 0.7%); Low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.82 (95%CI 0.62 to 1.07); RD -1.8% (95%CI -3.9% to 0.7%);</p>

					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. ⁴⁵¹ 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. ⁴⁵² 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.	Mortality: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○ Hospitalization: No information

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 ; ⁴⁵³ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁴⁵⁴ 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
Covid19DPP4i trial ; ⁴⁵⁵ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

<p style="text-align: center;">Lincomycin Uncertainty in potential benefits and harms. Further research is needed.</p>					
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 ; ⁹⁶ 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. ⁴⁵⁶ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ⁴⁵⁷ 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 ⊕⊕⊕⊕
ELACOI trial ; ⁴⁵⁸ 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.	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 ⊕○○○
RECOVERY - Lopinavir-ritonavir trial ; ⁴⁵⁹	Patients with mild to critical COVID-19 infection. 1616	Mean age 66.2 ± 15.9, male 60.5%, diabetes 27.5%,	NR	Low for mortality and invasive mechanical ventilation; some	

Horby et al; other; 2020	assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days and 3424 assigned to standard of care	chronic lung disease 23.5%, coronary heart disease 26%		concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	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 ⊕⊕○○ Hospitalization: Very low certainty ⊕○○○
Huang et al; peer-reviewed; ³⁰⁵ 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; ⁴⁶⁰ 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; ⁴⁶¹ 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	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	

	days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir			probably inappropriate.	
WHO SOLIDARITY trial ; ³²³ 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 ; ⁴⁶² 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 ; ⁴⁶³ 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 ; ⁴⁶⁴ peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	chronic lung disease 2%		infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
Yadollahzadeh et al ; ⁴⁶⁵ 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 ; ³³⁷ 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 ; ⁴⁶⁶ 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.

<p>Ghanei et al.,¹⁰³ peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 110 assigned to 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</p>	<p>Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%</p>	<p>Convalescent plasma 1.8%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>FIGHT-COVID-19 trial,²⁶⁸ Atipornwanich et al; preprint; 2021</p>	<p>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.</p>	<p>Mean age 42 ± 15.7, male 47.8%, obesity 24.6%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>SEV-COVID trial,³⁴⁶ Panda et al; peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	

	600 mg orally every 12 hours) for 10 days and 24 assigned to SOC				
Nekoukar et al ; ⁸⁶ peer reviewed; 2021	Patients with severe COVID-19 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	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 Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hassaniyazad et al ; ²⁷⁴ 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 ; ²⁷⁵ Lowe et al; preprint; 2021	Patients with mild recent 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 ; ²⁷⁶ 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	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	

	lopinavir-ritonavir 400/100 mg a day for 7 days			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 ; ⁴⁶⁷ 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 ⊕○○○
WINCOVID trial ; ⁴⁶⁸ 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.	Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○
IMpaCt-RT trial ; ⁴⁶⁹ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

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 ; ⁴⁷⁰ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ⁴⁷¹ 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 ⊕○○○
Davoodian et al ; ⁴⁷² 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	Symptom resolution or improvement: Very low certainty ⊕○○○
Alizadeh et al ; ⁴⁷³ 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.	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: No information Hospitalization: No information
Mousavi et al ; ⁴⁷⁴ 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 ; ⁴⁷⁵ 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 ; ⁴⁷⁶ 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 ; ⁴⁷⁷ 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 ; ⁴⁷⁸ 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 , ⁴⁷⁹ 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.	
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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 ; ⁴⁸⁰ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

Meplazumab Meplazumab may not increase symptom resolution. 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					
DEFLECT trial ; ⁴⁸¹ Bian et al; peer reviewed; 2023	Patients with severe COVID-19 infection. 126 assigned to meplazumab 0.12 to 0.3 mg/kg once and 41 assigned to SOC	Mean age 48, male 69.6%,	Remdesivir 4.8%, Vaccinated 3.6%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: RR 1.03 (95%CI 0.9 to 1.29); RD 2% (95%CI -10.6% to 17.6%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Mesenchymal stem-cells					
Mesenchymal stem cells probably reduces mortality 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					
Shu et al ; ⁴⁸² 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 0.82 (95%CI 0.64 to 1.03); RD -2.9% (95%CI -5.8% to 0.5%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: Very low certainty ⊕○○○
Shi et al ; ⁴⁸³ preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem cell three infusions with 4.0×10^7 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	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
Lanzoni et al ; ⁴⁸⁴ preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell $100 \pm 20 \times 10^6$ UC-MSC twice and 12 assigned to standard of care	Mean age 58.7 ± 17.5 , male 54.1%, hypertension 66.7%, diabetes 45.8%, coronary heart disease 12.5%, , cancer 4.2%, obesity 66.6%	Corticosteroids 90.4%, remdesivir 66.7%, hydroxychloroquine 12.5%, tocilizumab 20.8%, convalescent plasma 29.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably	Adverse events: RR 0.95 (95%CI 0.78 to 1.15); RD -0.5% (95%CI -2.2% to 1.5%); Low certainty

				inappropriate.	⊕⊕○○
Dilogo et al. ⁴⁸⁵ 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	Hospitalization: No information
Zhu et al. ⁴⁸⁶ peer reviewed; 2021	Patients with severe COVID-19 infection. 29 assigned to mesenchymal stem cell 1 × 10 ⁶ 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. ⁴⁸⁷ 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. ⁴⁸⁸ peer reviewed; 2021	Patients with critical COVID-19 infection. 11 assigned to mesenchymal stem cell three doses of 5 × 10 ⁵ 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 ⁴⁸⁹ Karyana et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 6 assigned to	Age range 31 to 47, male 66.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution,	

	mesenchymal stem cell 5.0×10^7 cells to 1.0×10^8 cells and 3 assigned to SOC			infection and adverse events	
Farkhad et al ; ⁴⁹⁰ 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 ; ⁴⁹¹ preprint; 2023	Patients with severe COVID-19 infection. 21 assigned to mesenchymal stem cell 1×10^6 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.	
STROMA-CoV-2 trial ; ⁴⁹² Monsel et al; peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 21 assigned to mesenchymal stem cell three intravenous infusions of 10^6 UC-MSCs/kg and 24 assigned to SOC	Mean age 63, male 82.2%, hypertension 70%, COPD 2.3%, CHD 13.3%, cerebrovascular disease 10%, immunosuppressive therapy 0%, cancer 0%	Corticosteroids 77.3%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
REALIST trial ; ⁴⁹³ Gorman et al; peer reviewed; 2023	Patients with critical COVID-19 infection. 30 assigned to mesenchymal stem	Mean age 58.4 ± 10.8 , male 74.6%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse	

	cell 200 ml containing 400 x10 ⁶ cells and 29 assigned to SOC			events	
Bowdish et al , ⁴⁹⁴ peer reviewed; 2023	Patients with critical COVID-19 infection. 112 assigned to mesenchymal stem cell two infusions of 2 x 10 ⁶ MSC/kg and 110 assigned to SOC	Mean age 61, male 69.4%, hypertension 59%, diabetes 40.7%, COPD 15.3%, CKD 12.5%, cancer 10.7%,	Corticosteroids 84.7%, remdesivir 67.6%, tocilizumab 5%, plasma 24.8%;	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
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 , ⁴⁹⁵ 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 information
DMMETCOV19-2 trial , ⁴⁹⁶ 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	Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
COVID-OUT trial , ²⁹¹ 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	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	Adverse events: Very low certainty ⊕○○○ Hospitalization: RR 0.92 (95%CI 0.61 to 1.37); RD -

	to SOC				0.4% (95%CI - 1.9% to 1.8%); Low certainty ⊕⊕○○
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. ⁴⁹⁷ 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 , ⁴⁹⁸ 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 ; ⁴⁹⁹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁵⁰⁰ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 , ⁵⁰¹ 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 ⊕○○○
AGILE trial , ⁵⁰² 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.	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 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 ⊕⊕⊕○
Fischer et al , ⁵⁰³ 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	Symptomatic infection (prophylaxis studies): No information
MOVE-OUT trial ; et al , ⁵⁰⁴ 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	Adverse events: RR 0.75 (95%CI 0.48 to 1.19); RD -2.6% (95%CI -5.3% to -1.9%); Low certainty

					⊕⊕○○
HCR/III/MOLCO V/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	Hospitalization: RR 0.66 (95%CI 0.43 to 1.01); RD - 1.6% (95%CI - 2.7% to 0%); Moderate certainty ⊕⊕⊕○
CR216-21 trial ; ⁵⁰⁵ 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 ; ⁵⁰⁶ 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 ; ⁵⁰⁷ 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 ; ⁵⁰⁸ Ariibas et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 226 assigned to	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	

	molnupiravir 400 to 1600 mg a day for 5 days and 78 assigned to SOC			events	
MOVE-OUT - ph2 trial ; ⁵⁰⁹ 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 ; ⁵¹⁰ 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 ; ⁵¹¹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁵¹² 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 ; ⁵¹³ 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 mouthwash with water or no mouthwash	Median age 28.9, 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.	Symptomatic infection (prophylaxis studies): No information
KILLER trial ; ⁵¹⁴ 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.	Adverse events: No information Hospitalization: No information

Elzein et al. ⁵¹⁵ 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. ⁵¹⁶ 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 ⁵¹⁷ Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to mouthwash with β-cyclodextrin-citrox three times a day and 78 assigned to SOC	Mean age 43.8 ± 15.5, male 45.7%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events
Huang et al. ⁵¹⁸ 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. ⁵¹⁹ peer reviewed;	Patients with moderate to severe	Mean age 54.7, male 74.4%, hypertension	NR	Low for mortality and mechanical

2021	COVID-19 infection. 34 assigned to mouthwash cetylpyridinium chloride, zinc, chlorhexidine, hydrogen peroxide and 9 assigned to SOC	30.2%, diabetes 23.2%, COPD 11.6%, CHD 18.6%, CKD 11.6%, obesity 13.9%		ventilation; low for symptom resolution, infection, and adverse events	
Di-Domênico et al. ⁵²⁰ 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 imbalances in baseline risks	
ACPREGCOV trial ⁵²¹ Damiano Costa et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to mouthwash 15 mL of 0.12% chlorhexidine gluconate and 50 assigned to SOC	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	
BUCOSARS trial ⁵²² 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	

<p>Poleti ML et al trial;⁵²³ Poleti et al; ; 2021</p>	<p>Patients with mild COVID-19 infection. 59 assigned to mouthwash with antimicrobial phthalocyanine derivative and 75 assigned to SOC</p>	<p>Mean age 34 ± 21, male 38%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Significant loss to follow-up.</p>	
<p>Alemany et al;⁵²⁴ peer reviewed; 2022</p>	<p>Patients with mild COVID-19 infection. 60 assigned to mouthwash with 0.07% cetylpyridinium and 58 assigned to SOC</p>	<p>Mean age 46, male 41.5%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p> <p>Notes:</p>	
<p>Barrueco et al;⁵²⁵ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 62.4 ± , male 54.5%,</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	

Bonn et al ; ⁵²⁶ peer reviewed; 2023	Patients with mild COVID-19 infection. 31 assigned to Mouthwash 0.05% CPC and 0.05% CHX once and 30 assigned to SOC	Mean age 29 ± , male 50.8%	Vaccinated 85.9%	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 ; ⁵²⁷ 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 ⊕○○○

<p style="text-align: center;">Mycobacterium w Uncertainty in potential benefits and harms. Further research is needed.</p>					
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 ; ⁵²⁸ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁵²⁹ 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 ⊕○○○
Gaynitdinova et al ; ⁵³⁰ 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.	Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
Taher et al ; ⁵³¹ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 47 assigned to NAC 40 mg/kg a day for 3 days and 45 assigned to SOC	Mean age 57.6 ± 18.7, male 58.7%, diabetes 23.9%, COPD 15.2%, asthma %, CHD 28.2%,	Corticosteroids 69.6%, hydroxychloroquine 90.2%, azithromycin 51.1%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

				inappropriate.	
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. ¹²⁹ 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
Panahi et al. ⁵³² 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information 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 ; ⁵³³ 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 ; ³⁷⁷ 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

<p style="text-align: center;">Nano-curcumin Uncertainty in potential benefits and harms. Further research is needed.</p>					
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 ; ⁵³⁴ 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
Sadeghizadeh et al ; ⁵³⁵ peer reviewed; 2023	Patients with moderate to severe COVID-19 infection. 21 assigned to nano-curcumin 140 mg a day for 14 days and 21 assigned to SOC	Median age 53.5 ± , male 66.6%, hypertension 16.6%, diabetes 16.6%, COPD 2.4%, asthma %, CHD 2.4%, CKD %, cerebrovascular disease %, immunosuppressive therapy %, cancer %, obesity %	Corticosteroids %, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated %	High for mortality and 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

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. ⁵³⁶ 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 ⊕○○○
Yildiz et al. ⁵³⁷ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information
George et al. ⁵³⁸ peer reviewed; 2021	Patients with mild COVID-19 infection. 20 assigned to nasal	Age range 22-45		Low for mortality and mechanical ventilation; low for symptom resolution,	Hospitalization: No information

	hypertonic saline (Caesium rich hypertonic salts) and 20 assigned to SOC			infection and adverse events	
Baxter et al ; ⁵³⁹ 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%, immunocompromise 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
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RCT

Nesari et al ; ⁵⁴⁰ 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 inappropriate. Significant loss to follow-up.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○
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					Adverse events: No information Hospitalization: No information
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Nelfinavir

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
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RCT

Miyazaki et al. ⁵⁴¹ peer reviewed; 2023	Patients with mild COVID-19 infection. 63 assigned to nelfinavir 2250 mg a day for 14 days and 60 assigned to SOC	Mean age 45.2 ± , male 60.2%	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.	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
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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					
Abdulmir et al ; ⁵⁴² preprint; 2021	Patients with mild to critical COVID-19 infection. 75 assigned to nicosamaide 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
Cairns et al ; ⁵⁴³ peer reviewed; 2021	Patients with mild COVID-19 infection. 33 assigned to nicosamide 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	Symptomatic infection (prophylaxis studies): No information 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 , ⁵⁴⁴ 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%, immunosuppression 6%,	Corticosteroids 64.5%, tocilizumab 0.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: RR 1.02 (95%CI 0.67 to 1.57); RD 0.3% (95%CI -5.2% to 5.7%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
<i>Nigella sativa +/- Honey</i> 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 ; ⁵⁴⁵ Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + <i>Nigella sativa</i> 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 Hospitalization: Very low certainty ⊕○○○
Koshak et al , ⁵⁴⁶ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 91 assigned to <i>Nigella sativa</i> 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.	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: Very low certainty ⊕○○○
Nirmatrelvir-ritonavir Nirmatrelvir-ritonavir probably reduces hospitalizations 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					
EPIC-HR trial , ⁵⁴⁷ 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: Very low certainty ⊕○○○
Liu et al , ⁵⁴⁸ peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 132 assigned to Nirmatrelvir/ritonavir 600/200 mg a day for 5 days and 132 assigned to SOC	Mean age 70.35, male 53.7%, diabetes 36.7%, COPD 20%, CKD 4.2%, immunosuppressive therapy 0.4%, cancer 23.9%	Corticosteroids 3%, Vaccinated 26.5%	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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.53 (95%CI 0.33 to 0.87); RD -4.8% (95%CI -6.8% to -1.3%); 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 ; ⁵⁴⁹ 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 ⊕○○○
Fontanesi et al ; ⁵⁵⁰ 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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○
Silva et al ; ⁵⁵¹ 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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○
Vanguard trial ; ⁵⁵² Rossignol et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 184	Mean age 40.3 ± 15.4, male 43.5%, comorbidities 34%	NR	Low for mortality and mechanical ventilation; low for symptom resolution,	

	assigned to nitazoxanide 600 mg a day for 5 days and 195 assigned to SOC			infection, and adverse events	
NACOVID trial ; ⁵⁵³ 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 ; ⁵⁵⁴ 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 ; ⁵⁵⁵ 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 ; ⁵⁵⁶ 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 ⊕○○○
Winchester et al ; ⁵⁵⁷ peer-reviewed; 2021	Patients with mild COVID-19 infection. 40 assigned to nitric oxide nasal spray (NONS) 4 sprays 5 to 6 times a day for 9 days and 40 assigned to SOC	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 Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
NO COV-ED trial ; ⁵⁵⁸ 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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Tandon et al ; ⁵⁵⁹ 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 comorbidities 12.1%	Vaccinated 46.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
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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
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RCT

Mobarak et al ; ⁵⁶⁰ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 39 assigned to naproxen 1000 mg a day and 38 assigned to SOC	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:	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization:</p>
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					No information
Non-RCT					
Eilidh et al ; ⁵⁶¹ 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 ; ⁵⁶² 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 ; ⁵⁶³ peer-reviewed;	Patients with mild to severe COVID-	Median age 54 ± 23, male 41.5%, chronic	Corticosteroids 7.1%	High for mortality and invasive mechanical	

2020	19 infection. 224 received NSAID and 896 received alternative treatment schemes	lung disease 3.9%, asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%		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. , ⁵⁶⁴ 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. , ⁵⁶⁵ preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 535519 received NSAID and 1924095 received alternative treatment schemes	Median age 51 ± 23, male 42.7%, hypertension 19.6%, diabetes 9.6%, chronic lung disease 2.4%, asthma %, coronary heart disease 0.5%, chronic kidney disease 2.8%, cancer 5.2%,	Corticosteroids 2.2%, hydroxychloroquine 0.6%	High for mortality Notes: Non-randomized study 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. , ⁵⁶⁶ 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%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential

		chronic kidney disease 17.5%, immunosuppression 1%, cancer 6.4%,		confounders (not specified).	
Esba et al ; ⁵⁶⁷ 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 ; ⁵⁶⁸ 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. ⁴⁶⁰ 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 ; ⁵⁶⁹ 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 ; ⁵⁷⁰ 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
Doaei et al ; ⁵⁷¹ 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.	Adverse events: No information Hospitalization: No information
COVID-Omega-F trial ; ⁵⁷² 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.	Adverse events: No information Hospitalization: No information
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 , ⁵⁷³ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 , ⁵⁷⁴ 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 ⊕⊕○○ 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
Carvalho Neuenschwander et al , ⁵⁷⁵ 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	
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 , ⁵⁷⁶ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ⁵⁷⁷ 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 ⊕○○○
SEOT trial ; ⁵⁷⁸ 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 blood once a day for 10 days and 30 assigned to SOC	Mean age 43.8 ± 9, male 80%, diabetes 10%	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.	Symptomatic infection (prophylaxis studies): No information 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 ; ⁵⁷⁹ 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 to 1.02); RD -1.8% (95%CI -3.6% to 1.2%); Low certainty ⊕⊕○○
REMAP-CAP - P2Y12 trial ; ⁸³ 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 prasugrel 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.	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

Pacritinib

Pacritinib may not increase symptom resolution or improvement. 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					
PRE-VENT trial ; ⁵⁸⁰ Cafardi et al; peer reviewed; 2023	Patients with Severe COVID-19 infection. 99 assigned to pacritinib 400 mg a day for 14 days and 101 assigned to SOC	Mean age 59.5, male 60%, hypertension 57%, diabetes 40%, COPD 20.5%, CKD 6.5%, cancer 11.5%,	Corticosteroids 96.5%, remdesivir 84.5%, tocilizumab 2%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: RR 0.94 (95%CI 0.8 to 1.12); RD -3.8% (95%CI -13% to 7.3%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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					

<p>Fessler et al.,⁵⁸¹ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 25.5, male %, hypertension 3.3%, asthma 6.6%</p>	<p>Vaccinated 0%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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 ; ⁵⁸² 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 ⊕○○○
Bushan et al ; ⁵⁸³ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 119 assigned to Peg Interferon Alfa 1 µg/kg subcutaneous [SC] injection once and 123 assigned to SOC	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, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Peg-interferon (IFN) lamda

Pegylated Interferon lambda may not have an important effect on hospitalizations and may not increase severe adverse events. 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					

ILIAD trial ; ⁵⁸⁴ 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: Very low certainty ⊕○○○
COVID-Lambda trial ; ⁵⁸⁵ 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.	Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
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	Adverse events: RR 0.76 (95%CI 0.5 to 1.16); RD - 2.4% (95%CI - 5.1% to 1.6%); Low certainty ⊕⊕○○
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	Hospitalization: RR 0.63 (95%CI 0.39 to 1.03); RD - 1.8% (95%CI - 2.9% to 0.1%); Low certainty ⊕⊕○○
TOGHETER IFN trial ; ⁵⁸⁶ Reis et al; peer reviewed; 2023	Patients with mild COVID-19 infection. 931 assigned to Peg-IFN lambda 180 µg once and 1018 assigned to SOC	Median age 43, male 42.9%, hypertension 29.8%, diabetes 9.3%, COPD 2.4%, asthma 9.9%, CHD 2.4%, cancer 1.3%, obesity 36.9%	Vaccinated 83.6%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:	⊕⊕○○
Kim et al ; ⁵⁸⁷ peer reviewed; 2023	Patients with mild to moderate	Mean age 54, male 78.6%, hypertension	Corticosteroids 50%, remdesivir	Low for mortality and mechanical	

	COVID-19 infection. 7 assigned to Peg-IFN lambda 180 mcg on days 1 and 7 and 6 assigned to SOC	57.1%, diabetes 21.4%, COPD 7.1%, asthma 21.4%, CHD 21.4%, obesity 42.9%	50%; Vaccinated 0%	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.	
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 ; ⁵⁸⁸ 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
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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 ; ⁵⁸⁹ 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
Azizi et al ; ⁵⁹⁰ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to pentoxifylline 1200 mg a day for 10 days and 32 assigned to SOC	Mean age 59, male 35%, hypertension 18%, diabetes 32%, CHD 12.5%, cerebrovascular disease 5.5%	Corticosteroids 55.5%,	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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information
Sarhan et al ; ⁵⁹¹ peer reviewed;	Patients with severe to critical	Mean age 64.4, male 64.7%, hypertension	Remdesivir 86.7%, hydroxychloroquine	High for mortality and mechanical	Hospitalization: No information

2023	COVID-19 infection. 30 assigned to pentoxifylline 1200 mg a day for 7 days and 38 assigned to SOC	55.8%, diabetes 39.7%, COPD 4.4%, asthma 11.7%, CHD 20.6%, CKD 2.9%, cerebrovascular disease 1.5%, cancer 8.8%, obesity 11.7%	2.9%, lopinavir-ritonavir 4.4%, tocilizumab 54.4%	ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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. ⁵⁹² 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

Plasmapheresis 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					
Sadeghi et al. ⁵⁹³ peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 45 assigned to plasmapheresis three times every other day and 41 assigned to SOC	Mean age 52, male 53.5%, hypertension 9.3%, diabetes 11.6%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	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

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 ; ⁵⁹⁴ 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:	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement:No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ⁵⁹⁵ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁵⁹⁶ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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 ; ⁵⁹⁷ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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. ³³⁶ 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
Batioglu-Karaaltin et al. ⁵⁹⁸ peer reviewed; 2023	Patients with mild COVID-19 infection. 30 assigned to povidone iodine (nasal) 1% four times a day and 30 assigned to SOC	Mean age 39.7 ± , male 40%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	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 , ⁵⁹⁹ 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 ⊕○○○
PROCOV-19-2020 trial , ⁶⁰⁰ Ivashkin et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 99 assigned to probiotics three times a day for 14 days and 101 assigned to SOC	Mean age 64 ± , male 46%	NR	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: No information 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 ⊕⊕○○
PROTECT-EHC trial , ⁶⁰¹ 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	Adverse events: No information Hospitalization: No information
ABB-COVID19 trial , ⁶⁰² Gutiérrez-Castrellón et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 147 assigned to	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	

	probiotics 1 capsule a day for 30 days and 146 assigned to SOC			events	
Saviano et al ; ⁶⁰³ peer reviewed; 2022	Patients with severe COVID-19 infection. 40 assigned to probiotics (<i>Bifidobacterium lactis</i> LA 304, <i>Lactobacillus salivarius</i> LA 302) and <i>Lactobacillus acidophilus</i> 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 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
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RCT

Ghandehari et al ; ⁶⁰⁴ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis)</p>
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					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 ; ⁶⁰⁵ Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 g a day and 5 assigned to standard of care	Mean age 28.5 ± 3.85, male 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: 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

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
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RCT

Bee-Covid trial ; ⁶⁰⁶ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>COMBAT-COVID trial;⁶⁰⁷ Johansson et al; peer reviewed; 2021</p>	<p>Patients with critical COVID-19 infection. 41 assigned to prostacyclin 1 ng/kg/min for 3 days and 39 assigned to SOC</p>	<p>Mean age 67, male 66.2%, hypertension 61.2%, COPD 12.5%, CKD 2.5%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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					
Thlo trial , ⁶⁰⁸ 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	<p>Mortality: RR 1.05 (95%CI 0.64 to 1.7); RD 0.8% (95%CI -5.7% to 11.2%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁶⁰⁹ 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 ⊕○○○
AB-DRUG-SARS-004 trial ; ⁶¹⁰ Cadegiani et al; peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 171 assigned to proxalutamide 200 mg a day for 15 days and 65 assigned to SOC	Mean age 45.3 ± 13, male 54.2%, hypertension 22.5%, diabetes 8.9%, COPD 0%, asthma 5%, CKD 0.4%, cancer 17%, obesity 15.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
KP-DRUG-SARS-003 trial ; ⁶¹¹ 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.	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 ⊕○○○
AB-DRUG-	Patients with mild	Mean age 44.2 ±	NR	High for mortality and	

SARS-005 trial ; ⁶¹² Cadegiani et al; peer reviewed; 2021	to moderate COVID-19 infection. 75 assigned to proxalutamide 200 mg a day for 7 days and 102 assigned to SOC	12.1, male 0%, hypertension 31.1%, diabetes 8.5%, COPD 0.6%, obesity 18.1%		mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Randomization process presented as "Blocked" but described as a cluster randomization.	
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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 ; ⁶¹³ Fragoso-Saavedra et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 94 assigned to pyridostigmine 60 mg a day for 14 days and 94 assigned to SOC	Median age 52 ± 20, male 59.6%, hypertension 35.1%, diabetes 36.2%, COPD 4.3%, asthma %, CHD 2.1%, obesity 43.1%	Corticosteroids 74.5%, tocilizumab 5.3%	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: 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. ⁶¹⁴ 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
Di Piero et al. ⁶¹⁵ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to quercetin 400-600 mg a day for 14 days 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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○
Shohan et al. ⁶¹⁶ 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:	Adverse events: No information Hospitalization: Very low certainty ⊕○○○
Rondanelli et al. ⁶¹⁷ peer	Individuals exposed to SARS-CoV-2	Mean age 49.3 ± 12.9, male 52.5%	NR	Low for mortality and mechanical	

reviewed; 2021	infection. 60 assigned to quercetin 500 mg a day and 60 assigned to SOC			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.	
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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
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RCT

Nicastri et al , ⁶¹⁸ peer reviewed; 2021	Patients with moderate COVID-19 infection. 42 assigned to raloxifene 60 to 120 mg for 14 days and 19 assigned to SOC	Mean age 56.7 ± 10.1, male 54.1%, hypertension 26.2%, diabetes 0.66%, COPD %, asthma 1.6%	Corticosteroids 14.7%, remdesivir 1.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 : ⁶¹⁹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

Ravulizumab

Ravulizumab may not 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					
Annane et al ; ⁶²⁰ peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 135 assigned to ravulizumab 2400 to 3000 mg once and 600 to 900 mg on days 5, 10 and 15 and 66 assigned to SOC	Mean age 63, male 68.1%, hypertension 67.2%, diabetes 50.1%, COPD 35.3%, asthma %, CHD 30.8%, CKD 17.4%, obesity 35.3%	Corticosteroids 97.5%, remdesivir 61.7%, hydroxychloroquine 3.5%, tocilizumab 11.9%, convalescent plasma 16.9%;	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: RR 1.01 (95%CI 0.75 to 1.36); RD 0.1% (95%CI -4.1% to 5.8%); 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

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
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RCT

<p>EB-P12-01 trial.⁶²¹ Stasko et al; peer reviewed; 2021</p>	<p>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</p>	<p>Median age 40 ± 20.6, male 52%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Li et al,⁶²² peer-reviewed; 2020</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 9.6%, ATB 22.3%, intravenous immunoglobulin 3.2%, lopinavir-ritonavir 44.7%</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

Streinu-Cercel et al. ⁶²³ 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 ⁶²⁴ Kim et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 15 assigned to regdanvimab 20 to 80 mg once and 3 assigned to SOC	Median age 52 ± 8, male 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	Symptom resolution or improvement: RR 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
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RCT

RCT					
Weinreich et al. ⁶²⁵ 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	<p>Mortality: RR 0.83 (95%CI 0.63 to 1.09); RD -2.7% (95%CI -5.9% to 1.4%); Low certainty ⊕⊕○○</p> <p>Mortality (seronegative): RR 0.79 (95%CI 0.71 to 0.89); RD -3.2% (95%CI -4.6% to -1.8%); Moderate certainty ⊕⊕⊕○</p>
RECOVERY - REGEN-COV trial. ⁶²⁶ 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%	<p>Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Invasive mechanical ventilation: RR 0.79 (95%CI 0.54 to 1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕○○</p> <p>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 ⊕⊕⊕○</p>
O'Brien et al. ⁶²⁷ peer reviewed; 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	<p>Symptom resolution or improvement: RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕○○</p>
Herman et al. ⁶²⁸ peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 841 assigned to REGEN-COV2 (Regeneron) 1200 mg once and 842 assigned to SOC	Median age 43 ± 25, male 45.9%, 6.8%, CKD 1.9%, immunosuppressive therapy 1%, obesity 34.1%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Symptom resolution or improvement: RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕○○</p>
OPTIMISE-C19	Patients with mild	Mean age 56 ± 16,	NR	Low for mortality and	<p>Symptom resolution or improvement</p>

trial ; ¹¹⁴ McCreary et al; peer reviewed; 2022	COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2 (Regeneron) and 1013 assigned to bamlanivimab +/- etesevimab	male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD 6.5%, immunosuppressive therapy 27%, obesity 48%		mechanical ventilation; low for symptom resolution, infection, and adverse events	(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% (95%CI -16% to -4.2%); High certainty ⊕⊕⊕⊕ 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 ⊕⊕⊕○
Somersan-Karakaya et al ; ⁶²⁹ peer-reviewed; 2021	Patients with moderate to severe COVID-19 infection. 804 assigned to REGN-COV2 (Regeneron) 2.4 to 8 gr once and 393 assigned to SOC	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	
R10933-10987-COV-20145 trial ; ⁶³⁰ 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:	
Isa et al ; ⁶³¹ 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 ; ⁶³² 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 ; ⁶³³ Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD	NR	Low for mortality and mechanical ventilation; low for symptom resolution,	

	assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	16%, CKD 4.7%		infection and adverse events	
MANTICO trial ; ¹¹⁷ 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.	
PLATCOV - Regen trial ; ⁴³² 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
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RCT

<p>ACTT-1 trial; Beigel et al;⁶³⁴ peer-reviewed; 2020</p>	<p>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 to standard of care</p>	<p>Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Mortality: RR 0.93 (95%CI 0.89 to 1.03); RD -1.1% (95%CI -1.8% to 0.5%); Moderate certainty ⊕⊕⊕○</p> <p>Invasive mechanical ventilation: RR 0.76 (95%CI 0.56 to 1.04); RD -4.2% (95%CI -7.6% to 0.7%); Moderate certainty ⊕⊕⊕○</p>
<p>SIMPLE trial; Goldman et al;⁶³⁵ peer-reviewed; 2020</p>	<p>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)</p>	<p>Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Symptom resolution or improvement: RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
<p>CAP-China remdesivir 2 trial;⁶³⁶ Wang et al; peer-reviewed; 2020</p>	<p>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</p>	<p>Median age 65 ± 7.5, male 60.5%, hypertension 43%, diabetes 23.7%, coronary heart disease 7.2%</p>	<p>Corticosteroids 65.6%, lopinavir-ritonavir 28.4%, IFN 32.2%, ATB 91.1%</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Severe Adverse events: RR 0.77 (95%CI 0.46 to 1.29); RD -2.3% (95%CI -5.5% to 3%); Low certainty ⊕⊕○○</p> <p>Hospitalization: RR 0.28 (95%CI 0.11 to 0.75); RD -3.4% (95%CI -4.3% to -1.2%); Low certainty ⊕⊕○○</p>
<p>SIMPLE 2 trial; Spinner et al;⁶³⁷ peer-reviewed; 2020</p>	<p>Patients with moderate COVID-19 infection. 384 assigned to remdesivir 200 mg on day 1 followed by 100 mg a day</p>	<p>Median age 57 ± 9, male 61.3%, hypertension 42%, diabetes 40%, asthma 14%, coronary heart disease 56%</p>	<p>Corticosteroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%</p>	<p>Some concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p>	<p>Hospitalization: RR 0.28 (95%CI 0.11 to 0.75); RD -3.4% (95%CI -4.3% to -1.2%); Low certainty ⊕⊕○○</p>

	for 5 to 10 days and 200 assigned to standard of care			Notes: Non-blinded study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY , ³²³ Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 4146 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 4129 assigned to SOC	Age range 50 – 69 years old 46.2%, male 63.4%, diabetes 27.2%, COPD 6.8%, asthma 5.9%, CHD 22.5%	Steroids 67.7%, convalescent plasma 3.3%, Anti IL6 4.5%	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.	
Mahajan et al , ⁶³⁸ 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 , ⁶³⁹ 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 , ⁶⁴⁰ 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 , ⁶⁴¹ 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%, immunosuppression 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 , ⁶⁴² 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
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RCT

<p>Gilead et al; NCT04539262; other; 2021</p>	<p>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</p>	<p>Age > 60 years old 12.9%, male 50%</p>	<p>NR</p>	<p>NA</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe Adverse events: No information</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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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
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RCT

<p>REPAVID-19 trial;⁶⁴³ Landoni et al; peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 36 assigned to reparixin 3600 mg a day for 7 days and 19 assigned to SOC</p>	<p>Mean age 61.7, male 76.4%, hypertension 43.6%, diabetes 23.6%, COPD %, CHD 12.7%, CKD 7.3%, obesity 20%</p>	<p>Corticosteroids 92.7%, remdesivir 23.6%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p>
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				have introduced bias to symptoms and adverse events outcomes results.	<p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

McCreary et al. ⁶⁴⁴ 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 ⊕○○○
Reszinate trial. ⁶⁴⁵ 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	Symptom resolution or improvement: No 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
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RCT

<p>Cheng et al;⁶⁴⁶ peer-reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100 assigned to standard of care</p>	<p>Mean age 45 ± 15, male 56%</p>	<p>Lopinavir-ritonavir 15.5%, IFN 9%, umifenovir 18%</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

SARPAC trial , ⁶⁴⁷ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>BTI-202 trial,⁶⁴⁸ DiNubile et al; peer reviewed; 2022</p>	<p>Patients with severe COVID-19 infection. 31 assigned to rhu- pGSN 12 mg/kg three times and 30 assigned to SOC</p>	<p>Mean age 62.1 ± 11.6, male 57.4%, hypertension 41%, diabetes 32.8%</p>	<p>Corticosteroids 100%, remdesivir 98.4%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Chen et al;⁴⁶¹ preprint; 2020</p>	<p>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 ribavirin plus lopinavir-ritonavir</p>	<p>Mean age 42.5 ± 11.5, male 45.5%</p>	<p>NR</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Hung et al;⁶⁴⁹ peer-reviewed; 2020</p>	<p>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</p>	<p>Median age 52 ± 15, male 54%, hypertension 18.3%, diabetes 13.3%, coronary heart disease 7.9% cerebrovascular disease 1.5%, cancer 1.5%</p>	<p>Corticosteroids 6.2%, ATB 53.3%</p>	<p>Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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RP7214 (DHODH 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
<p>RCT</p>					

Ajit Nair et al ; ⁶⁵⁰ preprint; 2023	Patients with mild to moderate COVID-19 infection. 82 assigned to RP7214 800 mg a day and 81 assigned to SOC	Mean age 46 ± 15, male 70.6%, hypertension 48.5%, diabetes 40.5%, COPD 5.5%, CKD 0.6%, cancer 0.6%, obesity 18.4%	Vaccinated 44.2%	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.	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: Very low certainty ⊕○○○
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Ruxolitinib

Ruxolitinib may reduce mortality but probably does not increase 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					
Cao et al ; ⁶⁵¹ 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 0.73 (95%CI 0.59 to 0.9); RD -4.3% (95%CI -6.6% to -1.6%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: Very
RUXCOVID	Patients with	Mean age 56.5 ±	NR	Low for mortality and	

trial ; ⁶⁵² Han et al; peer reviewed; 2021	moderate to severe COVID-19 infection. 287 assigned to ruxolitinib 10 mg a day for 14 to 28 days and 145 assigned to SOC	13.3, male 54%, diabetes 21.9%, obesity 47%		mechanical ventilation; low for symptom resolution, infection and adverse events	low certainty ⊕○○○ Symptom resolution or improvement: RR 1 (95%CI 0.94 to 1.07); RD 0% (95%CI -3.6% to 4.2%); Moderate certainty ⊕⊕⊕○
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	Symptomatic infection (prophylaxis studies): No information
Garcia-Donas et al ; ⁶⁵³ peer reviewed; 2023	Patients with mild COVID-19 infection. 46 assigned to ruxolitinib 5 mg for 7 days followed by 10 mg for 7 days + sinvastatin 40 mg for 14 days and 46 assigned to SOC	Mean age 64 ± 17, male 69.6%, hypertension 38%, diabetes 16.3%, CHD 13%, cerebrovascular disease 1.1%, cancer 12%, obesity 8.7%	Corticosteroids 77.2%; tocilizumab 29.3%;	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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

SA58 (nasal anti-SARS-COV-2 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 and GRADE certainty of the evidence
RCT					

<p>Song et al;⁶⁵⁴ peer reviewed; 2023</p>	<p>Persons exposed to COVID-19 infection. 824 assigned to SA58 (nasal) 2 mg 5-6 times a day and 299 assigned to SOC</p>	<p>Median age 46, male 89.2%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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					
<p>Barnette et al;⁶⁵⁵ peer reviewed; 2022</p>	<p>Patients with severe COVID-19 infection. 98 assigned to sabizabulin 9 mg for up to 21 days and 52 assigned to SOC</p>	<p>Mean age 59.7 ± 14.7, male 68%, hypertension 60%, diabetes 37.3%, COPD %, CHD 4.7%, CKD 10%, cancer 5.3%, obesity 32.4%</p>	<p>Corticosteroids 82.7%, remdesivir 32.7%, tocilizumab 10%, baricitinib 12%; vaccinated 44.7%,</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom</p>

					<p>resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ⁶⁵⁶ 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	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	Mortality: RR 0.99 (95%CI 0.89 to 1.15); RD -0.2% (95%CI -1.8% to 2.4%); Low certainty ⊕⊕○○ Invasive

	402 assigned to SOC			have introduced bias to symptoms and adverse events outcomes results.	mechanical ventilation: RR 0.98 (95%CI 0.68 to 1.42); RD -0.3% (95%CI -5.5% to 7.3%); Low certainty ⊕⊕○○
Lescure et al ; ⁶⁵⁷ 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	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-COVID19 Study trial ; ⁶⁵⁸ 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	Symptomatic infection (prophylaxis studies): No information
CORIMUNO-SARI trial ; ⁶⁵⁹ 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	Severe adverse events: RR 1.01 (95%CI 0.9 to 1.13); RD 0.1% (95%CI -1% to 1.3%); Moderate certainty ⊕⊕⊕○
CORIMUNO-SARI ICU trial ; ⁶⁶⁰ 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.	Hospitalization: No information
SARCOVID trial ; ⁶⁶¹ García Vicuña et al;	Patients with moderate to severe COVID-19	Median age 61.5, male 67%, hypertension 43%	Steroids 83%, remdesivir 0%, hydroxychloroquine	Low for mortality and mechanical ventilation; high for	

peer reviewed; 2021	infection. 20 assigned to sarilumab 400 mg once and 10 assigned to SOC	diabetes 17%, COPD 7%, CHD 10%, CKD 13%, obesity 10%	20%, lopinavir-ritonavir 17%, tocilizumab %, azithromycin 60%, convalescent plasma 0%	symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SARICOR trial ; ⁶⁶² 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 ; ⁶⁶³ 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 ; ⁶⁶⁴ Branch-Elliman et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to sarilumab 200 to 400 mg (subcutaneous) once and 30 assigned to SOC	Mean age 72.3 ± 12.7, male 92%, hypertension 86%, diabetes 50%, COPD 32%, asthma 16%, CHD 70%, CKD 18%, cancer 48%, obesity 62%	Corticosteroids 86%, remdesivir 80%, hydroxychloroquine 4%, tocilizumab 2%, convalescent plasma 2%;	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

ESCAPE trial , ⁶⁶⁵ 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

<p>BISHOP trial;⁶⁶⁶ Gomes Resende et al; peer reviewed; 2022</p>	<p>Patients with severe COVID-19 infection. 25 assigned to secukinumab 300 mg once and 23 assigned to SOC</p>	<p>Mean age 54 ± 21.5, male 52%, hypertension 48%, diabetes 34%, CHD 8%, obesity 48%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>COVIPOC trial;⁶⁶⁷ Granfeldt et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 20 assigned to senicapoc 50 mg twice and 26 assigned to SOC</p>	<p>Median age 66, male 65.2%, hypertension 34.8%, diabetes 28.3%, COPD 26%, CKD 4.5%, cancer 15.2%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Panatto et al;⁶⁶⁸ peer reviewed; 2022</p>	<p>Patients with mild COVID-19 infection. 36 assigned to sentinox 0.005% 3 to 5 times a day and 18 assigned to SOC</p>	<p>Mean age 40.1 ± 13.7, male 81%, any commorbidities 4%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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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
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RCT

<p>Tian et al.,⁶⁶⁹ peer reviewed; 2021</p>	<p>Patients with moderate COVID-19 infection. 27 assigned to short-wave diathermy and 13 assigned to SOC</p>	<p>Median age 65 ± 18, male 62.5%, hypertension 30%, diabetes %, COPD 45%, CHD 30%, CKD 7.5%, cerebrovascular disease 27.5%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Concealment of allocation and blinding probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>UNAB-003 trial;⁶⁷⁰ Santamarina et al; peer reviewed; 2022</p>	<p>Patients with moderate to severe COVID-19 infection. 20 assigned to sildenafil 75 mg a day for 7 days and 20 assigned to SOC</p>	<p>Median age 57, male 82.5%, diabetes 20%, COPD 0%, asthma 5%</p>	<p>Corticosteroids 82.5%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Blinding and concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>COV-AID-2 trial;⁶⁷¹ other; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 77 assigned to siltuximab 11 mg/kg once and 72 assigned to SOC</p>	<p>Median age 64</p>	<p>Corticosteroids 59%, remdesivir 3.4%, convalescent plasma 0%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p> <p>Notes: Risk of bias assessment extracted from a systematic review.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: No information</p> <p>Hospitalization: No information</p>
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Silver nanoparticles

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
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RCT

<p>Wieler et al;⁶⁷² peer reviewed; 2023</p>	<p>Patients with moderate to severe COVID-19 infection. 19 assigned to silver nanoparticles 1.8 mg a day for 3 days and 19 assigned to SOC</p>	<p>Mean age 69.5 ± 13.5, male 75%, hypertension 62.5%, diabetes 77.5%, COPD 10%, CHD 10%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Aryan et al;⁶⁷³ peer reviewed; 2022</p>	<p>Patients with severe COVID-19 infection. 25 assigned to silymarin 210 mg a day for 14 days and</p>	<p>Mean age 49 ± 11.1, male 48%</p>	<p>Corticosteroids 100%, remdesivir 100%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No</p>
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	25 assigned to SOC			Notes: Concealment of allocation probably inappropriate.	<p>information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ⁶⁷⁴ preprint; 2021	Patients with moderate to severe COVID-19 infection. 66 assigned to sitagliptin 100 mg a	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical</p>

	day and 87 assigned to SOC	6.4%, cancer 5.9%, obesity 18.7%		Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: No information</p> <p>Hospitalization: No information</p>
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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. ⁴⁶⁴ ; peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	Mortality: RR 1.11 (95%CI 0.83 to 1.49); RD 2.2% (95%CI -2.7% to

	sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	chronic lung disease 2%		infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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 ⊕⊕○○
Sadeghi et al ; ⁶⁷⁵ 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.	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 ⊕○○○
Yakoot et al ; ⁶⁷⁶ 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.	Adverse events: RR 0.85 (95%CI 0.31 to 2.34); RD -1.5% (95%CI -7% to 13.7%); Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○
Roosbeh et al ; ⁶⁷⁷ 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 ; ⁴⁶² 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 ; ⁶⁷⁸ 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 ; ⁶⁷⁹ 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 ; ⁴⁶⁵ 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.	

<p>Khalili et al,⁶⁸⁰ Peer reviewed; 2020</p>	<p>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</p>	<p>Median age 62.2 ± 23.1, hypertension 45.1%, diabetes 45.1%, COPD 4.9%, CHD 31.7%, cancer 3.6%</p>	<p>Corticosteroids 8.5%, hydroxychloroquine 10.9%,</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>
<p>Elgohary et al,⁶⁸¹ preprint; 2021</p>	<p>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</p>	<p>Mean age 43 ±, male 0.4%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>
<p>SOVECOD trial,⁶⁸² Sayad et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 40 assigned to sofosbuvir/velpatasvir 400/100 mg once a day for 10 days and 40 assigned to SOC</p>	<p>Mean age 54.1 ± 17.8, male 55%, hypertension 30%, diabetes 20%, COPD 10%, CHD 17.5%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>
<p>El-Bendari et al,⁶⁸³ peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 53 ± 15, male 54.6%, hypertension 21.3%, diabetes 37.3%, asthma 1.7%, CHD 10.9%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably</p>

				inappropriate.	
Abbass et al , ⁶⁸⁴ 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 , ⁶⁸⁵ 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 , ⁶⁸⁶ peer reviewed; 2022	Patients with severe COVID-19 infection. 50 assigned to sofosbuvir 400 mg a day for 7 days and 50 assigned to SOC	Mean age 53.8 ± , male 44%, diabetes 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.	

<p>COVER HCW trial;⁵⁵⁵ Sokhela et al; peer reviewed; 2022</p>	<p>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</p>	<p>Median age 24, male 51.9%, hypertension 8.2%, diabetes 1.1%, COPD 2.2%</p>	<p>Vaccinated 0%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.</p>	
<p>REVOLUTION trial;⁸⁷ Maia et al; peer reviewed; 2023</p>	<p>Patients with severe COVID-19 infection. 67 assigned to sofosbuvir/daclatasvir 2 pills once followed by one pill a day for 10 days and 56 assigned to SOC</p>	<p>Mean age 54.2 ± 14, male 68%, hypertension 41.6%, diabetes 23%, COPD 2%, asthma %, CHD 1%, CKD 1%, cancer 2%, obesity 24%</p>	<p>Corticosteroids 83%, tocilizumab 1%,</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events</p>	

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 ; ⁶⁸⁷ 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 ⊕○○○
OPTIMISE-C19 trial ; ⁶³³ 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	Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
MANTICO trial ; ¹¹⁷ 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.	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 ⊕⊕⊕○
COMET-TAIL	Patients with mild	Mean age 50.9, male	Vaccinated 4.9%	Low for mortality and	Mortality: Very

trial ; ⁶⁸⁸ Shapiro et al; preprint; 2023	COVID-19 infection. 378 assigned to sotrovimab 500 mg IV infusion once and 559 assigned to sotrovimab	45.6%, diabetes 12.4%, COPD 18.2%, CKD 1%, immunosuppressive therapy 3%, obesity 62.4%		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.	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: RR 0.36 (95%CI 0.14 to 0.98); RD -1.1% (95%CI -3.3% to 1.2%); Low certainty ⊕⊕○○
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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 ; ⁶⁷⁴ preprint; 2021	Patients with moderate to severe COVID-19 infection. 50 assigned to spironolactone	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	Mortality: Very low certainty ⊕○○○ Invasive

	100 mg a day and 87 assigned to SOC	6.4%, cancer 5.9%, obesity 18.7%		Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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. ⁶⁸⁹ 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.	Mortality: Very low certainty ⊕○○○ Invasive

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. ⁶⁹⁰ preprint; 2022	Patients with severe COVID-19 infection. 68 assigned to spirulina 5 gr a day	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	Mortality: Very low certainty ⊕○○○ Invasive

	for 14 days and 58 assigned to SOC			adverse events Notes:	mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Severe adverse events: No information Hospitalization: No information
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Statins

Statins may reduce mortality but may not have an important effect on 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
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RCT

RESIST trial ; ⁸¹ 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 0.93 (95%CI 0.78 to 1.1); RD -1.1% (95%CI -3.5% to 1.6%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 0.90 (95%CI 0.65 to 1.25); RD -1.7% (95%CI -6% to 4.3%); Low certainty ⊕⊕○○
INSPIRATION/INSPIRATION-S trial ; ⁶⁹¹ Bikdeli et al; peer	Patients with severe to critical COVID-19 infection. 290	Median age 57 ± , male 56.4%, hypertension 31.5%, diabetes 16.7%,	Corticosteroids 93.4%, remdesivir 66.3%, hydroxychloroquine	Low for mortality and mechanical ventilation; low for symptom resolution,	

reviewed; 2022	assigned to atorvastatin 20 mg a day for 30 days and 297 assigned to SOC	COPD 8%	7.5%, lopinavir-ritonavir 0.7%, tocilizumab 14.5%,	infection and adverse events	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
Ghafouri et al ; ⁶⁹² 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 ; ⁴⁴ 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 %, immunosuppressive 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.	
Eltahan et al ; ⁶⁹³ preprint; 2023	Patients with severe to critical COVID-19 infection. 104 assigned to atorvastatin 40 mg a day for 28 days and 103 assigned to SOC	Mean age 61, male 43.6%, hypertension 43.6%, diabetes 38.6%, COPD 6.8%, CHD 12.3%, CKD 1.4%,	Corticosteroids 100%, remdesivir %; Vaccinated 3.6%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

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
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RCT

SENTAD-COVID trial ; ⁶⁹⁴ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ⁶⁹⁵ Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone	Mean age 69.5 ± 11.5, male 61.9%, hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%,	Hydroxychloroquine 96.8%, lopinavir-ritonavir 84.1%, azithromycin 92%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	Mortality: RR 0.90 (95%CI 0.80 to 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate

	40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	cerebrovascular disease 12.7%		Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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 ⊕⊕⊕○
Metcovid trial ; ⁶⁹⁶ 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	Symptom resolution or improvement: RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⊕⊕⊕○
RECOVERY - Dexamethasone trial ; ⁶⁹⁷ 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.	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 ⊕⊕○○
DEXA-COVID19 trial ; ⁶⁹⁸ 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.	Hospitalization: No information
CoDEX trial ; ⁶⁹⁹ 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	Mean age 61.4 ± 14.4, male 62.5%, hypertension 66.2%, diabetes 42.1%, coronary heart disease 7.7%,	hydroxychloroquine 21.4%, azithromycin 71.2%, ATB 87%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	

	a day for 5 days and 148 assigned to standard of care	chronic kidney disease 5.3%, obesity 27%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
REMAP-CAP trial ; ⁷⁰⁰ 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 ; ⁷⁰¹ 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 ; ⁷⁰² 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 ; ⁶⁹⁸ Unpublished; 2020	Patients with severe to critical COVID-19. 24 assigned to methylprednisolone 40 mg twice a day for 5 days and 23 assigned to	NR	NR	Low for mortality and invasive mechanical ventilation Notes: Risk of bias judgment from published SR.

	standard of care				
Farahani et al ; ⁷⁰³ 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 ; ⁷⁰⁴ 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 ; ⁷⁰⁵ 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 ; ⁷⁰⁶ 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 day 10 and 25 assigned to SOC	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 study. Concealment of allocation is probably inappropriate.	

<p>Rashad et al;⁷⁰⁷ peer reviewed; 2021</p>	<p>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</p>	<p>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%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>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.</p>	
<p>Ghanei et al;¹⁰³ peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 116 assigned to prednisolone 25 mg a day for 5 days and 110 assigned to SOC</p>	<p>Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%</p>	<p>Convalescent plasma 1.8%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>CORTIVID trial;⁷⁰⁸ Les et al; peer reviewed; 2021</p>	<p>Patients with moderate COVID-19 infection. 34 assigned to methylprednisolone and 37 assigned to SOC</p>	<p>Mean age 58.4, male 69%, hypertension 32.4%, diabetes 18.3%, COPD 1.4%, asthma 2.8%, CKD 7%</p>	<p>Remdesivir 8.5%, tocilizumab 28.2%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p> <p>Notes:</p>	
<p>Ranjbar et al;⁷⁰⁹ Preprint; 2020</p>	<p>Patients with severe to critical COVID-19 infection. 44 assigned to methylprednisolone 2 mg/kg daily for 5 days followed by tapering using same scheme at half dose every 5 days, 42 assigned</p>	<p>Mean age 58.7 ± 17.4, male 56.9%, hypertension 45.3%, diabetes 32.5%, CHD 30.2%, CKD 2.3%</p>	<p>NR</p>	<p>Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Unbalanced prognostic factors (age and gender).</p>	<p>Mortality: RR 1 (95%CI 0.82 to 1.21); RD 0% (95%CI -2.9% to 3.4%); Moderate certainty ⊕⊕⊕○</p> <p>Invasive mechanical ventilation: RR 1.11 (95%CI 0.61</p>

	to dexamethasone 6 mg a day for 10 days				to 2.01); RD 1.9% (95%CI -6.7% to 17.5%); Low certainty ⊕⊕○○
COVID STEROID 2 trial ; ⁷¹⁰ 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	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 ⊕⊕⊕⊕
Maskin et al ; ⁷¹¹ 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	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
Toroghi et al ; ⁷¹² 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 ; ⁷¹³ Taboada et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 98 assigned to dexamethasone 20 mg once a day for 5 days	Mean age 64.3 ± 14.3, male 61.8%, hypertension 48%, diabetes 19%, COPD 7%, asthma 5%, CHD 13.5%, CKD 3.5%, obesity	Remdesivir 10%, tocilizumab 12%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	dexamethasone and 102 assigned to dexamethasone 6 mg once a day for 10 days	53%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Naik et al ; ⁷¹⁴ 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 ; ⁷¹⁵ 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 ; ⁷¹⁶ 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
Dastena et al ; ⁷¹⁷ peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 73 assigned to methylprednisolone 60 mg a day for 10 days and 71	Mean age 63, male 55.9%, hypertension 47.6%, diabetes 25.9%, COPD 12.6%, asthma %, CHD 11.9%, CKD 6.3%,	Remdesivir 88.1%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded

	assigned to dexamethasone 8 mg a day for 10 days			study. Concealment of allocation probably inappropriate.	
MEDEAS trial ; ⁷¹⁸ 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 ; ⁷¹⁹ 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
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RCT

<p>STOIC trial;⁷²⁰ Ramakrishnan et al; peer reviewed; 2020</p>	<p>Patients with mild to moderate COVID-19. 71 assigned to inhaled budesonide 800 µg twice a day and 69 assigned to SOC</p>	<p>Mean age 45 ± 56, male 42.4%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p>
<p>PRINCIPLE trial;⁷²¹ Yu et al; peer reviewed; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 787 assigned to inhaled budesonide 800µg twice daily for 14 days and 1069 assigned to SOC</p>	<p>Mean age 64.2 ± 7.6, male 48%, hypertension 44.3%, diabetes 21.4%, COPD 12.6%, CHD 15.8%, cerebrovascular disease 5.6%</p>	<p>NR</p>	<p>Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Significant loss to follow-up.</p>	<p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
<p>Song et al;⁷²² peer reviewed; 2021</p>	<p>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</p>	<p>Median age 53 ± 26, male 47%, hypertension 27.8%, diabetes 14.7%, cerebrovascular disease 3.3%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Hospitalization: RR 0.9 (95%CI 0.7 to 1.15); RD -0.5% (95%CI -1.4% to 0.7%); Moderate certainty ⊕⊕⊕○</p> <p>Adverse events: Very low certainty ⊕○○○</p>
<p>ALV-020-001 trial;⁷²³ Clemency et al; peer reviewed; 2021</p>	<p>Patients with mild COVID-19 infection. 197 assigned to inhaled ciclesonide 640 µg a day for 30 days and 203 assigned to SOC</p>	<p>Mean age 43.3 ± 16.9, male 44.8%, hypertension 22.3%, diabetes 7.5%, asthma 6.5%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p></p>

<p>CONTAIN trial;⁷²⁴ Ezer et al; peer reviewed; 2021</p>	<p>Patients with mild COVID-19 infection. 105 assigned to inhaled ciclesonide 1200 µg + 200 µg intranasal a day and 98 assigned to SOC</p>	<p>Median age 35 ± 19, male 46.3%, hypertension 5.9%, diabetes 2.5%, asthma 5%, CHD 0.5%, cancer 1%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>Alsultan et al;¹⁶⁷ peer reviewed; 2021</p>	<p>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</p>	<p>age 60 to 80 65.3, male 38.8%, diabetes 53.1%, CKD 8.2%, cerebrovascular disease 4.1%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>COVERAGE trial;⁷²⁵ Duvignaud et al; peer reviewed; 2021</p>	<p>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</p>	<p>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%</p>	<p>Vaccinated 13.8%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>TACTIC-COVID trial;⁷²⁶ Agusti et al; other; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 58 assigned to budesonide (inh) 400 µg/12 h and 62 assigned to SOC</p>	<p>Mean age 51.1 ± 13.7, male 47.1%,</p>	<p>Corticosteroids 17.8%, remdesivir 8.5%, hydroxychloroquine 8.5%, lopinavir-ritonavir 5.9%, tocilizumab 0.8%, azithromycin 9.3%,</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	

<p>Terada et al,¹⁴⁴ peer reviewed; 2022</p>	<p>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</p>	<p>Mean age 58.3, male 64.9%, diabetes 24.8%, COPD 9.4%, CHD 2.6%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>
<p>ACTIV-6 - Fluticazone trial;⁷²⁷ Naggie et al; preprint; 2022</p>	<p>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</p>	<p>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%,</p>	<p>Corticosteroids %, remdesivir 0.1%, monoclonar antibodies 2.7%, paxlovid 0.1%; Vaccinated 65.2%,</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>
<p>HALT COVID trial;⁷²⁸ Brodin et al; peer reviewed; 2023</p>	<p>Patients with severe COVID-19 infection. 48 assigned to ciclesonide (inh) 640 µg a day for 14 days and 50 assigned to SOC</p>	<p>Median age 59.5 ± 18, male 68%, hypertension 46%, diabetes 18%, COPD 3%, asthma 8%, CHD 8%, CKD 9%, cerebrovascular disease %, immunosuppressive therapy %, cancer 10%, obesity %</p>	<p>Corticosteroids 49%, remdesivir 18.4%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated %</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>

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 ; ⁵³⁷ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁷²⁹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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. ⁷³⁰ 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: : Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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. ⁷³¹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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					
ARO-CORONA trial ; ⁷³² Parienti 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 ⊕⊕○○
ARTAN-C19 trial ; ⁷³³ 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.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○
EPICOS trial ; ³⁵⁰ 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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○
Gaitan-Duarte et	Patients with	Mean age 55.4 ±	Corticosteroids	Low for mortality and	

<p>al;¹⁷⁴ preprint; 2021</p>	<p>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</p>	<p>12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%</p>	<p>98%,</p>	<p>mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>PanCOVID19 trial;¹²⁵ Montejano et al; peer reviewed; 2022</p>	<p>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</p>	<p>Median age 67, male 64.5%, hypertension 61.1%, diabetes 27.3%, obesity 16.1%</p>	<p>Corticosteroids 100%, remdesivir 12.7%, baricitinib 50.5%; Vaccinated 91%</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	

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 ; ⁷³⁴ preprint; 2021	Patients with severe COVID-19 infection. 28 assigned to thalidomide 100 mg a day for 14 days and 23 assigned to SOC	Mean age 62 ± 10, male 54.9%, hypertension 33.3%, diabetes 37.2%, COPD 5.9%, CHD 9.8%	Corticosteroids 100%, 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
Haghighi et al ; ⁷³⁵ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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					
Bencheqroun et al ; ⁷³⁶ 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:	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ⁷³⁷ 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
TACOVID trial ; ⁶¹ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

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 ; ⁷³⁸ Levin et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 3441 assigned to tixagevimab-cilgavimab 300 mg once and 1731 assigned to SOC	Mean age 53.5 ± 15, male 53.9%, hypertension 35.9%, diabetes 14.1%, COPD 5.3%, asthma 11.1%, CHD 8.1%, CKD 5.2%, immunosuppressive therapy 3.3%, cancer 7.4%, obesity 41.7%	Vaccinated 0%	Low for mortality and mechanical 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.	Mortality: RR 0.72 (95%CI 0.54 to 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 0.98 (95%CI 0.73 to 1.31); RD -0.2% (95%CI -2.8% to 3.2%); Low certainty ⊕⊕○○
TACKLE trial ; ⁷³⁹ 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 ; ⁷⁴⁰ 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	
Bender et al ; ⁷⁴¹ peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 154 assigned to	Mean age 40.7, male 47.4%	Vaccinated 4.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse	

	Tixagevimab-Cilgavimab 300 to 600 mg IV or IM once and 173 assigned to SOC			events	Hospitalization: RR 0.42 (95%CI 0.26 to 0.69); RD -2.8% (95%CI -3.6% to -1.5%); Moderate certainty ⊕⊕⊕○
Tocilizumab					
Tocilizumab reduces mortality and mechanical ventilation requirements 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 and GRADE certainty of the evidence
RCT					
COVACTA trial ; Rosas et al; ⁷⁴² 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 ⊕⊕○○
Wang et al ; ⁷⁴³ 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.	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 ⊕⊕○○
Zhao et al ; ²⁶⁵ 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	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	Symptomatic infection (prophylaxis studies): No information

	assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir plus tocilizumab			of allocation is probably inappropriate.	Adverse events: RR 0.95 (95%CI 0.87 to 1.04); RD - 0.5% (95%CI - 1.3% to 0.4%); Moderate certainty ⊕⊕⊕○
RCT-TCZ-COVID-19 trial ; ⁷⁴⁴ 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.	Hospitalization: No information
BACC Bay Tocilizumab Trial ; ⁷⁴⁵ 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 ; ⁷⁴⁶ 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.	
EMPACKTA trial ; ⁷⁴⁷ Salama et al; preprint; 2020	Patients with moderate to severe COVID-19. 249 assigned to tocilizumab 8	Mean age 55.9 ± 14.4, male 59.2%, hypertension 48.3%, diabetes 40.6%, COPD 4.5%, asthma	Corticosteroids 59.4%, remdesivir 54.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and	

	mg/kg once and 128 assigned to standard of care	11.4%, coronary heart disease 1.9%, cerebrovascular disease 3.4%, obesity 24.4%		adverse events	
REMAP-CAP - tocilizumab trial ; ⁶⁵⁶ 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.	
Veiga et al ; ⁷⁴⁸ 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 ; ⁷⁴⁹ 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.	

<p>PreToVid trial;⁷⁵⁰ Rutgers et al; preprint; 2021</p>	<p>Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice and 180 assigned to SOC</p>	<p>Median age 66.5 ± 16.5, male 67%, comorbidities 74.3%</p>	<p>Corticosteroids 88.4%, remdesivir 18.4%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>Talaschian et al;⁷⁵¹ preprint; 2021</p>	<p>Patients with severe COVID-19 infection. 17 assigned to TCZ 8 mg/kg once or twice and 19 assigned to SOC</p>	<p>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%</p>	<p>Corticosteroids 33.3%, hydroxychloroquine 63.9%, lopinavir-ritonavir 8.3%</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Concealment of allocation and blinding probably inappropriate.</p>	
<p>Hamed et al;⁷⁵² peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 23 assigned to TCZ 400 mg once and 26 assigned to SOC</p>	<p>Mean age 48 ±, male 85.5%, hypertension 36.8%</p>	<p>Corticosteroids 100%</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	
<p>ARCHITECTS trial;⁶⁷¹ other; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 10 assigned to TCZ 8 mg/kg once or twice and 11 assigned to SOC</p>	<p>Median age 61 ±</p>	<p>Corticosteroids 95.2%, remdesivir 90.4%, convalescent plasma 100%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p> <p>Notes: Risk of bias assessment extracted from a systematic review.</p>	

<p>CORIMUNO-TOCI ICU trial;⁶⁶⁰ Hermine et al; Peer reviewed; 2021</p>	<p>Patients with critical COVID-19 infection. 49 assigned to TCZ 8 mg/kg once or twice and 43 assigned to SOC</p>	<p>Mean age 64.2 ± , male 71.7%, diabetes 35.5%, COPD 7.8%, asthma 5.5%, CHD %, CKD 6.6%, cancer 2.2%,</p>	<p>Steroids 33.6%, remdesivir 0%, hydroxychloroquine 0%, lopinavir-ritonavir 4.3%, azithromycin 4.3%, convalescent plasma 0%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>COV-AID trial; et al;⁶⁷¹ other; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 81 assigned to TCZ 8 mg/kg once and 72 assigned to SOC</p>	<p>Median age 63</p>	<p>Corticosteroids 52.6%, remdesivir 5.8%, convalescent plasma 0%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p> <p>Notes: Risk of bias assessment extracted from a systematic review.</p>	
<p>COVIDOSE-2 trial; et al;⁶⁷¹ other; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 20 assigned to TCZ 40-120 mg once and 8 assigned to SOC</p>	<p>Median age 65</p>	<p>Corticosteroids 30%, remdesivir 75%, convalescent plasma 0%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p> <p>Notes: Risk of bias assessment extracted from a systematic review.</p>	
<p>COVIDSTORM trial;⁷⁵³ Broman et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 57 assigned to TCZ 400 to 800 mg once and 29 assigned to SOC</p>	<p>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%</p>	<p>Steroids 77%, remdesivir 0%, convalescent plasma 0%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	

COVITOX-01 trial; et al; ⁶⁷¹ 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; ⁶⁷¹ other; 2021	Patients with severe to critical COVID-19 infection. 37 assigned to TCZ 8 mg/kg once and 17 assigned to SOC	Median age 63	Corticosteroids 85.2%, remdesivir 22.2%, convalescent plasma 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
REMDACTA trial; et al; ⁷⁵⁴ 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; ⁶⁷¹ 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; ⁶⁷¹ other;	Patients with moderate to severe	Median age 53	Corticosteroids 35%, remdesivir	Low for mortality and mechanical	

2021	COVID-19 infection. 136 assigned to TCZ 400 to 600 mg once and 134 assigned to SOC		0.5%, convalescent plasma 0%	ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.
COVINTOC trial; et al. ⁷⁵⁵ Soin et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91 assigned to TCZ 6 mg/kg once or twice and 88 assigned to SOC	Median age 55 , male 85.5%, hypertension 39.4%, diabetes 41.1%, COPD 2.2%, CHD 15%, CKD 4.4%	Corticosteroids 91%, remdesivir 41.6%, 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.
TOCIDEX trial; ⁷⁵⁶ 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. ⁷⁵⁷ 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.

<p>MARIPOSA trial;⁷⁵⁸ Kumar et al; peer reviewed; 2021</p>	<p>Patients with moderate to severe COVID-19 infection. 49 assigned to TCZ 4 mg/kg and 48 assigned to TCZ 8 mg/kg</p>	<p>Mean age 56.8 ± 14.3, male 58.7%</p>	<p>Corticosteroids 22.7%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ⁷⁵⁹ Guimaraes et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 144 assigned to tofacitinib 10 mg twice a day for 14 days and 145 assigned to SOC	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, infection, and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
Murugesan et al ; ⁷⁶⁰ 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%	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>

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 ; ⁷⁶¹ peer reviewed; 2021	Patients with severe COVID-19 infection. 30 assigned to tranilast 300 mg a day for 7 days and 30 assigned to SOC	Mean age 59.5, male 63.3%, hypertension 36.7%, diabetes 26.7%, COPD 16.6%, CKD 6.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

Transcranial direct current stimulation (tDCS)

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					
Pinto et al ; ⁷⁶² peer reviewed; 2023	Patients with mild to moderate COVID-19 infection. 20 assigned to Transcranial direct current stimulation (tDCS) 30-minute session once and 20 assigned to SOC	Mean age 50, male 82.5%,	Vaccinated 0%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Tregs (regulatory T cells)

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					

Gladstone et al , ⁷⁶³ peer reviewed; 2023	Patients with critical COVID-19 infection. 30 assigned to Tregs (regulatory T cells) 100 to 300 million cells and 15 assigned to SOC	Median age 60, male 60%, hypertension 56.8%, diabetes 28.9%, COPD 13.3%, CHD 28.9%, CKD 8.9%	Corticosteroids 93%, remdesivir 88.9%, tocilizumab 15.6%, convalescent plasma 8.9%	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: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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 , ⁷⁶⁴ peer-reviewed; 2020	Patients with mild to critical COVID-19. 26 assigned to triazavirin 250 mg orally three or four times a day for 7 days and 26	Median age 58 ± 17, male 50%, hypertension 28.8%, diabetes 15.4%, chronic lung disease 5.8%, coronary heart disease 15.4%,	Corticosteroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%,	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No

	assigned to standard of care	cerebrovascular disease 7.7%	umifenovir 61.5%, ribavirin 28.9%		information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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TRV-027

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					
Self et al ; ⁷⁶⁵ peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 145 assigned to TRV-027 12-mg/h	Age >65 27.3%, male 57.9%, hypertension 47.2%, diabetes 27.2%, COPD 17.2%, CHD 6.9%, CKD 8.6%,	Corticosteroids 77.5%, remdesivir 65.6%, tocilizumab 0.3%, Vaccinated 31%, Baricitinib 13.8%	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse	Mortality: Very low certainty ⊕○○○ Invasive mechanical

	continuous for 5 days and 145 assigned to SOC	cancer 6.6%, obesity 62.4%		events 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
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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 ; ⁷⁶⁶ Wagener et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 11 assigned to TXA-127 0.5 mg/kg a day for 10 days and 9 assigned to SOC	Mean age 56, male 65%	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 ⊕○○○
Self et al ; ⁷⁶⁵ peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 170 assigned to TXA-127 0.5-mg/kg a day for 5 days and 173 assigned to SOC	Age >65 28.8%, male 58.3%, hypertension 51.3%, diabetes 30%, COPD 10.2%, CHD 7.3%, CKD 9.6%, cancer 7.9%, obesity 63%	Corticosteroids 83%, remdesivir 70.3%, tocilizumab 0.3%, baricitinib 13.7%; Vaccinated 32.1%	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded	Symptom resolution or improvement: No information Symptomatic infection

				study which might have introduced bias to symptoms and adverse events outcomes results.	<p>(prophylaxis studies): No information</p> <p>Adverse events: Very low certainty</p> <p>Hospitalization: No information</p>
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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
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RCT

Lau et al ; ⁷⁶⁷ peer reviewed; 2022	Patients with severe COVID-19 infection. 15 assigned to UVB escalating protocol for 8 days and 15 assigned to SOC	Mean age 66.9, male 60%, hypertension 50%, diabetes 16.7%	Corticosteroids 93.3%, remdesivir 76.7%, tocilizumab 30%, vaccinated 33.3%, Regeneron 3.3%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis</p>
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					<p>studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Chen et al.²⁵⁵ preprint; 2020</p>	<p>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</p>	<p>Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%</p>	<p>NR</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p>
<p>ELACOI trial.⁴⁵⁸ Li et al; peer-reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19 infection. 34 assigned to</p>	<p>Mean age 49.4 ± 14.7, male 41.7%</p>	<p>Corticosteroids 12.5%, IVIG 6.3%</p>	<p>Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and</p>	<p>Symptomatic infection (prophylaxis studies): No</p>

	lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care			adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
Nojomi et al ; ⁷⁶⁸ 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 ; ⁷⁶⁹ 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 ; ⁷⁷⁰ 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 ; ⁷⁷¹ Darazam et al;	Patients with severe COVID-19	Mean age 61.2 ± 15.8, male 56.4%,	Corticosteroids 3%	Low for mortality and mechanical	

peer reviewed; 2021	infection. 51 assigned to umifenovir 600 mg a day for 10 days and 50 assigned to SOC	hypertension 46.4%, diabetes 31.6%, COPD 10%, asthma 6.1%, CHD 11.2%, CKD 7.1%, cancer 1%		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 ; ⁷⁷² 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
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RCT

ReCOVery-SIRIO trial ; ²¹ Navarese et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 72 assigned to verapamil 120 to 480 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
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					<p>(prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Vehreschild et al;⁷⁷³ peer reviewed; 2022</p>	<p>Patients with moderate COVID-19 infection. 110 assigned to vidofludimus calcium 45 mg a day and 110 assigned to SOC</p>	<p>Mean age 54.1, male 54%, diabetes 17.7%, COPD 7, cancer 0.9%,</p>	<p>Corticosteroids 63.6%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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</p>
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					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. ⁷⁷⁴ peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to vilobelimab 800 mg IV with a maximum of seven doses and 15 assigned to standard of care	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 Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: RR 0.76 (95%CI 0.6 to 0.98); RD -3.8% (95%CI -6.4% to -0.3%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: No information
PANAMO trial (phase 3) ⁷⁷⁵ 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

					<p>Adverse events: RR 0.94 (95%CI 0.8 to 1.11); RD - 0.6% (95%CI -2% to 1.1%); Moderate certainty ⊕⊕⊕○</p> <p>Hospitalization: No information</p>
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 ; ⁷⁷⁶ peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 40 assigned to Vit B 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	Mean age 61.2	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p>

					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 ; ⁷⁷⁷ preprint; 2020	Patients with severe COVID-19 infection. 26 assigned to vitamin C 12 g twice a day for 7 days and 28 assigned to standard of care	Mean age 67.4 ± 12.4, male 66.7%, hypertension 44.4%, diabetes 29.6%, chronic lung disease 5.6%, coronary heart disease 22.2%, chronic kidney disease 1.85%, cancer 5.6%, nervous system disease 20.4%	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 0.84 (95%CI 0.72 to 0.97); RD -2.6% (95%CI -4.5% to -0.5%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: Very low certainty ⊕○○○
Kumari et al ; ⁷⁷⁸ 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	Symptom resolution or improvement: RR 1.16 (95%CI 1.01 to 1.33); RD 9.7% (95%CI 0.6% to 20%); Low

				study. Concealment of allocation is probably inappropriate.	certainty ⊕⊕○○
Jamali Moghadam Siahkali et al ; ⁷⁷⁹ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○
COVIDAtoZ - Vit C trial ; ⁷⁸⁰ 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 ; ⁷⁸¹ Tehrani et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 18 assigned to Vit C 8 gr a day for 5 days and 26 assigned to SOC	Mean age 59.5, male 59%, hypertension 40.9%, diabetes 34%, COPD 7%, CHD 22.7%, CKD 9.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Beigmohammadi et al ; ⁷⁸² peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin vitamin	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	

	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			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Majidi et al , ⁷⁸³ 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 , ⁷⁸⁴ 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 , ⁷⁸⁵ peer reviewed; 2021	Patients with severe COVID-19 infection. 44 assigned to vitamin C 0.3 to 0.9 g/kg a day for 5 days and 22 assigned to SOC	Mean age 60, male 50%, hypertension 62.1%, diabetes 34.8%, COPD 19.7%	Corticosteroids 77.3%, remdesivir 92.4%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Fogleman C et al trial , ⁴⁷⁸ peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 32 assigned to vitamin C 1000 mg a day	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	

	for 14 days and 34 assigned to SOC				
Kumar et al ; ⁷⁸⁶ 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.	
Labani-Motlagh et al ; ⁷⁸⁷ peer reviewed; 2023	Patients with severe to critical COVID-19 infection. 37 assigned to Vit C 12 gr a day for 4 days and 37 assigned to SOC	Mean age 58.3, male 56.8%, hypertension 13.5%, diabetes 16.2%, CHD 18.9%, obesity 2.7%	Corticosteroids 58.1%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

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 ; ⁷⁸⁸ peer-reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to vitamin D 0.532 once	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and	Mortality: Very low certainty ⊕○○○

	followed by 0.266 twice and 26 assigned to standard of care	7.9%, coronary heart disease 3.9%, immunosuppression 9.2%		adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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 ⊕⊕⊕⊕
SHADE trial ; ⁷⁸⁹ 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.	Adverse events: RR 1.03 (95%CI 0.84 to 1.26); RD 0.3% (95%CI -1.6% to 2.7%); Low certainty ⊕⊕○○
Murai et al ; ⁷⁹⁰ 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	Hospitalization: RR 1.2 (95%CI 0.83 to 1.74); RD 1% (95%CI -0.8% to 3.6%); Moderate certainty ⊕⊕⊕○
Lakkireddy et al ; ⁷⁹¹ 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 ; ⁷⁹² peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 36 assigned to vitamin D 5000 IU for 14 days and 33	Mean age 49.8 ± 14.3, male 49.3%, hypertension 55%, diabetes 51%, COPD %, asthma 4%, CHD 6%, CKD 7%, obesity 33%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	assigned to vitamin D 1000 IU for 14 days			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Maghbooli et al ; ⁷⁹³ 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 ; ⁷⁹⁴ 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 ; ⁷⁹⁵ 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 ; ⁷⁹⁶ peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 45 assigned to cholecalciferol	Mean age 35 ± 2, male 15.3%, obesity 16.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse

	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			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
COVID-VIT-D trial ; ⁷⁹⁷ 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 ; ⁷⁹⁸ 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 ; ⁷⁹⁹ 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 ; ⁸⁰⁰ Mariani et al; peer	Patients with moderate COVID-19 infection. 115	Mean age 59.1 ± 10.6, male 52.8%, hypertension 43.1%,	NR	Low for mortality and mechanical ventilation; low for

reviewed; 2021	assigned to vitamin D 500 000 IU of vitamin D3 once and 103 assigned to SOC	diabetes 26.6%, COPD 11.9%, CHD 4.6%, cancer 0.9%, obesity 39.9%		symptom resolution, infection and adverse events	
COVIT-TRIAL trial ; ⁸⁰¹ 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 ; ⁸⁰² 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 ; ⁸⁰³ 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 ; ⁸⁰⁴ peer reviewed; 2022	Patients with severe COVID-19 infection. 41 assigned to vitamin D cholecalciferol 10000 IU a day for 14 days and 44 assigned to Vit D 2000 IU a day for 14 days	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 Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Abroug et al. ⁸⁰⁵ 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. ⁸⁰⁶ 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. ⁸⁰⁷ 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. ⁸⁰⁸ 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.
Rahimi et al. ⁸⁰⁹ peer reviewed; 2023	Patients with severe COVID-19 infection. 31 assigned to Vit D 300,000 IU once	Mean age 53, male 70.4%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse

	and 30 assigned to SOC			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Domazet et al. ⁸¹⁰ peer reviewed; 2023	Patients with critical COVID-19 infection. 69 assigned to 10,000 IU of cholecalciferol and 70 assigned to SOC	Mean age 65, male 72.4%, hypertension 45.4%, diabetes 27.6%, COPD 9.9%, CHD 22.4%, cerebrovascular disease 5.3%, cancer 5.9%	Corticosteroids 100%; Vaccinated 24.3%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Wang et al. ⁸¹¹ preprint; 2023	Patients with exposed COVID-19 infection. 99 assigned to Vit D calciferol 5 mg in days 0 and 14 and 103 assigned to SOC	Mean age 38.5, male 20.3%, hypertension 6.4%, diabetes 2.5%, COPD 0.5%, asthma 14.9%, CHD 0.5%,	Vaccinated 98%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Taslim et al. ⁸¹² peer reviewed; 2023	Patients with moderate COVID-19 infection. 30 assigned to Vit D 10000 IU a day for 14 days and 30 assigned to Vit D 1000 IU a day for 14 days	Mean age 39, male 53.3%, hypertension 20%, diabetes 15%, CHD 15%, cancer 11.6%, obesity 13.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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.

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 ; ⁸¹³ 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	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>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 ⊕⊕⊕⊕</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

POLYCOR trial ; ⁸¹⁴ 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	Mean age 71 ± 24, male 64.7%, hypertension 47.1%, diabetes 11.8%, COPD %, asthma 17.6%, CHD 29.4%, CKD 5.9%, cancer	Corticosteroids 100%, remdesivir 47.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No</p>
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	SOC	11.8%, obesity 17.6%			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. ⁸¹⁵ 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 ; ⁸¹⁶ 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 ; ⁸¹⁷ 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 ⊕○○○
Abd-Elsalam et al ; ⁸¹⁸ 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.	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 studies): Very low certainty ⊕○○○
Abdelmaksoud et al ; ⁸¹⁹ 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	Adverse events: No information Hospitalization: Very low certainty ⊕○○○

				study. Concealment of allocation is probably inappropriate.	
COVIDAtoZ - Zinc trial ; ⁷⁸⁰ 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 ; ⁸²⁰ 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 ; ³³⁶ 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 ; ⁶⁴⁵ 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 ; ²³⁷ 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 ; ⁸²¹ 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
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RCT

Zhong et al ; ⁸²² 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 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
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					Hospitalization: No information
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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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Standard of care	Steroids		
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	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	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	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	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	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	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Remdesivir		
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	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	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	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	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	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	HCQ		
Mortality 15 days	Relative risk: 1.09 (CI 95% 1.0 - 1.19) Based on data from 11005 participants in 17 studies	160 per 1000	174 per 1000	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	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	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: 0.84 (CI 95% 0.72 - 0.97) Based on data from 11298 participants in 16 studies	174 per 1000	146 per 1000	Low Due to serious imprecision, Due to serious inconsistency ⁴	Hcq may reduce covid-19 infections (in exposed individuals)
Hospitalizations (in patients with non- severe disease)	Relative risk: 0.83 (CI 95% 0.63 - 1.1) Based on data from 5829 participants in 14 studies	48 per 1000	40 per 1000	Moderate Due to serious inconsistency ⁵	Hcq probably has little or no difference on hospitalizations (in patients with non-severe disease)
Severe adverse events	Relative risk: 0.92 (CI 95% 0.68 - 1.23) Based on data from 10649 participants in 21 studies	102 per 1000	94 per 1000	Low Due to serious risk of bias, Due to serious imprecision ⁶	Hcq may have little or no difference on severe adverse events

- 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;
- 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;
- 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.** 12 82%; **Imprecision: no serious.** Secondary to inconsistency;
- Inconsistency: serious.** The direction of the effect is not consistent between the included studies; **Imprecision: serious.** 95%CI includes no infection reduction;

5. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies;
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
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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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	CP		
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	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 24200 participants in 51 studies Follow up Median 28 days	160 per 1000	157 per 1000	High 1	Convalescent plasma has little or no difference on mortality
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.96 - 1.02) Based on data from 15557 participants in 14 studies Follow up 28 days	606 per 1000	600 per 1000	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	Moderate Due to serious imprecision ²	Convalescent 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	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	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 lpv 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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	TCZ		
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	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	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	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	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	ACO		
Mortality (full or intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.95 (CI 95% 0.8 - 1.12) Based on data from 12273 participants in 20 studies	160 per 1000	152 per 1000	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 or intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.56 (CI 95% 0.44 - 0.72) Based on data from 12041 participants in 17 studies	70 per 1000	39 per 1000	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: 1.66 (CI 95% 1.2 - 2.3) Based on data from 12961 participants in 17 studies	19 per 1000	32 per 1000	High	Anticoagulantes in intermediate or full dose increase major bleeding
Hospitalization (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 1.09 (CI 95% 0.81 - 1.47) Based on data from 3590 participants in 6 studies	48 per 1000	52 per 1000	Moderate Due to serious imprecision ²	Anticoagulants probably 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	Low Due to very serious imprecision ³	Anticoagulants may have little or no difference on symptom resolution or improvement

1. **Imprecision: serious.** Low number of patients;
2. **Imprecision: serious.** 95%CI includes harms and absence of harms;
3. **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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	IFN		
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	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	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	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	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	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Bamlanivimab +/- etesevimab		
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	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	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	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	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	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Favipiravir		
Mortality (Low RoB studies) 28 days	Relative risk: 1.09 (CI 95% 0.76 - 1.54) Based on data from 2927 participants in 8 studies Follow up Median 28 days	160 per 1000	174 per 1000	Low Due to very serious imprecision ¹	Favipiravir may increase mortality
Mechanical ventilation 28 days	Relative risk: 1.24 (CI 95% 0.9 - 1.71) Based on data from 1729 participants in 7 studies Follow up Median 28 days	173 per 1000	215 per 1000	Low Due to very serious imprecision ²	Favipiravir 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	High	Favipiravir has little or no difference on symptom resolution or improvement
Hospitalization (in patients with non- severe disease)	Relative risk: 1.48 (CI 95% 0.82 - 2.62) Based on data from 901 participants in 6 studies Follow up 28 days	48 per 1000	71 per 1000	Low Due to very serious imprecision ³	Favipiravir 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	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

- Imprecision: very serious.** 95%CI includes significant mortality reduction and increase;
- Imprecision: very serious.** 95%CI includes significant benefits and harms;
- Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits ;
- 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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Ivermectin		
Mortality (Low risk of bias studies)	Relative risk: 1.0 (CI 95% 0.8 - 1.25) Based on data from 7728 participants in 14 studies	160 per 1000	160 per 1000	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	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: 1.03 (CI 95% 0.99 - 1.07) Based on data from 4444 participants in 8 studies	606 per 1000	624 per 1000	High ₃	Ivermectin 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 studies	174 per 1000	176 per 1000	Very low Due to very serious imprecision ⁵	We are uncertain whether ivermectin increases or decreases symptomatic infection
Severe adverse events	Relative risk: 1.1 (CI 95% 0.73 - 1.65) Based on data from 5628 participants in 10 studies Follow up 28 days	102 per 1000	112 per 1000	Moderate Due to serious imprecision ⁶	Ivermectin probably has little or no difference on severe adverse events
Hospitalization (in non-severe patients)	Relative risk: 0.91 (CI 95% 0.75 - 1.11) Based on data from 6315 participants in 11 studies	48 per 1000	44 per 1000	High	Ivermectin 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: no 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: serious.** 95%CI includes significant benefits and absence of benefits ;

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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Baricitinib		
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	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	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	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	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Azythromycin		
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	Moderate Due to serious imprecision ¹	Azythromycin 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	Moderate Due to serious imprecision ²	Azythromycin 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	High	Azythromycin 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	Very low Due to very serious imprecision, Due to very serious risk of bias ⁴	We are uncertain whether azythromycin 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	Low Due to serious risk of bias, Due to serious imprecision ⁵	Azythromycin 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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Colchicine		
Mortality	Relative risk: 0.99 (CI 95% 0.93 - 1.06) Based on data from 18353 participants in 13 studies	160 per 1000	158 per 1000	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 participants in 7 studies Follow up 30 days	173 per 1000	170 per 1000	Moderate Due to serious imprecision ²	Colchicine probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.0 (CI 95% 0.98 - 1.02) Based on data from 11784 participants in 5 studies Follow up 30 days	606 per 1000	173 per 1000	High	Colchicine has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.85 (CI 95% 0.68 - 1.05) Based on data from 8913 participants in 5 studies Follow up 30 days	102 per 1000	87 per 1000	High	Colchicine has little or no difference on severe adverse events
Pulmonary embolism	Relative risk: 2.82 (CI 95% 0.79 - 10.8) Based on data from 8280 participants in 2 studies Follow up 30 days	0.9 per 1000	2.54 per 1000	Very low Extremely serious imprecision ³	We are uncertain whether colchicine increases or decreases pulmonary embolism
Hospitalization (in patients with non- severe disease)	Relative risk: 0.88 (CI 95% 0.73 - 1.07) Based on data from 8810 participants in 4 studies Follow up 30 days	48 per 1000	42 per 1000	High	Colchicine 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: ~extreme_serious.** Wide confidence intervals, 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		
Mortality (Low RoB studies)	Relative risk: 1.11 (CI 95% 0.83 - 1.49) Based on data from 1834 participants in 4 studies	160 per 1000	178 per 1000	Low Due to very serious imprecision ¹	Sofosbuvir alone or in combination may have little or no difference on mortality
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	Low Due to very serious imprecision ²	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir may have little or no difference on invasive mechanical ventilation
Severe adverse events	Relative risk: 0.85 (CI 95% 0.31 - 2.34) Based on data from 751 participants in 3 studies	102 per 1000	87 per 1000	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	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 studies	174 per 1000	90 per 1000	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		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	REGEN-COV (casirivimab and imdevimab)		
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	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	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	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	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	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	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)	48 per 1000	13 per 1000	Moderate Due to serious imprecision ⁷	Regen-cov (casirivimab and imdevimab) probably reduces hospitalization in

	Based on data from 6732 participants in 4 studies Follow up 30 days	Difference: 35 fewer per 1000 (CI 95% 39 fewer - 28 fewer)		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

- 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;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis; **Imprecision: very serious.**
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: very serious.** Wide confidence intervals;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis;
- 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;
- Indirectness: serious.** Subgroup analysis;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: serious.** Low number of events;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up;
- Imprecision: serious.** Wide confidence intervals.

Summary of findings Table 18. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Aspirin

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Aspirin		
Mortality	Relative risk: 0.95 (CI 95% 0.89 - 1.02) Based on data from 21174 participants in 5 studies	160 per 1000	152 per 1000	Moderate Due to serious imprecision ¹	Aspirin probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 0.95 (CI 95% 0.87 - 1.04) Based on data from 15598 participants in 4 studies Follow up 30 days	173 per 1000	164 per 1000	Moderate Due to serious imprecision ²	Aspirin probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.02 (CI 95% 1.0 - 1.04) Based on data from 14892 participants in 1 studies	606 per 1000	618 per 1000	Moderate Due to serious imprecision ³	Aspirin probably has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.1 (CI 95% 0.71 - 1.73) Based on data from 5854 participants in 3 studies Follow up 30 days	102 per 1000	112 per 1000	Low Due to very serious imprecision ⁴	Aspirin may have little or no difference on severe adverse events
Hospitalization (in patients with non- severe disease)	Relative risk: 0.8 (CI 95% 0.57 - 1.11) Based on data from 4161 participants in 2 studies	48 per 1000	38 per 1000	Moderate Due to serious imprecision ⁵	Aspirin 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: serious.** Wide confidence intervals;

4. **Imprecision: very serious.** Wide confidence intervals;

5. **Imprecision: serious.** Wide confidence intervals;

Summary of findings Table 19. [\(Interactive online version\)](#)

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	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	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	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	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	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 20. [\(Interactive online version\)](#)

Patients with COVID-19 infection
Intervention: Inhaled corticosteroids
Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Inhaled corticosteroids		
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	Low Due to serious risk of bias, Due to serious imprecision ²	Inhaled corticosteroids 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	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	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	Very low Due to serious risk of bias, Due to very serious imprecision ⁵	We are uncertain whether inhaled corticosteroids 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	Moderate Due to serious risk of bias ⁶	Inhaled corticosteroids 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 21. [\(Interactive online version\)](#)

Patients with COVID-19 infection

Intervention: Fluvoxamine

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Fluvoxamine		
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	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	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	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	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	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 22. [\(Interactive online version\)](#)

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	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	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	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	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	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 23. [\(Interactive online version\)](#)

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		
Mechanical ventilation	Relative risk: 1.67 (CI 95% 0.62 - 4.45) Based on data from 264 participants in 1 study	173 per 1000	289 per 1000	Very low Due to very serious imprecision ¹	We are uncertain whether nirmatrelvir-ritonavir increases or decreases mortality
Mortality	Relative risk: 0.44 (CI 95% 0.16 - 1.21) Based on data from 2349 participants in 2 studies	160 per 1000	70 per 1000	Very low Due to very serious imprecision ²	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	Moderate Due to serious imprecision ³	Nirmatrelvir-ritonavir probably decrease hospitalizations
Severe adverse events	Relative risk: 0.53 (CI 95% 0.33 - 0.87) Based on data from 2488 participants in 2 studies Follow up 29	102 per 1000	54 per 1000	Moderate Due to serious imprecision ⁴	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: very serious.** 95%CI includes significant benefits and harms, Low number of patients;
3. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
4. **Imprecision: serious.** Low number of events;

Summary of findings Table 24. [\(Interactive online version\)](#)

Patients with COVID-19 infection

Intervention: Ruxolitinib

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Ruxolitinib		
Mortality	Relative risk: 0.73 (CI 95% 0.59 - 0.9) Based on data from 777 participants in 4 studies	160 per 1000	117 per 1000	Low Due to serious imprecision, Due to serious inconsistency ¹	Ruxolitinib may improve mortality
Invasive mechanical ventilation	Relative risk: 0.99 (CI 95% 0.49 - 1.99) Based on data from 474 participants in 2 studies	173 per 1000	171 per 1000	Very low Due to extremely serious imprecision ²	We are uncertain whether ruxolitinib increases or decreases invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.0 (CI 95% 0.94 - 1.07) Based on data from 777 participants in 4 studies	606 per 1000	606 per 1000	Moderate Due to serious imprecision ³	Ruxolitinib probably has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.12 (CI 95% 0.69 - 1.82) Based on data from 678 participants in 3 studies	102 per 1000	114 per 1000	Very low Due to extremely serious imprecision ⁴	We are uncertain whether ruxolitinib increases or decreases severe adverse events

1. **Inconsistency: serious.** Point estimates vary widely; **Imprecision: serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: ~extreme_serious.** 95%CI includes benefits and harms;
3. **Imprecision: serious.** Low number of patients;
4. **Imprecision: ~extreme_serious.** Wide confidence intervals;

Summary of findings Table 25. [\(Interactive online version\)](#)

Patients with COVID-19 infection

Intervention: CD24Fc

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	CD24Fc		
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	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	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	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	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 26. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Vitamin D

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Vitamin D		
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	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: 1.08 (CI 95% 0.79 - 1.48) Based on data from 1434 participants in 8 studies	160 per 1000	173 per 1000	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	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	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	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	Low Due to serious risk of bias, Due to serious imprecision ⁵	Vitamin D may not increase severe adverse events

- 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;
- 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;
- 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;
- Imprecision: serious.** Low number of patients;
- Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals, Low number of patients;

Summary of findings Table 27. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Tixagevimab–Cilgavimab

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Tixagevimab– Cilgavimab		
Symptom resolution or improvement	Relative risk: 1.03 (CI 95% 0.99 - 1.08) Based on data from 1417 participants in 1 studies	606 per 1000	624 per 1000	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	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 studies Follow up 29 days	174 per 1000	31 per 1000	Moderate Due to serious risk of bias ³	Tixagevimab– cilgavimab probably decreases symptomatic infection
Severe adverse events	Relative risk: 0.98 (CI 95% 0.73 - 1.31) Based on data from 7819 participants in 4 studies	102 per 1000	100 per 1000	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% 0.26 - 0.69) Based on data from 1230 participants in 2 studies	102 per 1000	43 per 1000	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 28. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Vilobelimab

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Vilobelomab		
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	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	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 29. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Vitamin C

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Vitamin C		
Mortality	Relative risk: 0.84 (CI 95% 0.72 - 0.97) Based on data from 640 participants in 8 studies	160 per 1000	134 per 1000	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	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	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	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 30. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Sarilumab

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Sarilumab		
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	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	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	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	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 31. [\(Interactive online version\)](#)

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	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	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

Summary of findings Table 32. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Peg-Interferon lambda

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Peg-Interferon lambda		
Mortality	Relative risk: 0.73 (CI 95% 0.21 - 2.58) Based on data from 1949 participants in 1 studies	160 per 1000	117 per 1000	Very low Due to very serious imprecision ¹	We are uncertain whether peg-interferon lambda increases or decreases mortality
Invasive mechanical ventilation	Relative risk: 0.71 (CI 95% 0.23 - 2.23) Based on data from 1962 participants in 2 studies Follow up 30 days	173 per 1000	107 per 1000	Very low Due to very serious imprecision ²	We are uncertain whether peg-interferon lambda increases or decreases invasive mechanical ventilation
Severe adverse events	Relative risk: 0.76 (CI 95% 0.5 - 1.16) Based on data from 2143 participants in 4 studies Follow up 30 days	102 per 1000	78 per 1000	Low Due to very serious imprecision ³	Peg-interferon lambda may have little or no difference on severe adverse events
Hospitalization (in patients with non- severe disease)	Relative risk: 0.63 (CI 95% 0.39 - 1.03) Based on data from 2129 participants in 3 studies	48 per 1000	30 per 1000	Low Due to very serious imprecision ⁴	Peg-interferon lambda may have little or no difference on hospitalization (in patients with non-severe disease)

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: very serious.** 95%CI includes benefits and harms;
3. **Imprecision: very serious.** Wide confidence intervals;
4. **Imprecision: very serious.** Wide confidence intervals;

Summary of findings Table 33. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Empaglifozin

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Empaglifozin		
Mortality	Relative risk: 0.96 (CI 95% 0.83 - 1.12) Based on data from 4271 participants in 1 studies Follow up 28 days	160 per 1000	154 per 1000	Moderate Due to serious imprecision ¹	Empaglifozin probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 1.01 (CI 95% 0.8 - 1.27) Based on data from 4227 participants in 1 studies Follow up 28 days	173 per 1000	175 per 1000	Moderate Due to serious imprecision ²	Empaglifozin probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.02 (CI 95% 1.0 - 1.05) Based on data from 4271 participants in 1 studies Follow up 28 days	606 per 1000	618 per 1000	Moderate Due to serious risk of bias ³	Empaglifozin probably has little or no difference on symptom resolution or improvement

1. **Imprecision: serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: serious.** 95%CI includes benefits and harms;
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;

Summary of findings Table 34. [\(Interactive online version\)](#)

Population: Patients with COVID-19 infection

Intervention: Amubarvimab + romlusevimab

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Amubarvimab + romlusevimab		
Mortality	Relative risk: 0.06 (CI 95% 0.0 - 1.05) Based on data from 807 participants in 1 study Follow up 28 days	160 per 1000	10 per 1000	Very low Due to very serious imprecision ¹	We are uncertain whether amubarvimab + romlusevimab increases or decreases mortality
Hospitalization	Relative risk: 0.21 (CI 95% 0.1 - 0.43) Based on data from 807 participants in 1 study Follow up 28 days	48 per 1000	10 per 1000	Moderate Due to serious imprecision ²	Amubarvimab + romlusevimab probably decreases hospitalizations
Severe adverse events	Relative risk: 0.24 (CI 95% 0.12 - 0.47) Based on data from 807 participants in 1 study Follow up 28 days	102 per 1000	24 per 1000	Moderate Due to serious risk of bias ³	Amubarvimab + romlusevimab probably has little or no difference on severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: serious.** 95%CI includes benefits and harms;
3. **Imprecision: serious.** 95%CI includes benefits and harms;

Summary of findings Table 35. [\(Interactive online version\)](#)

Population: Patients with severe to critical COVID-19 infection

Intervention: Mesenchymal stem cells

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Mesenchymal stem cells		
Mortality (Low risk of bias studies)	Relative risk: 0.81 (CI 95% 0.64 - 1.03) Based on data from 432 participants in 6 studies	160 per 1000	130 per 1000	Moderate Due to serious imprecision ¹	Mesenchymal stem cells probably decreases mortality
Invasive mechanical ventilation	Relative risk: 0.93 (CI 95% 0.03 - 1.83) Based on data from 99 participants in 2 studies	173 per 1000	161 per 1000	Very low Due to extremely serious imprecision ²	We are uncertain whether mesenchymal stem cells increases or decreases invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.45 (CI 95% 0.87 - 2.42) Based on data from 321 participants in 3 studies	606 per 1000	879 per 1000	Very low Due to extremely serious imprecision ³	We are uncertain whether mesenchymal stem cells increases or decreases symptom resolution or improvement
Severe adverse events	Relative risk: 0.95 (CI 95% 0.78 - 1.15) Based on data from 350 participants in 4 studies	102 per 1000	97 per 1000	Low Due to very serious imprecision ⁴	Mesenchymal stem cells may have little or no difference on severe adverse events

1. **Imprecision: serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: ~extreme_serious.** 95%CI includes benefits and harms;
3. **Imprecision: ~extreme_serious.** Wide confidence intervals;
4. **Imprecision: very serious.** Wide confidence intervals;

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