ONGOING LIVING UPDATE OF COVID-19 THERAPEUTIC OPTIONS

Summary of Evidence • Rapid Review, 14 September 2021

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Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence. Rapid Review, 13 September 2021

PAHO/IMS/EIH/COVID-19/21-027

Disclaimer

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

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Executive summary

Background

The urgent need for evidence on measures to respond to the COVID-19 pandemic had led to a rapid escalation in numbers of studies testing potential therapeutic options. The vast amount of data generated by these studies must be interpreted quickly so that physicians have the information to make optimal treatment decisions and manufacturers can scale-up production and bolster supply chains. Moreover, obtaining a quick answer to the question of whether or not a particular intervention is effective can help investigators involved in the many ongoing clinical trials to change focus and pivot to more promising alternatives. Since many physicians are currently using treatments that rely on compassionate-use exemptions or off-label indications to treat patients with COVID-19, 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.

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. Table 3, below, summarizes the status of evidence for the 143 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=407)

Intervention		Overall number of studies including the intervention, n=407	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Hydroxychloroquine or Chloroquine	NEW	49	13	9	9	9	17	7
Ivermectin		32	6 (*)	6	3 (*)	4	4	4
Tocilizumab	NEW	26	20	21	6		12	
Convalecent plasma	NEW	24	9(*)	7(*)	9		3(*)	
Corticosteroids		16	14(@)	6	5		6	
Favipiravir	NEW	15	5	4	1(*)		3	1
Lopinavir-Ritonavir		15	4	4	2	1	2	1
Sofosbuvir +/- Daclatasvir or others		13	2(*)	2(*)	2(*)			
Azithromycin		9	4	3	4		1	2
Sarilumab		9	9	7	2		3	
ACEIs or ARBs		9	8	8	2			1
Anticoagulants (Intermediate or full dose)		7	7				5 (^)	
Mouthwash		7	2	1	1			
Bamlanivimab +/- etesevimab	NEW	7	3		3	1	5	2
Remdesivir		6	5 **(#)**	5	3		3	
Umifenovir		6	1	2			1	
Zinc		6	2	1	2		1	
Coclchicine		5	4(**)	3(**)	1(**)		1	1
IVIG		5	8	8				
REGEN-COV (casirivimab and imdevir	NEW	5	1(##)	1(##)	2(##)	2	2	2
Vitamin D		5	2	1			1	
Bromhexine Hydrochloride		4	2	1	2	1	1	
Corticosteroids (inhaled)	NEW	4	1	1	4			2
Interferon beta-1a		4	3	3	2			
Melatonin	NEW	4	2		3			
Mesenchimal cell tranplantation		4	3		1		2	
Nitazoxanide		4	1	1	1		2	2
Proxalutide		4	3	3	2			2
Vitamin C		4	4	4	2			
N-acetylcysteine		3	2	2			1	
Molnupiravir		3					3	
Anakinra		2	2	1	2		2	
Aspirin		2	2	2	1			
Baricitinib		2	2	1	2		2	
Canakinumab		2	2	1	1		1	
Doxycycline		2	1	1	2		1	1
Dutasteride		2			1			
Fluvoxamine		2	1	1			2	2
Iota-Carrageenan		2	1				2	1
Leflunomide		2						
Nigella sativa +/- Honey		2	1		1			1
Nitric oxide		2	1	1			2	
Omega-3 fatty acids		2	1					
Ozone		2	2		1		1	
Peg-IFN alfa	NEW	2	2		2			
Querceritin		2	2		1			1
99mTc-MDP		1						
Adalimumab	NEW	1	1	1				
Ammonium chloride		1	1	1				
Aprepitant		1						
Artemisinin		1			1		1	
Auxora		1	1	1				
Aviptadil		1	1		1		1	
Azvudine		1						
Baloxavir		1			1			
BCG		1	1					
Bioven		1	1				1	
Camostat mesilate		1	1	1	1		1	
CERC-002		1	1				1	
Chloroquine nasal drops		1						
Clarithromycin		1						
CIGB-325		1			1		1	
Cofactors		1			1		1	
Colchicine + rosuvastatin		1	1	1			1	
Darunavir-Cobicistat		1						

Intervention		Overall number of studies including the intervention, n=407	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)
Dapagliflozin		1	1		1		1	
Dimethyl sulfoxide (DSMO)		1				1		
Electrolyzed saline		1	1		1			1
Emtricitabine/tenofovir		1	1	1			1	
Enisamium		1			1			
Famotidine		1	1					
Febuxostat		1						1
Finasteride		1	1					
Fostamatinib	NEW	1	1		1		1	
Helium (inhaled)		1						
Hyperbaric oxygen		1	1	1	1			
Hyperimmune anti-COVID-19 IVIG		1	1		1		1	
iC1e/K		1	1					
Icatibant		1	1					
Icosapent ethyl	NEW	1			1			
IFN-alpha2b + IFN-gamma		1						
IFX-1		1	1				1	
Imatinib		1	1	1			1	
Indomethacin		1	1	1			1	
Infliximab		1	1		1		1	
INM005 (equine antibodies)		1	1	1	1		1	
Interferon beta-1b		1	1	1	1			
Interferon beta-1a (inhaled)		1	1	1	1		1	
Interferon gamma		1						
Interferon kappa + TFF2		1	1				1	
Itolizumab		1	1	1			1	
Ivermectin (inhaled)		1			1			
KB109		1	1		1		1	
L-arginine	NEW	1	1				1	
Lactococcus Lactis (intranasal)		1			1		1	
Lenzilumab		1	1	1			1	
Levamizole		1			1			1
Lincomecin		1						
Low-dose radiation therapy		1	1					
Mavrilimumab		1	1	1	1		1	
Metisoprinol		1						
Methylene blue		1	1					
Metoprolol	NEW	1	1					
Mycobacterium w		1	1					
Namilumab		1	1		1		1	
Nasal hypertonic saline		1			1			
Neem (Azadirachta Indica A. Juss)		1				1		
Niclosamaide		1	1	1			1	
Novaferon		1						
Otilimab		1	1				1	
Peg-IFN lambda		1					1	
PNB001 (CCK-A antagonist)		1	1		1			
Polymerized type I collagen (PT1C)		1						1
Povidone iodine		1	1				1	1
Probiotics		1				1		
Progesterone		1	1	1			1	
Prolectin-M		1	1	1			1	
Propolis		1	1	1	1			
Pyridostigmine		1	1	1	1		1	
Ramipril		1	1			1		
Recombinant Super-Compound IFN		1	1		1			
Regdanvimab		1			1		1	1
Ribavirin		1						
Ribavirin + Interferon beta-1b		1						
Ruxolitinib		1			1			
rhG-CSF		1	1		1		1	
Secukinumab		1	1	1			1	
Short-wave diathermy		1	1		1		1	
Sitagiptin		1	1	1				
Sofosbuvir/ledipasvir		1	1	1	1			1

Intervention	Overall number of studies including the intervention, n=407	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)
Sotrovimab	1	1	1	1		1	1
Spironolactone	1	1	1				
Statins	1	1	1				
Stem cell nebulization	1	1		1		1	
Sulodexide	1	1	1			1	1
TD-0903 (inhaled JAK-inhibitor)	1	1				1	
Thalidomide	1	1	1			1	
Tenofovid + emtricitabine	1	1				1	1
Triazavirin	1	1		1		1	
Tofacitinib	1	1		1		1	
XAV-19 (swine polyclonal antibodies)	1	1				1	
α-Lipoic acid	1	1					

(*) Based on low risk of bias subgroup of studies; (#) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-statitically significant mortality reduction (RR 0.95, 95%CI 0.83 - 1.08); (^) Major bleeding; (**) Observed results apply mostly to hospitalized patients with moderate to critical disease. The COLCORONA trial that included patients with recent onset mild disease showed a tendency to less hospitalizations, less mortality and less mechanical ventilation requirements. However the certainty on those potential benefits was low because of very serious imprecision as the number of events was low; (##) Subgroup of seronegative patients; (@) High dose schemes (i.e dexamethasone 12 mg a day) may be more effective than standard dose schemes (i, e dexamethasone 6 mg a day).

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

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

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				

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

Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=143), as at 13 September 2021

	Intervention	Summary of findings
1	**99mTc-MDP**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Adalimumab**	Uncertainty in potential benefits and harms. Further research is needed.
3	**Ammonium chloride**	Uncertainty in potential benefits and harms. Further research is needed.
4	**ACEIs or ARBs**	Continuing ACEIS or ARBs in patients with COVID-19 may increase mortality. However, the certainty of the evidence was low. Further research is needed.
5	**Anakinra**	It is uncertain if anakinra affects mortality, mechanical ventilation requirements, symptom resolution or increases severe adverse events. Further research is needed.
6	**Anticoagulants**	There are specific recommendations on the use of antithrombotic agents[8] for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) probably does not decrease mortality in comparison with prophylactic dose (i.e., enoxaparin 40 mg a day). Anticoagulants in intermediate or full dose may decrease venous thromboembolic events but increase major bleeding in comparison with prophylactic dose.
7	**Aprepitant**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Artemisinin**	Uncertainty in potential benefits and harms. Further research is needed.
9	**Aspirin**	Aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement.
10	**Auxora**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
11	**Aviptadil**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Azithromycin**	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
13	**Azvudine**	Uncertainty in potential benefits and harms. Further research is needed.
14	**Baricitinib**	Baricitinib probably reduces mortality and time to symptom resolution. Certainty of the evidence was moderate because of risk of bias.
15	**Baloxavir**	Uncertainty in potential benefits and harms. Further research is needed.
16	**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.
17	**BCG**	Uncertainty in potential benefits and harms. Further research is needed.
18	**Bioven**	Uncertainty in potential benefits and harms. Further research is needed.
19	**Bromhexine hydrochloride**	Uncertainty in potential benefits and harms. Further research is needed.
20	**Camostat mesilate**	Uncertainty in potential benefits and harms. Further research is needed.
21	**Canakinumab**	Uncertainty in potential benefits and harms. Further research is needed.
22	**CERC-002**	Uncertainty in potential benefits and harms. Further research is needed.
23	**Chloroquine nasal drops**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
24	**CIGB-325**	Uncertainty in potential benefits and harms. Further research is needed.
25	**Clarithromycin**	Uncertainty in potential benefits and harms. Further research is needed.
26	**Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)**	Uncertainty in potential benefits and harms. Further research is needed.
27	**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 may reduce hospitalizations. However, the certainty of the evidence was low because of imprecision.
28	**Colchicine + rosuvastatin**	Uncertainty in potential benefits and harms. Further research is needed.
29	**Convalescent plasma**	Convalescent plasma does not reduce mortality nor reduces mechanical ventilation requirements or improves time to symptom resolution with moderate to high certainty of the evidence. In mild patients' convalescent plasma may not reduce hospitalizations. Convalescent plasma probably increases severe adverse events.
30	**Dapagliflozin**	Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.
31	**Darunavir-cobicistat**	Uncertainty in potential benefits and harms. Further research is needed.
32	**Dimethyl sulfoxide (DSMO)**	Uncertainty in potential benefits and harms. Further research is needed.
33	**Doxycycline**	Doxycycline does not increase symptom resolution or improvement and may not reduce hospitalizations.
34	**Dutasteride**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
35	**Electrolyzed saline**	Uncertainty in potential benefits and harms. Further research is needed.
36	**Emtricitabine/tenofovir**	Uncertainty in potential benefits and harms. Further research is needed.
37	**Enisamium**	Uncertainty in potential benefits and harms. Further research is needed.
38	**Famotidine**	Uncertainty in potential benefits and harms. Further research is needed.
39	**Favipiravir**	Favipiravir may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution.
40	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
41	**Finasteride**	Uncertainty in potential benefits and harms. Further research is needed.
42	**Fluvoxamine**	Fluvoxamine probably reduces hospitalizations and may not increase severe adverse events. Certainty of the evidence was low to moderate. Further research is needed.
43	**Fostamatinib**	Uncertainty in potential benefits and harms. Further research is needed.
44	**Helium (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
45	**Hydroxychloroquine and chloroquine**	Hydroxychloroquine or chloroquine probably does not reduce mortality, invasive mechanical ventilation nor significantly improves time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19 it may reduce the risk of infection. However, certainty of the evidence is low because of risk of bias and imprecision.
46	**Hyperbaric oxygen**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
47	**Hyperimmune anti-COVID-19 Intravenous Immunoglobulin (C-IVIG)**	Uncertainty in potential benefits and harms. Further research is needed.
48	**Icatibant/iC1e/K**	Uncertainty in potential benefits and harms. Further research is needed.
49	**Icosapent ethyl**	Uncertainty in potential benefits and harms. Further research is needed.
50	**IFX-1**	Uncertainty in potential benefits and harms. Further research is needed.
51	**Imatinib**	Uncertainty in potential benefits and harms. Further research is needed.
52	**Indomethacin**	Uncertainty in potential benefits and harms. Further research is needed.
53	**Infliximab**	Uncertainty in potential benefits and harms. Further research is needed.
54	**INM005 (polyclonal fragments of equine antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
55	**Interferon alpha-2b and interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
56	**Interferon beta-1a**	IFN beta-1a probably does not reduce mortality nor invasive mechanical ventilation requirements. Inhaled interferon beta-1a may improve time to symptom resolution.
57	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
58	**Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
59	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
60	**Iota-carrageenan**	Uncertainty in potential benefits and harms. Further research is needed.
61	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
62	**Ivermectin**	Although pooled estimates suggest significant benefits with ivermectin, included studies' methodological limitations and a small overall number of events results in very low certainty of the evidence. Based on the results reported by the RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality nor mechanical ventilation requirements, and probably does not improve time to symptom resolution. However, ivermectin may reduce hospitalizations in non-severe patients. Further research is needed to confirm or discard these findings.
63	**Ivermectin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
64	**Intravenous immunoglobulin**	Uncertainty in potential benefits and harms. Further research is needed.
65	**KB109**	Uncertainty in potential benefits and harms. Further research is needed.
66	**L-arginine**	Uncertainty in potential benefits and harms. Further research is needed.
67	***Lactococcus lactis* (intranasal)**	Uncertainty in potential benefits and harms. Further research is needed.
68	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
69	**Lenzilumab**	Lenzilumab may reduce mortality and mechanical ventilation requirements in severe patients. However, the certainty of the evidence is low because of imprecision. Further research is needed.
70	**Levamisole**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
71	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.
72	**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.
73	**Low-dose radiation therapy**	Uncertainty in potential benefits and harms. Further research is needed.
74	**Mavrilimumab**	Uncertainty in potential benefits and harms. Further research is needed.
75	**Melatonin**	Uncertainty in potential benefits and harms. Further research is needed.
76	**Mesenchymal stem-cell transplantation**	Mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence is low. Further research is needed.
77	**Methylene blue**	Uncertainty in potential benefits and harms. Further research is needed.
78	**Metisoprinol**	Uncertainty in potential benefits and harms. Further research is needed.
79	**Metoprolol**	Uncertainty in potential benefits and harms. Further research is needed.
80	**Molnupiravir**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
81	**Mouthwash**	Uncertainty in potential benefits and harms. Further research is needed.
82	**Mycobacterium w**	Uncertainty in potential benefits and harms. Further research is needed.
83	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.
84	**Namilumab**	Uncertainty in potential benefits and harms. Further research is needed.
85	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
86	**Neem (*Azadirachta indica* A. Juss)**	Uncertainty in potential benefits and harms. Further research is needed.
87	**Niclosamide**	Uncertainty in potential benefits and harms. Further research is needed.
88	***Nigella sativa* +/- honey**	Uncertainty in potential benefits and harms. Further research is needed.
89	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.
90	**Nitric oxide**	Uncertainty in potential benefits and harms. Further research is needed.
91	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
92	**Non-steroidal anti-inflammatory drugs (NSAIDs)**	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.

	Intervention	Summary of findings
93	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed
94	**Otilimab**	Uncertainty in potential benefits and harms. Further research is needed
95	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
96	**Peg-interferon alfa**	Uncertainty in potential benefits and harms. Further research is needed.
97	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
98	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.
99	**PNB001 (CCK-A antagonist)**	Uncertainty in potential benefits and harms. Further research is needed.
100	**Polymerized type I collagen (PT1C)**	Uncertainty in potential benefits and harms. Further research is needed.
101	**Povidone iodine (nasal spray)**	Uncertainty in potential benefits and harms. Further research is needed.
102	**Probiotics**	Uncertainty in potential benefits and harms. Further research is needed.
103	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed
104	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed
105	**Propolis**	Uncertainty in potential benefits and harms. Further research is needed

	Intervention	Summary of findings
106	**Proxalutamide**	Proxalutamide may reduce mortality, mechanical ventilation and improve time to symptom resolution. However, the certainty of the evidence is low because of risk of bias, imprecision, and indirectness. Further research is needed.
107	**Pyridostigmine**	Uncertainty in potential benefits and harms. Further research is needed
108	**Quercetin**	Uncertainty in potential benefits and harms. Further research is needed
109	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
110	**Recombinant super-compound interferon**	Uncertainty in potential benefits and harms. Further research is needed.
111	**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 mild recent onset 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. The certainty of the evidence was high for symptomatic infections and low to moderate because of imprecision and indirectness for the remaining outcomes.
112	**Regdanvimab**	Regdanivimab may improve time to symptom resolution in mild to moderate patients. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.
113	**Remdesivir**	Remdesivir may slightly reduce mortality and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.
114	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.
115	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
116	**Ribavirin + interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
117	**Ruxolitinib**	Uncertainty in potential benefits and harms. Further research is needed.
118	**Sarilumab**	Sarilumab may not reduce mortality but may decrease mechanical ventilation requirements without increasing severe adverse events. However, the certainty is low because of imprecision and inconsistency.
119	**Secukinumab**	Uncertainty in potential benefits and harms. Further research is needed.
120	**Short-wave diathermy**	Uncertainty in potential benefits and harms. Further research is needed.
121	**Siltuximab**	Uncertainty in potential benefits and harms. Further research is needed.
122	**Sitagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
123	**Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir or ravidasvir**	Sofosbuvir with or without daclatasvir or ledipasvir may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.
124	**Sotrobimab**	Sotrobimab probably reduces hospitalizations in patients with recent onset mild COVID-19.
125	**Spironolactone**	Uncertainty in potential benefits and harms. Further research is needed.
126	**Statins**	Uncertainty in potential benefits and harms. Further research is needed.
127	**Stem-cell nebulization**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
128	**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., 12 mg a day) may be more effective but further research is needed).
129	**Steroids (corticosteroids, inhaled)**	Inhaled corticosteroids probably improve time to symptom resolution and may decrease hospitalizations. Further research is needed.
130	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
131	**TD-0903 (inhaled JAK-inhibitor)**	Uncertainty in potential benefits and harms. Further research is needed.
132	**Telmisartan**	Uncertainty in potential benefits and harms. Further research is needed.
133	**Tenofovir + emtricitabine**	Uncertainty in potential benefits and harms. Further research is needed.
134	**Thalidomide**	Uncertainty in potential benefits and harms. Further research is needed.
135	**Tocilizumab**	Tocilizumab reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
136	**Tofacitinib**	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low, further research is needed.
137	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
138	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
139	**Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
140	**Vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
141	**XAV-19 (swine glyco-humanized polyclonal antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
142	**Zinc**	Uncertainty in potential benefits and harms. Further research is needed.
143	**α-lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to WHO international registry of clinical trials 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 137 therapeutic options.

• **Corticosteroids:** The body of evidence on corticosteroids, which includes 16 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., 12 mg a day) may be more effective but further research is needed.

• **Remdesivir:** In the WHO SOLIDARITY trial, remdesivir resulted in little or no effect on overall mortality, initiation of ventilation and duration of hospital stay among hospitalized patients. When combining those findings with those from four other RCTs, remdesivir may slightly reduce mortality and invasive mechanical ventilation requirements and may improve time to symptom resolution. However, overall certainty of the evidence is low and further research is needed to confirm these findings.

• **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. Nine studies assessed hydroxychloroquine in exposed individuals and showed a non-statistically significant trend towards reduction in symptomatic infection. Further research is needed to confirm these findings.

• **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 24 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 may not significantly reduce hospitalizations with low certainty. Convalescent plasma probably increases severe adverse events with moderate certainty. No significant differences were observed between patients treated early (< 4 days since symptom onset) or with more advanced disease.

• **Tocilizumab:** The results of 26 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.

• **Sarilumab:** The results of nine RCTs assessing sarilumab show that, in patients with severe or critical disease, sarilumab may not reduce mortality, but may reduce mechanical ventilation requirements without significantly increasing severe adverse events. However, certainty of the evidence was low and further research is needed to confirm these findings.

• **Anakinra:** The results of two RCTs assessing anakinra in hospitalized patients with non-severe disease, show inconsistent results on mortality and symptom resolution. Certainty of the evidence was very low and further research is needed.

• **Tofacitinib:** The results of one RCT 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.

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

• **Ivermectin:** Although 32 RCTs assessed ivermectin in patients with COVID-19, only 13 of those studies reported on clinical important outcomes. Pooled estimates 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 four RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality nor mechanical ventilation requirements and probably does not improve time to symptom resolution. However, ivermectin may reduce hospitalizations in non-severe patients. Further research is needed to confirm these findings.

• **Favipiravir:** Fifteen RCTs assessed favipiravir vs SOC or other interventions. Their results suggest that favipiravir may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

• **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** Thirteen 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 not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

• **Baricitinib:** The results of two RCTs show that, in patients with moderate to severe disease, baricitinib probably reduces mortality and time to symptom resolution. The certainty of the evidence was moderate because of risk of bias.

• **REGEN-COV (casirivimab and imdevimab):** The results of five RCTs show that, in patients with severe to critical disease, overall REGEN-COV does not significantly reduce mortality, mechanical ventilation or increase symptom resolution or improvement. However, 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 mild recent onset 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. The certainty of the evidence was high for symptomatic infections and low to moderate because of indirectness and imprecision for the remaining outcomes. 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 one RCT show that, in patients with mild recent onset COVID-19, sotrobimab probably reduces hospitalizations and improves time to symptom resolution without increasing severe adverse events. The certainty of the evidence was moderate because of imprecision.

• **Regdanvimab:** The results of one RCT 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. It's effects on other important outcomes are uncertain. Further research is needed to confirm or discard these findings.

• **Proxalutamide:** The results of four RCTs show that, in patients with mild to severe, proxalutamide may reduce mortality, mechanical ventilation requirements and time to symptom resolution. However, the certainty of the evidence was low because of 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-cell transplantation:** The results of four RCTs show that, in patients with severe to critical, mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence was low because of imprecision. Further research is needed to confirm or discard these findings.

• **Inhaled corticosteroids:** The results of four RCTs suggest that inhaled corticosteroids probably improve time to symptom resolution and may reduce hospitalizations. However, the certainty of the evidence was moderate to low and its effects on other relevant outcomes are uncertain. Further research is needed.

• **Fluvoxamine:** The results of two RCTs suggest that in patients with mild disease, fluvoxamine probably reduces hospitalizations and may not increase adverse events. The certainty of the evidence was moderate to low because of imprecision. Further research is needed.

• **Lenzilumab:** The results of one RCT suggest that lenzilumab may reduce mortality and invasive mechanical ventilation requirements in severe patients. 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 seven 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. Results of two RCTs inform that aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement.

• **NSAIDS:** No association between NSAID 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 five low-risk of bias RCTs suggest that initiating or continuing ACEIs or ARBs in patients with COVID-19 may increase mortality. However, certainty of the evidence is low because of imprecision and further research is needed to confirm these findings.

Changes since previous edition

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

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

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

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

• **Peg-interferon (IFN) alfa:** New evidence included without significant changes.

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

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

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

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

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

• **Convalescent plasma:** New evidence included without significant changes.

• **Bamlinivimab +/- etesevimab**: New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **REGEN-COV (casirivimab and imdevimab)**: New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

• **Inhaled corticosteroids:** New evidence included without significant changes.

Concluding remarks

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

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

• There remains an urgent need for additional high-quality randomized controlled trials that include patients with COVID-19 before most therapeutic options can be administered with any confidence. 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 Internacional de Registro de Ensayos Clínicos (ICTRP) de la OMS, se están investigando cientos de posibles tratamientos o sus combinaciones en más de 10.000 ensayos clínicos y estudios observacionales. En esta revisión, examinamos 137 opciones terapéuticas potenciales.

• **Corticosteroides:** El conjunto de evidencia sobre los corticoesteroides incluye quince ensayos clínicos controlados aleatorizados (ECCA) y muestra que la administración de dosis bajas y moderadas (la dosis utilizada en el estudio RECOVERY fue dexametasona 6 mg diarios por vía oral o intravenosa durante 10 días) probablemente reducen la mortalidad en pacientes con infección grave por COVID-19. Los resultados se mantuvieron uniformes tras agregar al análisis estudios en los que pacientes con SDRA de otras etiologías recibieron corticosteroides o manejo estándar de forma aleatoria. Esquemas con dosis más altas (por ejemplo dexametasona 12 mg por día) podrían resultar más efectivos, pero se necesita más información.

• **Remdesivir:** En el estudio Solidaridad de la OMS, el remdesivir no tuvo un efecto clínicamente relevante sobre la mortalidad global, la necesidad de ventilación mecánica invasiva o la duración de la estadía hospitalaria. Tras combinar dichos resultados con otros cuatro ECCA, se observó que el remdesivir podría reducir la mortalidad, la necesidad de ventilación mecánica invasiva y mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y se necesita más información para confirmar estas conclusiones.

• **Hidroxicloroquina, interferón beta 1-a y Lopinavir-ritonavir:** El conjunto de evidencia sobre hidroxicloroquina, interferón beta 1-a y Lopinavir-ritonavir, incluidos los resultados preliminares de los estudios RECOVERY y Solidaridad, no muestra beneficios en la reducción de la mortalidad, necesidad de ventilación mecánica invasiva o el plazo necesario para la mejoría clínica. Incluso la evidencia sobre hidroxicloroquina sugiere que su utilización probablemente genere un incremento en la mortalidad. Nueve estudios que evaluaron la hidroxicloroquina en personas expuestas a la COVID-19 mostraron una tendencia hacia una reducción en el riesgo de infección, pero esta no resulta estadísticamente significativa. Se necesita más información para confirmar estas conclusiones.

• **Antibióticos:** El cuerpo de evidencia identificado sobre azitromicina y doxiciclina muestra ausencia de beneficios significativos en pacientes con COVID-19 leve a moderada, o grave a crítica.

• **Plasma de convalecientes:** Los resultados de 24 ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19, incluido el estudio RECOVERY que incorpora 11.558 pacientes, mostraron ausencia de reducción de la mortalidad, ausencia de reducción en la necesidad de ventilación mecánica invasiva y ausencia de mejoría en el tiempo de resolución de los síntomas con certeza moderada. En pacientes leves, el plasma de convalecientes podría no reducir las hospitalizaciones con baja certeza. El plasma de convalecientes probablemente se asocia a un aumento en los eventos adversos graves con moderada certeza. No se observó un efecto diferencial entre aquellos pacientes tratados rápidamente (menos de 4 días desde el inicio de los síntomas) y aquellos con enfermedad más avanzada al iniciar dicho tratamiento.

• **Tocilizumab:** Los resultados de 26 ECCA muestran que tocilizumab reduce la mortalidad y la necesidad de ventilación invasiva sin un incremento importante en efectos adversos graves en pacientes con enfermedad grave o crítica.

• **Sarilumab:** Los resultados de nueve ECCA muestran que sarilumab podría no reducir la mortalidad, aunque sí podría reducir la necesidad de ventilación invasiva sin un incremento importante en efectos adversos graves en pacientes con enfermedad grave o crítica. Sin embargo, la certeza en la evidencia es baja y se necesita más información para confirmar estas conclusiones.

• **Anakinra:** Los resultados de dos ECCA que evaluaron anakinra en pacientes hospitalizados con enfermedad no grave muestran resultados incongruentes en mortalidad y resolución de síntomas. La certeza en la evidencia es muy baja y se necesita más información.

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

• **Colchicina:** Los resultados de cinco 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 colchicina probablemente no reduce la mortalidad, la necesidad de ventilación mecánica o mejora la velocidad de resolución de los síntomas. Estos resultados están fundamentalmente sustentados en el estudio RECOVERY. El estudio COLCORONA, que incluyó pacientes ambulatorios con enfermedad leve, apunta una posible reducción en las hospitalizaciones, la necesidad de ventilación mecánica y la mortalidad en este subgrupo. Sin embargo, la certeza en la evidencia es baja por imprecisión muy grave, ya que el número de eventos fue bajo.

• **Ivermectina:** A pesar de que 32 ECCA evaluaron ivermectina en pacientes con COVID-19, solo 13 de estos estudios notificaron desenlaces clínicamente importantes. Los resultados combinados de estos estudios indican una reducción en la mortalidad con ivermectina. Sin embargo, la certeza en la evidencia es muy baja por limitaciones metodológicas y un número reducido de eventos. Con base en la información facilitada por los cuatro estudios con riesgo bajo de sesgo, la ivermectina podría no reducir de forma significativa la mortalidad ni la necesidad de ventilación mecánica invasiva, y probablemente no se asocie a una mejoría en la velocidad de resolución de los síntomas. Sin embargo, la ivermectina podría reducir las hospitalizaciones en pacientes con enfermedad leve. Se necesita más información para confirmar estas conclusiones.

• **Favipiravir:** Quince ECCA evaluaron favipiravir en comparación con la prestación de cuidados estándares u otras intervenciones. Sus resultados sugieren que favipiravir podría no reducir la mortalidad ni la necesidad de ventilación invasiva mecánica, y probablemente no mejore el tiempo de resolución de los síntomas. Se necesita más información para confirmar estas conclusiones.

• **Sofosbuvir con o sin daclatasvir, ledipasvir, velpatasvir o ravidasvir:** Trece ECCA evaluaron 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 con un riesgo bajo de sesgo mostraron resultados sustancialmente diferentes. Los resultados de los dos estudios clasificados como con riesgo bajo de sesgo sugieren que sofosbuvir solo o en combinación podría no reducir la mortalidad ni la necesidad de ventilación invasiva mecánica, y probablemente no mejore el tiempo de resolución de los síntomas. Se necesita más información para confirmar estas conclusiones.

• **Baricitinib:** Los resultados de dos ECCA muestran que, en pacientes con enfermedad de moderada a grave, baricitinib probablemente reduce la mortalidad y mejora el tiempo de resolución de los síntomas. La certeza en la evidencia es moderada por riesgo de sesgo.

• **REGEN-COV (casirivimab e imdevimab):** Los resultados de cinco ECCA muestran que, en pacientes con enfermedad grave o crítica, REGEN-COV probablemente no reduzca la mortalidad, la necesidad de ventilación invasiva ni mejore la resolución de los síntomas de forma significativa. Sin embargo, un análisis de subgrupo mostró un efecto diferencial en pacientes con anticuerpos negativos. En este subgrupo, REGEN-COV probablemente reduzca la mortalidad, la necesidad de ventilación mecánica e incremente la resolución de síntomas. En pacientes con enfermedad leve de comienzo reciente, REGEN-COV probablemente reduce las hospitalizaciones y mejora el tiempo de resolución de los síntomas sin aumentar el riesgo de eventos adversos graves, y en personas asintomáticas, expuestas a SARS-CoV-2,2 REGEN-COV reduce las infecciones sintomáticas. La certeza en la evidencia es alta para infecciones sintomáticas y de baja a moderada por información indirecta e imprecisión para los restantes desenlaces. Un estudio que comparó REGEN-COV (casirivimab and imdevimab) contra bamlanivimab con o sin etesevimab en pacientes leves con factores de riesgo para enfermedad severa reportó ausencia de diferencias importantes en las hospitalizaciones.

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

• **Sotrovimab:** Los resultados de un ECCA muestran que, en pacientes con enfermedad leve de comienzo reciente, sotrovimab probablemente reduce las hospitalizaciones y mejora el tiempo de resolución de los síntomas sin aumentar el riesgo de eventos adversos graves. La certeza en la evidencia es moderada por imprecisión.

• **Regdanvimab:** Los resultados de un ECCA muestran que, en pacientes con enfermedad leve a moderada, regdanivimab podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja por imprecisión. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información para confirmar o descartar estas conclusiones.

• **Proxalutamide:** Los resultados de cuatro ECCA muestran que, en pacientes con enfermedad de leve a moderada, proxalutamide podría reducir la mortalidad, la ventilación mecánica y mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja por riesgo 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, dapagliflozina podría reducir la mortalidad, pero probablemente no mejora la resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.

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

• **Corticosteroides inhalados:** Los resultados de cuatro ECCA sugieren que los corticosteroides inhalados probablemente mejoran el tiempo de resolución de los síntomas y podrían reducir las hospitalizaciones. Sin embargo, la certeza en la evidencia es de moderada a baja y sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Fluvoxamina:** Los resultados de dos ECCA sugieren que, en pacientes con enfermedad leve, fluvoxamina probablemente reduzca las hospitalizaciones y podría no incrementar los eventos adversos. La certeza en la evidencia es de baja a moderada por imprecisión. Se necesita más información.

• **Lenzilumab:** Los resultados de un ECCA sugieren que lenzilumab podría reducir la mortalidad y la necesidad de ventilación invasiva en pacientes graves. Sin embargo, la certeza en la evidencia es baja por imprecisión. Se necesita más información.

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

• **Famotidina:** Hasta el momento, la evidencia sobre los efectos de la famotidina es de muy baja certeza.

• **Complicaciones tromboembólicas:** Las complicaciones tromboembólicas en pacientes con COVID-19 son frecuentes. Al igual que en pacientes hospitalizados por afecciones médicas graves, las directrices de práctica clínica vigentes indican que los pacientes hospitalizados por COVID-19 sean tratados con medidas tromboprofilácticas. En relación con el esquema tromboprofiláctico, los resultados de siete estudios aleatorizados y controlados que compararon dosis intermedias (p. ej., enoxaparina 1 mg/kg por día) o dosis completas (p. ej., enoxaparina 1 mg/kg cada 12 h por día) frente a dosis profilácticas (p. ej., enoxaparina 40 mg por día) mostraron ausencia de diferencias en la mortalidad con certeza moderada. Los resultados de dos estudios aleatorizados informan que la indicación de aspirina probablemente tampoco se asocia a una reducción en la mortalidad, la ventilación mecánica o la mejoría en la velocidad de resolución de los síntomas.

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

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

Cambios respecto a la versión anterior

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

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

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

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

• **Peg-interferon (IFN) alfa:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

• **Icosapent ethyl:** 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.

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

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

• **Bamlanivimab con o sin etesevimab:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **REGEN-COV (casirivimab e imdevimab):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

Conclusiones

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

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

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

• Sigue siendo apremiante la necesidad de elaborar ensayos clínicos aleatorizados de alta calidad que incluyan pacientes con COVID-19 a fin de poder desarrollar estrategias de manejo confiables. 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 uso y aplicación.

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 last version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on the L·OVE website.[2]

Search strategy

We systematically searched in L·OVE for COVID-19. The search terms and databases covered are described on the L·OVE search strategy methods page available at: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&section=methods. The repository is continuously updated, and the information is transmitted in real-time to the L·OVE platform, however, it was last checked for this review on 13 September 2021. 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 mean risk in the control groups from included RCTs until 14 April 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 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).[8] 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).[9] 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.

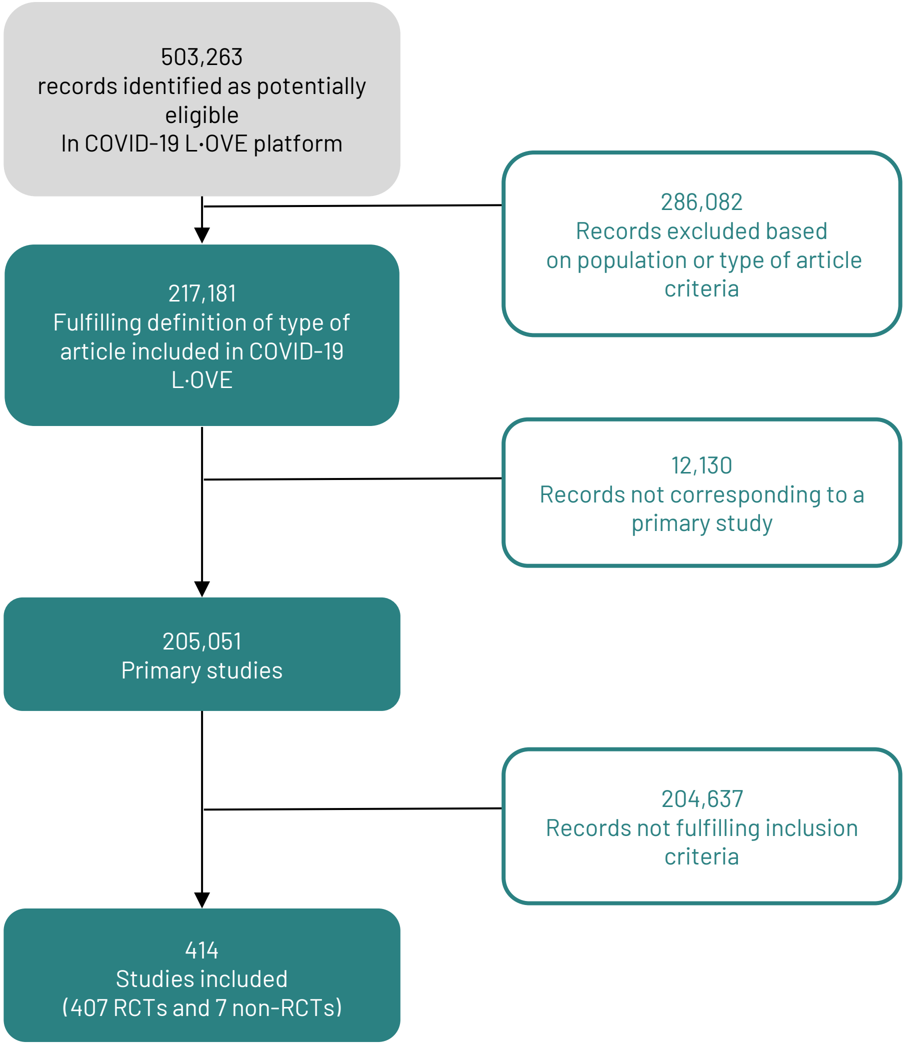
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in Figure 1. A total of 414 studies were selected for inclusion, 407 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 - Dexamethasone	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	NA	Some Concerns
ACTT-1	Low	Low	Low	Some Concerns	Low	Low	Low
COVID-19 PEP	Low	Low	High	Low	Low	NA	High
Cavalcanti et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kamran SM et al	High	Some Concerns	Low	High	Low	NA	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	NA	High
Chen C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CAP-China remdesivir 2	Low	Low	Low	Low	Low	Low	Low
LOTUS China	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Tang et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hung IF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
GRECCO-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Li L et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RASTAVI	Low	Some Concerns	Low	High	Low	NA	High
Chen, Zeng 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	Low	High
GLUCOCOVID	High	Some Concerns	Low	Low	Low	High	High
CloroCOVID19	Low	Low	Low	Some Concerns	Low	Low	Low
Davoudi-Monfared et al	High	Some Concerns	Low	Low	Low	High	High
Chen et al	High	Some Concerns	Low	Low	Low	High	High
Davoodi L et al	High	Some Concerns	Low	Low	Low	High	High
Ivashchenko AA et al	High	Some Concerns	Low	Low	Low	High	High
Rasheed AM 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
Mehboob 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
Lopes et al	High	Low	Low	Low	Low	High	High
Duarte M et al	High	Some Concerns	Low	Some Concerns	Some Concerns	High	High
Metcovid	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
Miller J et al	High	Some Concerns	Low	Some Concerns	Some Concerns	High	High
Abbaspour Kasgari 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-Elsalam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sekhavati E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zagazig University	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahmani H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ConPlas-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
REMAP-CAP	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
Li T et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Wang D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mohiuddin ATMM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLACID	Low	Some Concerns	Low	Some Concerns	Low	Low	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
Cheng LL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Farahani R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
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
Edalatifard M et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PREP	Low	Low	Low	Low	Low	Low	Low
Wang M, Hu 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
Podder CS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Edalatifard M et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PREP	Low	Low	Low	Low	Low	Low	Low
Wang M, Hu 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

Podder 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
Nojomi et al (Iran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PrEP_COVID	Low	Low	Low	Low	Low	Low	Low
de Alencar JCG et al (Universidade de São Paulo)	Low	Low	Low	Low	Low	Low	Low
Fu W et al (Shanghai Public Health Clinical Center)	High	Some Concerns	Low	Some Concerns	Low	High	High
Salehzadeh F (Ardabil University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
Dabbous H et al (Ain Shams University)	High	Some Concerns	Low	Some Concerns	Low	High	High
PATCH	Low	Low	Low	Low	Low	Low	Low
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLASM-AR	Low	Low	Low	Low	Low	Low	Low
COVID-19-MCS	Low	Low	Low	Some Concerns	High	Low	High
Ansarin K (Tabriz University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
WHO SOLIDARITY - HCQ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - LPV/r	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - remdesivir	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - IFN	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - IFN	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Yethindra V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shi L et al	Low	Low	Low	Low	Low	Low	Low
RCT-TCZ-COVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BACC Bay Tocilizumab Trial	Low	Low	Low	Low	Low	Low	Low
SARITA-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
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	Low	High
PROBIOZOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Padmanabhan U et al (Medical Education and Drugs Departmen	High	Low	Low	Low	Low	High	High
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khamis F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BLAZE-1	High	Low	Low	Low	Low	High	High
PETAL	Low	Low	Low	Low	Low	Low	Low
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
Yakoot M et al (Pharco Corporate)	High	Some Concerns	Low	Some Concerns	Low	High	High
Ghandehari 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
FAV052020 (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
Krolewiecki et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ILIAD	Low	Low	Low	Low	Low	Low	Low
AB-DRUG-SARS-004	High	Low	Low	Low	Low	High	High
Q-PROTECT	Low	Low	Low	Low	Low	Low	Low
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
Niaee 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
ITOLI-C19-02-I-00	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Prolectin-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
Roozbeh F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTIV-3/TICO	Low	Low	Some Concerns	Low	Low	Low	High
Chachar et al	High	Some Concerns	Low	Some Concerns	Low	High	High
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	Low	High
Abdelmaksoud AA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kirti et al	Low	Low	Low	Low	Low	Low	Low
Kumari P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FK/FAV00A-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	High
RECOVERY-Plasma	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Interferon in COVID (Alavi Darazam I et al)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AB-DRUG-SARS-004 (Cadegiani FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
JamaliMoghadamSiahkali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedighiyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Roostaei A et al	High	Low	Low	Low	Low	High	High
Bee-Covid	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEOT	High	Some Concerns	Low	Some Concerns	Low	High	High
Mohan et al	Low	Low	Low	Low	Low	Low	Low
Shahbaznejad et al	Low	Low	Low	Low	Low	Low	Low
Spoorthi et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Samaha et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Bukhari el al	High	Some Concerns	Low	Some Concerns	Low	High	High
Okumus 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
Thakar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Onal H et al	High	High	Low	Some Concerns	Low	High	High
Tang X et al	Low	Some Concerns	Low	Low	Low	Low	Low
COLCORONA	Low	Some Concerns	Low	Low	Low	Low	Low
Lopardo	Low	Low	Low	Low	High	Low	Low
Dabbous HM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATTRACT	Low	Some Concerns	Low	Low	Low	Low	Low
Ranjbar K et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
EAT-DUTA AndroCoV	Low	Low	High	Low	Low	High	High
Farnoosh G et al	Some Concerns	Some Concerns	High	Some Concerns	Low	High	High
Khalili H et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Baklaushev 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
NITFQM0320OR	High	Some Concerns	Low	Some Concerns	Low	High	High
SVU-MED-CHT019-420860	High	Some Concerns	Low	Some Concerns	Low	High	High
STOIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Borges M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY-TCZ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDAtoZ -Zinc	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDAtoZ - Vit C	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
EFC16844	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-N-IVIG-COVID-19/2020-CT2	High	Some Concerns	Low	Some Concerns	Low	High	High
Jamaati H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Beltran-HCQ	High	Some Concerns	Low	Some Concerns	Low	High	High
Beltran et al	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-Vaskeh 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
Bermejo 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
2GAMMACOVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
AAAS9924	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Tolouian et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ElZein R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PEGI.20.002	High	Some Concerns	Low	Some Concerns	Low	High	High
MASH-COVID	Low	Some Concerns	Low	Low	Low	Low	Low
INSPIRATION	Low	Some Concerns	Low	Low	Low	Low	Low
Zarychanski	Low	Some Concerns	Low	Low	Low	Low	Low
Santos PSS et al	Low	Some Concerns	Low	Low	Low	Low	Low
Solaymani-Dodaran M et al	Low	Some Concerns	Low	Low	Low	Low	Low
TD-0903-0188	High	Some Concerns	Low	Some Concerns	Low	High	High
DISCOVER	Low	Some Concerns	Low	Low	Low	Low	Low
SURG-2020-28683	Low	Some Concerns	Low	Low	Low	Low	Low
Alavi-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
Yadollahzadeh 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
Gaynitdinova 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
Doaei 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
Amra B et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ribakov AR et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kishoria N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CERC-002-CVID-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
Pouladzadeh M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
HBOTCOVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
RESIST	High	Some Concerns	Low	Some Concerns	Low	High	High
CARR-COV-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Seet	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SBU-COVID19-ConvalescentPlasma	Low	Some Concerns	Low	Low	Low	Low	Low
TOGETHER	Low	Some Concerns	Low	Low	Low	Low	Low
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High

OSCAR	Low	Some Concerns	Low	Low	Low	Low	Low
POLYCOR	Low	Some Concerns	Low	Low	Low	Low	Low
Vanguard	Low	Some Concerns	Low	Low	Low	Low	Low
Samimagham HR et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CamoCO-19	Low	Some Concerns	Low	Low	Low	Low	Low
BCR-PNB-001	High	Some Concerns	Low	Some Concerns	Low	High	High
ATOMIC2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Siami Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CLOROTRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High
PROBCO	High	Some Concerns	Low	Some Concerns	Low	High	High
Nesari 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
Moni 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	High	Some Concerns	Low	Some Concerns	Low	High	High
Mahmoudi M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AGILE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hamdy Salman O et al	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-RT-01	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-ARB	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Perepu U et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zarychanski-Non-critical	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Sarilumab-COVID19 Study	Low	Some Concerns	Low	Low	Low	Low	Low
CAPSID	Low	Some Concerns	Low	Low	Low	Low	Low
CHEER	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - Colchicine	High	Some Concerns	Low	Some Concerns	Low	High	High
Silvia Mendez-Flores S et al	Low	Some Concerns	Low	Low	Low	Low	Low
SAVE-MORE	Low	Some Concerns	Low	Low	Low	Low	Low
Winchester S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgohary MAS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ARMY-1	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Hamidi-Alamdari D et al	High	Low	Low	Low	Low	High	High
Zarehoseinzade E et al	Low	Some Concerns	Low	Low	Low	Low	Low
Mahmud et al	High	Low	Low	Low	Low	High	High
Abd-Elsalam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Biber et al	Low	Some Concerns	Low	Low	Low	Low	Low
Faisal et al	High	Some Concerns	Low	Some Concerns	Low	High	High
SOVECOD	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTION	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BLAZE-2	Low	Low	Some Concerns	Low	Low	Low	Low
ProPAC-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Tian F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY - ASA	Low	Some Concerns	Low	Low	Low	Low	Low
HONEST	Low	Low	Low	Low	Low	Low	Low
COMET-ICE	Low	Low	Low	Low	Low	Low	Low
ISMMSCCOVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
SENTAD-COVID	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
SEV-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CATALYST	Low	Low	Low	Low	Low	Low	Low
Ali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - REGEN-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Taher A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ACEI-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Covid-19 Phase 3 Prevention Trial	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EIDD-2801-2003	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
REMAP-CAP	High	Low	Low	Low	Low	High	High
STOP-COVID	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Vallejos et al	High	Low	Low	Low	Low	High	High
CONCOR-1	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
ALBERTA HOPE-Covid19	Low	Low	Low	Low	Low	Low	Low
Hamed DM et al	Low	Low	Low	Low	Low	Low	Low
COUNTER-COVID	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Abdulamir AS et al	Low	Low	Low	Low	Low	Low	Low
KP-DRUG-SARS-003	Low	Low	Low	Low	Low	Low	Low
Aref ZF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Di Pierro F et al	Low	Low	Low	Low	Low	Low	Low
AR0-CORONA	High	Some Concerns	Low	Some Concerns	Low	High	High
ARCHITECTS	Low	Low	Low	Low	Low	Low	Low
CORIMUNO-TOCI ICU	High	Some Concerns	Low	Some Concerns	Low	High	High
COV-AID	Low	Low	Low	Low	Low	Low	Low
COVIDOSE-2	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIDSTORM	High	Some Concerns	Low	Some Concerns	Low	High	High
COVITOZ-01	Low	Some Concerns	Low	Some Concerns	Low	Low	High
HMO-0224-20	Low	Low	Low	Low	Low	Low	Low
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	Low	Low	Low	Low	Low	Low
CORIMUNO-SARI	High	Low	Low	Low	Low	High	High
CORIMUNO-SARI ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SARCOVID	Low	Low	Low	Low	Low	Low	Low
SARICOR	Low	Low	Low	Low	Low	Low	Low
SARTRE	Low	Low	Low	Low	Low	Low	Low
COV-AID-2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
REGENERON Sari P3	Low	Low	Low	Low	Low	Low	Low
COPEP	Low	Low	Low	Low	Low	Low	Low
RAPID	Low	Low	Low	Low	Low	Low	Low

Wang Q et al	Low	Low	Low	Low	Low	Low	Low
Hosseinzadeh A et al	Low	Low	Low	Low	Low	Low	Low
BLAZE-1	Low	Some Concerns	Low	Low	Low	Low	Low
Najmeddin F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CAN-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Eduardo FP et al	Low	Some Concerns	Low	Low	Low	Low	Low
AB-DRUG-SARS-005	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID STEROID 2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTION	Low	Low	Low	Low	Low	Low	Low
Gaitan-Duarte HG et al	Low	Low	Low	Low	Low	Low	Low
Sabico S et al	Low	Low	Low	Low	Low	Low	Low
PLACOVID	High	Low	Low	Low	Low	High	High
UAIIC	Low	Low	Low	Low	Low	Low	Low
BISHOP	Low	Low	High	Low	Low	Some Concerns	Some Concerns
Asadipooya K et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Ravichandran et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
DARE-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
DOXYCOV	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PRINCIPLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Parikh D et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Covid-19 Phase 3 Prevention Trial - Exposed	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Three C	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIDIT	High	Some Concerns	Low	Some Concerns	Low	High	High
KUMC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Abbass S et al	Low	Low	Low	Low	Low	Low	Low
C3PO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kosak et al	Low	Low	Low	Low	Low	Low	Low
TOGHETER-Fluvoxamine	High	Some Concerns	Low	Some Concerns	Low	High	High
TOCIDEX	Low	Low	Low	Low	Low	Low	Low
Fakharian A et al	Low	Low	Low	Low	Low	Low	Low
HERO-HCQ	Low	Some Concerns	Low	Some Concerns	Low	Low	High
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	Low	Low	Low	Low	Low	Low	Low
Shinkai M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Rodrigues C et al	Low	Low	Low	Low	Low	Low	Low
Mousavi SA et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Strich	High	Some Concerns	Low	Some Concerns	Low	High	High
MADRID-COVID	Low	Low	Low	Low	Low	Low	Low
J2W-MC-PYAA	High	Some Concerns	Low	Some Concerns	Low	High	High
DAWn-Plasma	High	Some Concerns	Low	Some Concerns	Low	High	High
OPTIMISE-C19	High	Some Concerns	Low	Some Concerns	Low	High	High
Coppola	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ALV-020-001	Low	Low	Low	Low	Low	Low	Low

Main findings

Corticosteroids

See Summary of findings Table 1, Appendix 1

We identified 16 RCTs including 9,246 participants in which systemic corticosteroids (dexamethasone, methylprednisolone, or hydrocortisone) were compared against standard of care or other treatments. Ten of these trials provided information on relevant outcomes. The RECOVERY trial was the biggest with 2,104 patients assigned to dexamethasone and 4,321 to standard of care. All 10 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%. 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. Our results showed:

- Corticosteroids probably reduce mortality, RR 0.90 (95%CI 0.80 to 1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕◯ (Figure 2)
- Corticosteroids probably reduce invasive mechanical ventilation requirement, RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕◯
- Corticosteroids may improve time-to-symptom resolution, RR 1.27 (95%CI 0.98 to 1.65); RD 16.3% (95%CI -1.2% to 39.4%); 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) may reduce mortality compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.75 (95%CI 0.50 to 1.13); RD -4% (95%CI -8% to 2.1%); Low certainty ⊕⊕◯◯ (Figure 5)
- 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 0.85 (95%CI 0.61 to 1.19); RD -1.5% (95%CI -4% to 1.9%); Low certainty ⊕⊕◯◯

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

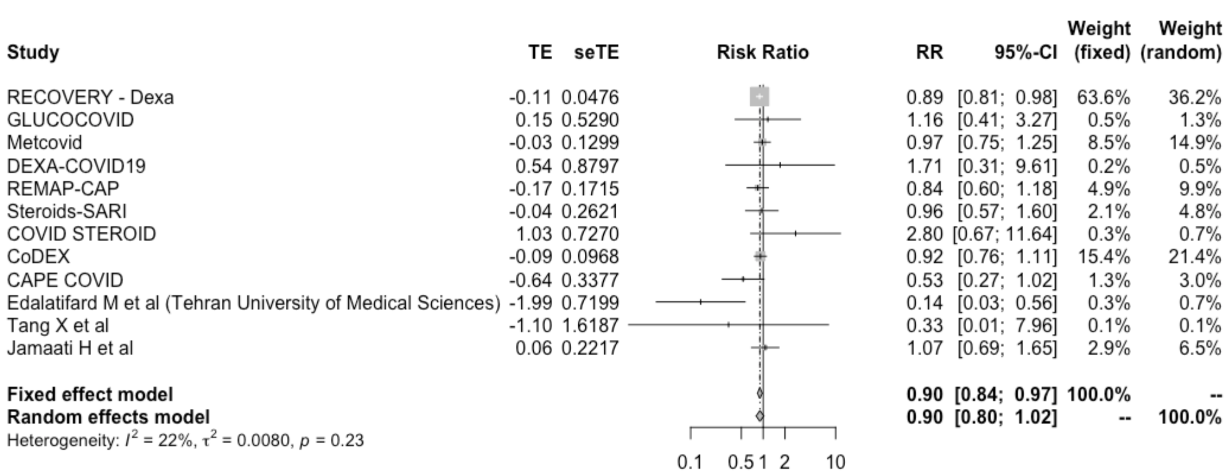


Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

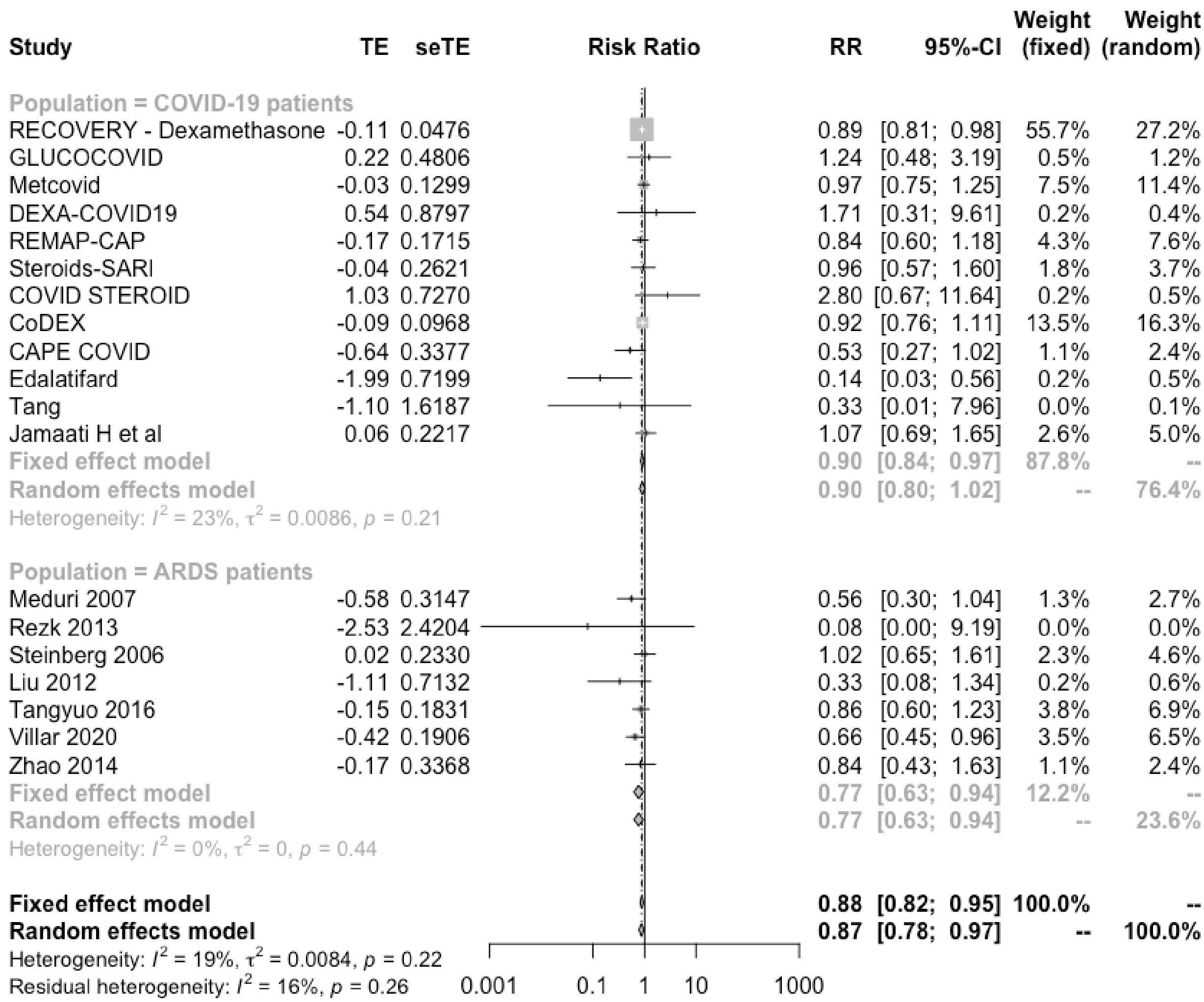


Figure 4. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
Drug = Dexamethasone						
RECOVERY - Dexamethasone	-0.11	0.0476	0.89	[0.81; 0.98]	55.7%	27.2%
DEXA-COVID19	0.54	0.8797	1.71	[0.31; 9.61]	0.2%	0.4%
CoDEX	-0.09	0.0968	0.92	[0.76; 1.11]	13.5%	16.3%
Villar 2020	-0.42	0.1906	0.66	[0.45; 0.96]	3.5%	6.5%
Jamaati H et al	0.06	0.2217	1.07	[0.69; 1.65]	2.6%	5.0%
Fixed effect model			0.89	[0.82; 0.96]	75.4%	--
Random effects model			0.89	[0.82; 0.96]	--	55.3%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.44$						
Drug = Methylprednisone						
GLUCOCOVID	0.22	0.4806	1.24	[0.48; 3.19]	0.5%	1.2%
Metcovid	-0.03	0.1299	0.97	[0.75; 1.25]	7.5%	11.4%
Steroids-SARI	-0.04	0.2621	0.96	[0.57; 1.60]	1.8%	3.7%
Meduri 2007	-0.58	0.3147	0.56	[0.30; 1.04]	1.3%	2.7%
Rezk 2013	-2.53	2.4204	0.08	[0.00; 9.19]	0.0%	0.0%
Steinberg 2006	0.02	0.2330	1.02	[0.65; 1.61]	2.3%	4.6%
Edalatifard	-1.99	0.7199	0.14	[0.03; 0.56]	0.2%	0.5%
Tang	-1.10	1.6187	0.33	[0.01; 7.96]	0.0%	0.1%
Fixed effect model			0.90	[0.75; 1.09]	13.8%	--
Random effects model			0.83	[0.61; 1.13]	--	24.4%
Heterogeneity: $I^2 = 40\%$, $\tau^2 = 0.0657$, $p = 0.11$						
Drug = Hydrocortisone						
REMAP-CAP	-0.17	0.1715	0.84	[0.60; 1.18]	4.3%	7.6%
COVID STEROID	1.03	0.7270	2.80	[0.67; 11.64]	0.2%	0.5%
CAPE COVID	-0.64	0.3377	0.53	[0.27; 1.02]	1.1%	2.4%
Liu 2012	-1.11	0.7132	0.33	[0.08; 1.34]	0.2%	0.6%
Tangyuo 2016	-0.15	0.1831	0.86	[0.60; 1.23]	3.8%	6.9%
Fixed effect model			0.81	[0.65; 1.01]	9.7%	--
Random effects model			0.79	[0.57; 1.10]	--	18.0%
Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0464$, $p = 0.18$						
Drug = Budesonide						
Zhao 2014	-0.17	0.3368	0.84	[0.43; 1.63]	1.1%	2.4%
Fixed effect model			0.84	[0.43; 1.63]	1.1%	--
Random effects model			0.84	[0.43; 1.63]	--	2.4%
Heterogeneity: not applicable						
Fixed effect model			**0.88**	**[0.82; 0.95]**	**100.0%**	**--**
Random effects model			**0.87**	**[0.78; 0.97]**	**--**	**100.0%**
Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.0084$, $p = 0.22$						
Residual heterogeneity: $I^2 = 31\%$, $p = 0.12$						

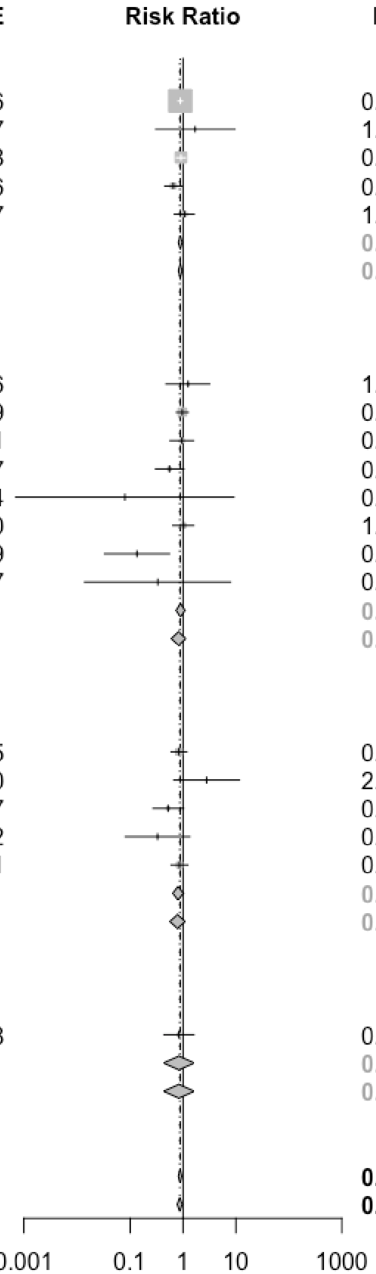
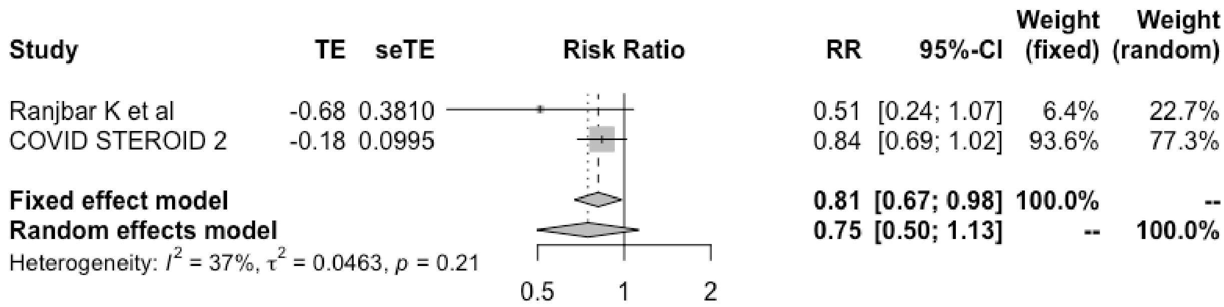


Figure 5. All-cause mortality in RCTs comparing high-dose corticosteroids (i.e., dexamethasone 12 mg a day) with standard-dose corticosteroids (i.e., dexamethasone 6 mg a day) in patients with COVID-19



Remdesivir

See Summary of findings Table 2, Appendix 1

We identified five RCTs including 7,400 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 2,734 patients assigned to remdesivir and 2,708 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 one study included non-severe patients with 2% mortality in the control arm. Our results showed:

- Remdesivir may slightly reduce mortality, RR 0.95 (95%CI 0.83 to 1.08); RD -0.8% (95%CI -2.7% to 1.3%); Low certainty ⊕⊕◯◯ (Figure 6)
- Remdesivir may reduce invasive mechanical ventilation requirement, RR 0.71 (95%CI 0.43 to 1.18); RD -5% (95%CI -9.9% to 3.1%); Low certainty ⊕⊕◯◯ (Figure 7)
- Remdesivir may improve time to symptom resolution, RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⊕⊕◯◯ (Figure 8)
- Remdesivir may not significantly increase the risk of severe adverse events, RR 0.8 (95%CI 0.48 to 1.33); RD -2% (95%CI -5.3% to 3.4%); Low certainty ⊕⊕◯◯

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

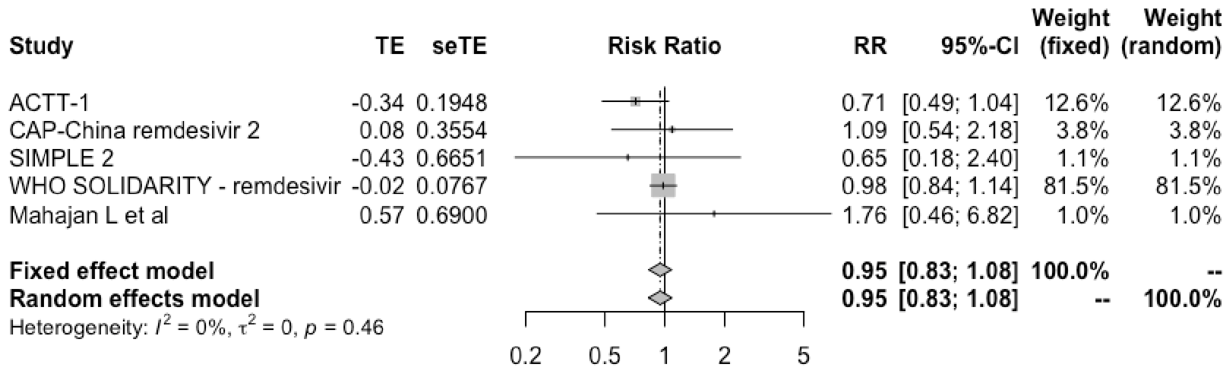


Figure 7. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

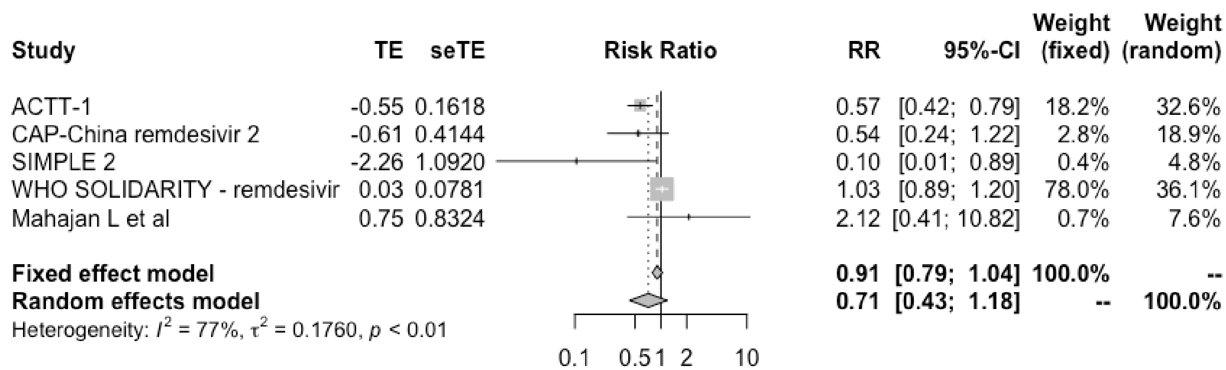
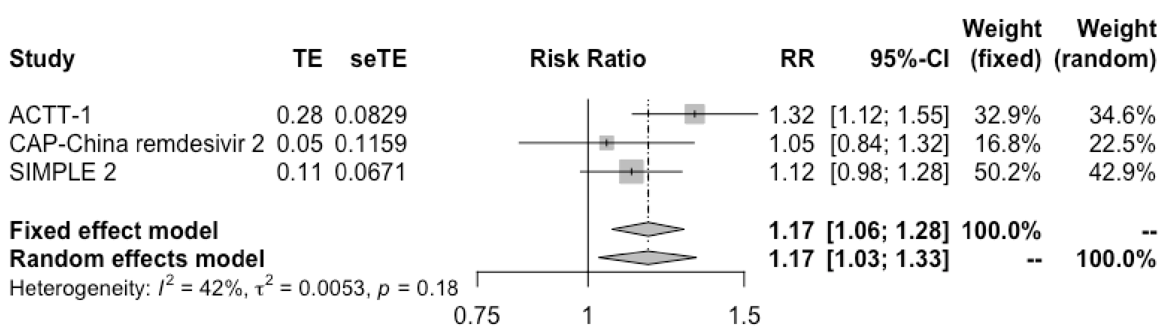


Figure 8. **S**ymptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 49 RCTs including 21,859 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 increase mortality, RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕○ (Figure 9)
- Hydroxychloroquine or chloroquine probably does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.93 to 1.24); RD 1.2% (95%CI -1.2% to 4.2%); Moderate certainty ⊕⊕⊕○
- Hydroxychloroquine or chloroquine probably does not improve time to symptom resolution, RR 1.02 (95%CI 0.94 to 1.1); RD 1.2% (95%CI -3.6% to 6.1%): Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine may reduce COVID-19 symptomatic infection in exposed individuals, RR 0.85 (95%CI 0.72 to 1.01); RD -2.6% (95%CI -4.9% to 0.2%); Low certainty ⊕⊕◯◯ (Figure 10) (based on low risk of bias studies)
- Hydroxychloroquine or chloroquine may not significantly increase the risk of severe adverse events, RR 0.94 (95%CI 0.66 to 1.34); RD -0.6% (95%CI -3.5% to 3.5%); Low certainty ⊕⊕◯◯
- It is uncertain if hydroxychloroquine or chloroquine affects hospitalizations in patients with mild COVID-19, RR 0.91 (95%CI 0.56 to 1.47); RD -0.7% (95%CI -3.3% to 3.5%); Very low certainty ⊕◯◯◯

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

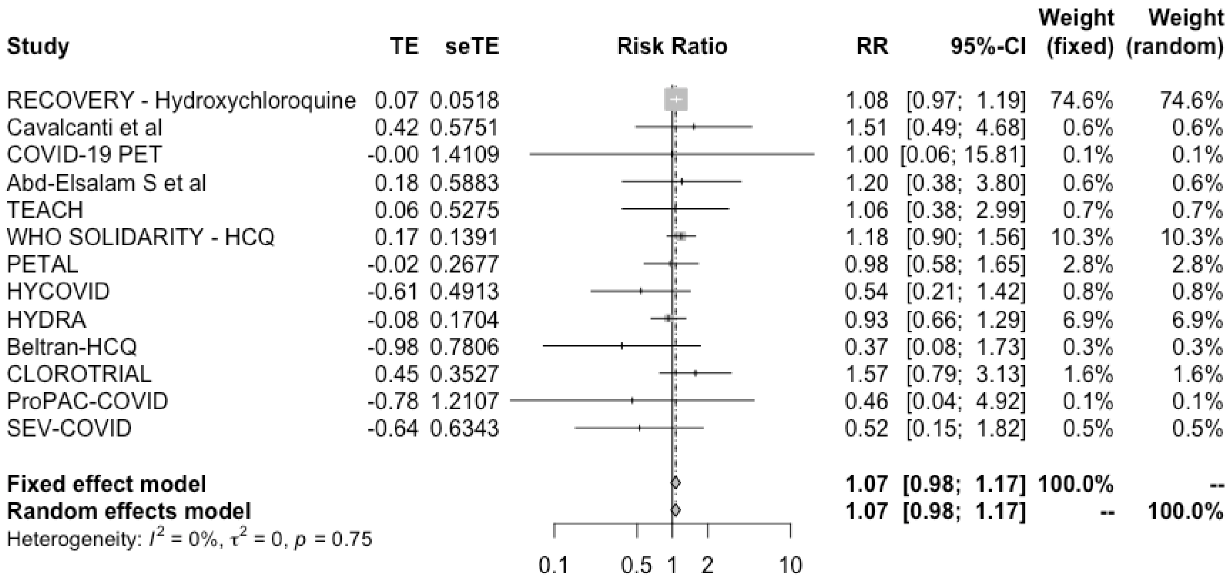
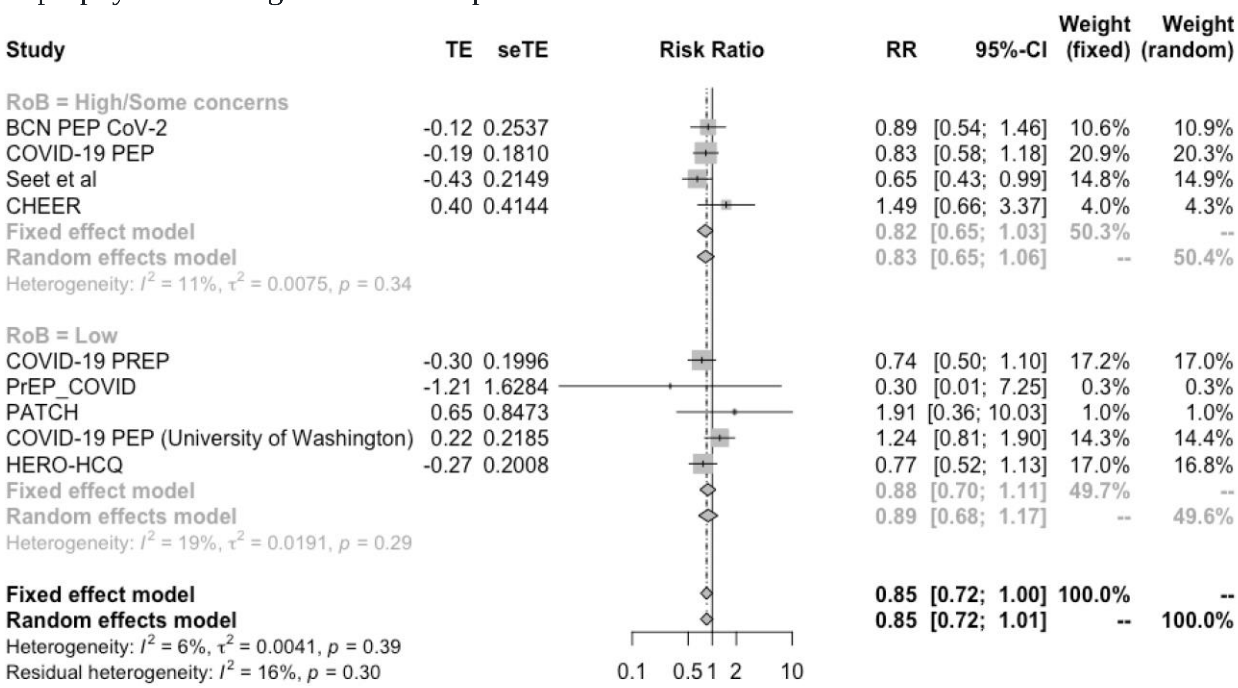


Figure 10. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



In addition, we identified a systematic review[10] 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).

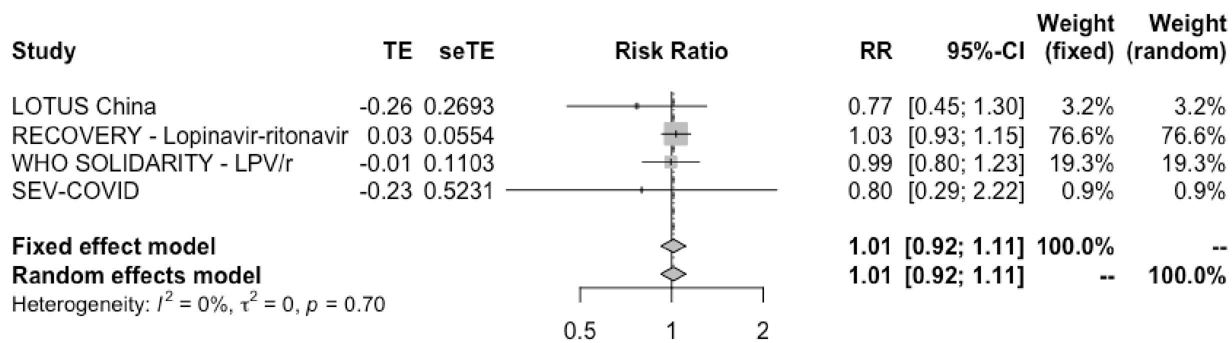
Lopinavir-ritonavir

[***See Summary of findings Table 4, Appendix 1***]

We identified 15 RCTs including 9,782 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 1.24 (95%CI 0.6 to 2.56); RD 1.8% (95%CI -3% to -11.6%); 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 24 RCTs including 17,930 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 (21/24) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 8.5% to 53%. The remaining studies included patients with recent onset symptoms and reported a control-arm mortality rate of 0.4% to 6.6%. Convalescent plasma was administered in one or two infusions to symptomatic patients in all cases. Our results showed:

- Convalescent plasma does not reduce mortality, RR 1 (95%CI 0.94 to 1.06); RD 0% (95%CI -1% to 1%); High certainty ⊕⊕⊕⊕ (Figure 12) (based on low risk of bias studies)
- Convalescent plasma does not significantly reduce invasive mechanical ventilation requirements, RR 1.05 (95% CI 0.94 to 1.17); RD 0.8% (95%CI -1% to 2.9%); High certainty ⊕⊕⊕⊕.
- Convalescent plasma probably does not improve symptom resolution or improvement, RR 0.99 (95% CI 0.94 to 1.05); RD -0.6% (95%CI -3.6% to 3%); Moderate certainty ⊕⊕⊕◯
- Convalescent plasma probably increases severe adverse events, RR 1.38 (95% CI 1.07 to 1.78); RD 3.9% (95%CI 0.7% to 8%); Moderate certainty ⊕⊕⊕◯ (Figure 13) (based on low risk of bias studies)
- Convalescent plasma may not significantly reduce hospitalizations, RR 0.90 (95% CI 0.64 to 1.26); RD -0.7% (95%CI -2.7% to 1.9%); Low certainty ⊕⊕◯◯

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

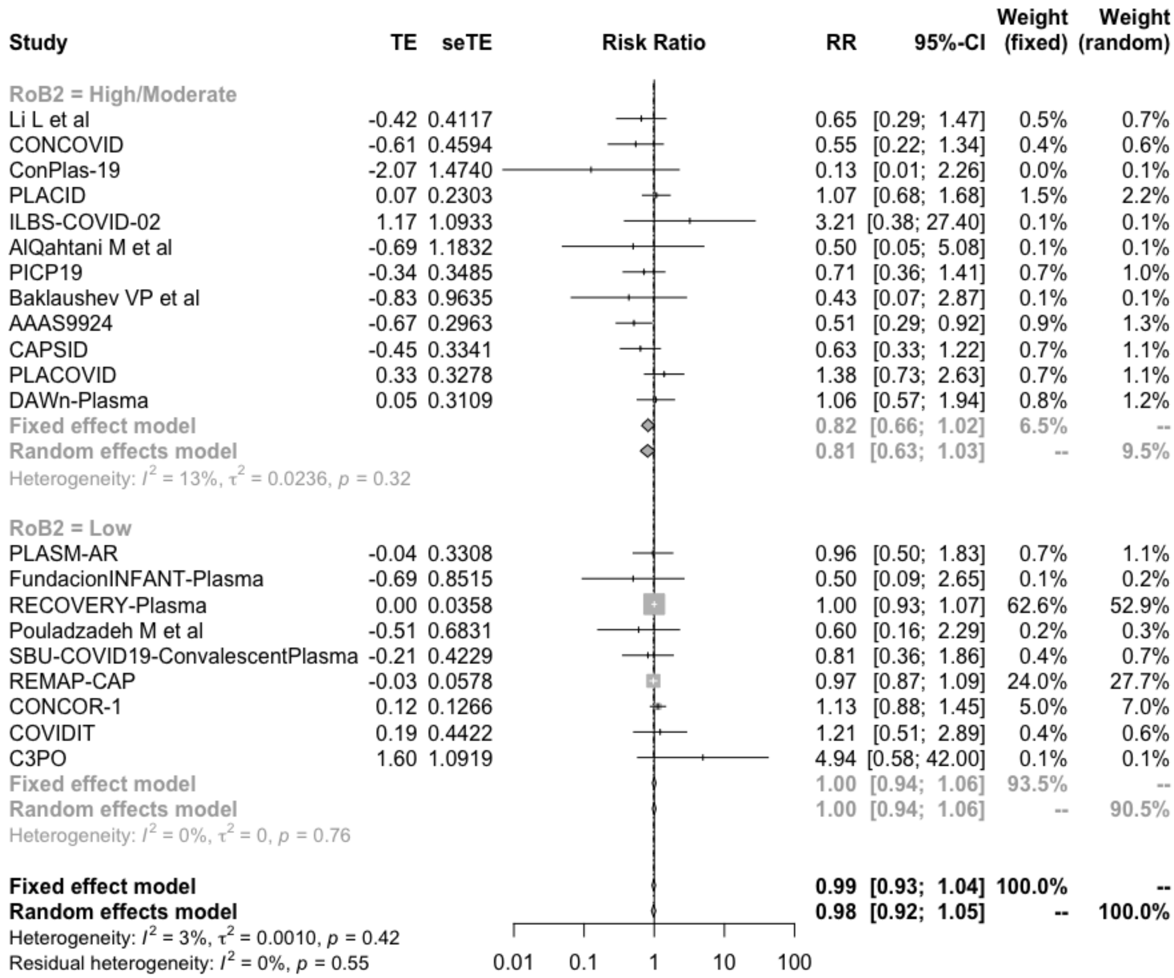
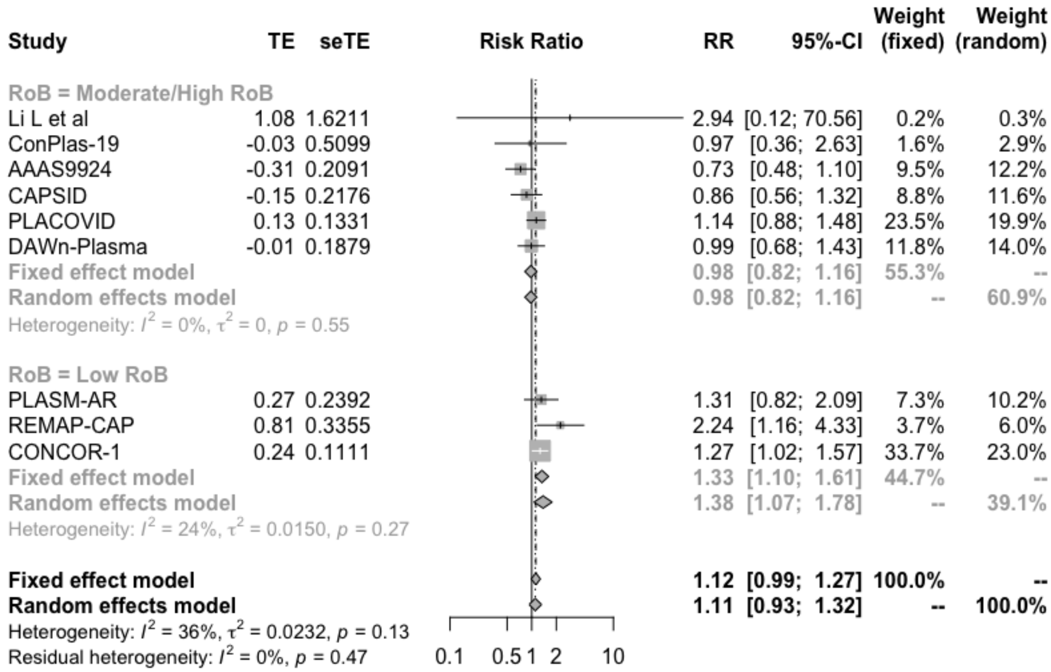


Figure 13. Severe adverse events in RCTs comparing convalescent plasma with standard of care for treatment of patients with COVID-19



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) nor 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 26 RCTs including 9,029 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 probably reduces mortality, RR 0.85 (95%CI 0.79 to 93); RD -2.4% (95%CI -3.4% to -1.1%); Moderate certainty ⊕⊕⊕⊕ (Figure 14)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.83 (95%CI 0.78 to 0.90); RD -2.9% (95%CI -3.8% to -1.7%); High certainty ⊕⊕⊕⊕ (Figure 15)
- Tocilizumab may improve time to symptom resolution, RR 1.1 (95%CI 1.02 to 1.2); RD 6.1% (95%CI 1.2% to 12.1%); Low certainty ⊕⊕◯◯
- Tocilizumab probably does not significantly increase severe adverse events at 28-30 days, RR 0.94 (95%CI 0.85 to 1.05); RD -0.6% (95%CI -1.5% to 0.5%); Moderate certainty ⊕⊕⊕◯

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

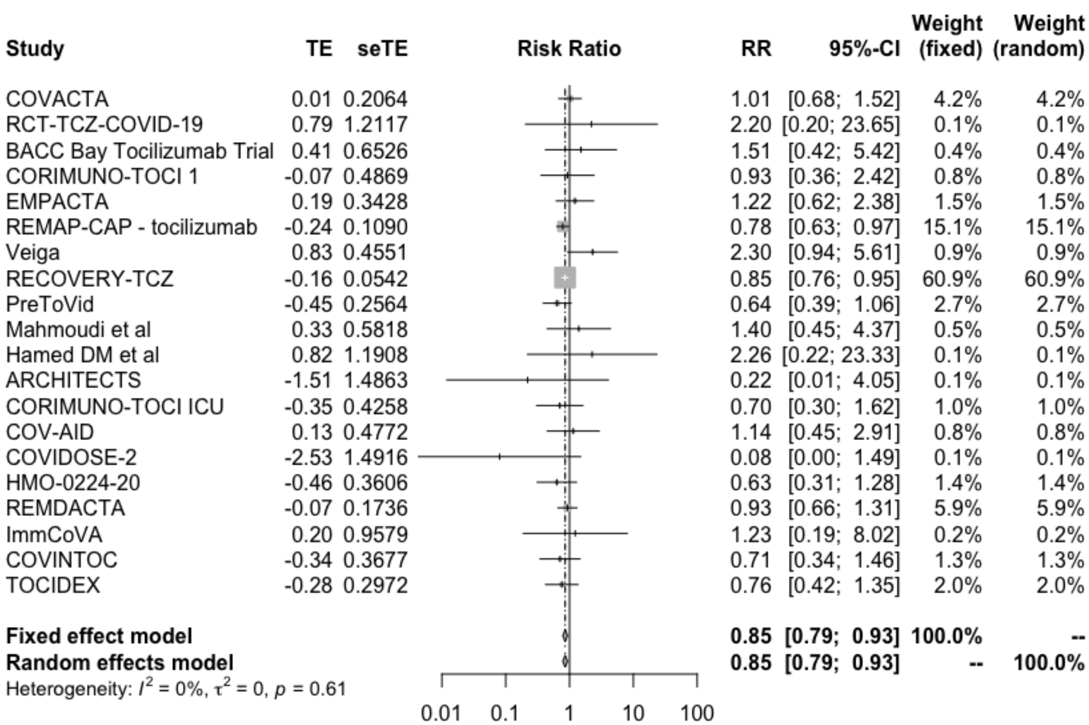
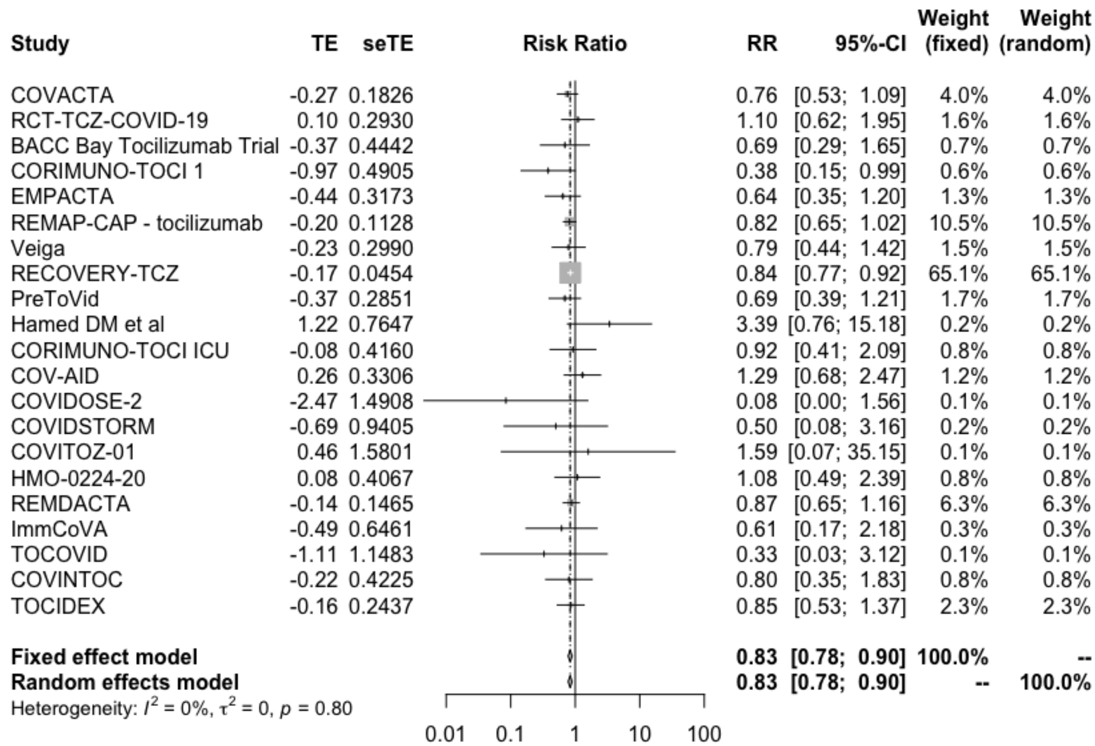


Figure 15. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



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).

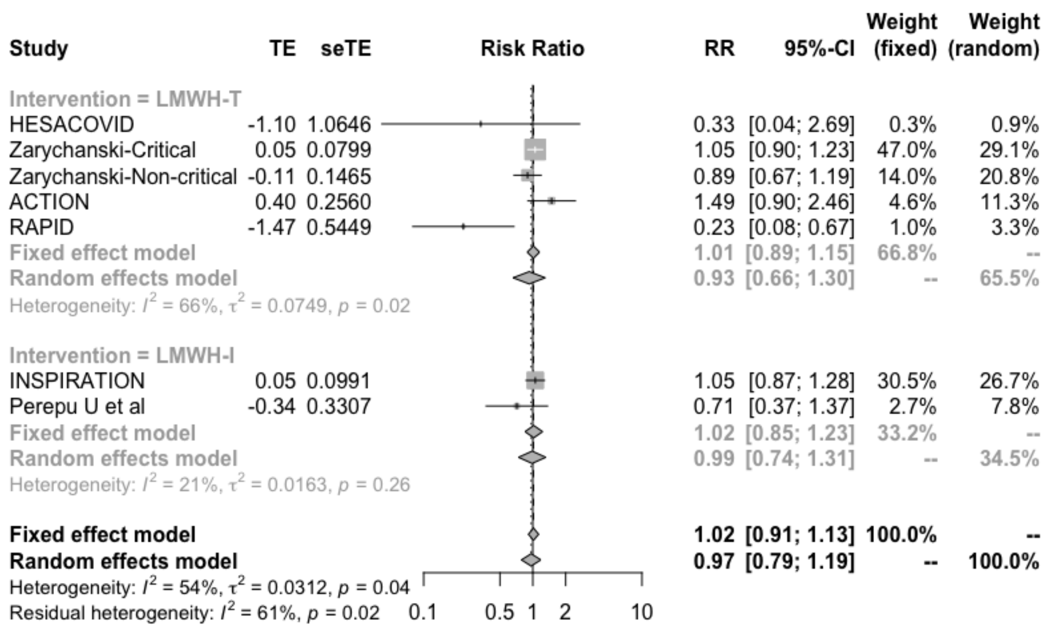
Anticoagulants

See Summary of findings Table 7, Appendix 1

Thromboembolic complications in patients infected with COVID-19 are relatively frequent.[11] As for hospitalized patients with severe medical conditions, current guidelines recommend thromboprophylaxis measures should be used for inpatients with COVID-19 infection.[12] Regarding the best thromboprophylactic scheme, we identified seven RCTs including 5,152 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). All studies included hospitalized patients with COVID-19. Our results showed:

- Anticoagulants in intermediate dose or full dose probably does not reduce mortality in comparison with prophylactic dose, RR 0.97 (95%CI 0.79 to 1.19); RD -0.5% (95%CI -3.4% to 3%); Moderate certainty ⊕⊕⊕◯ (Figure 16)
- Anticoagulants in intermediate dose may not reduce venous thromboembolic events in comparison with prophylactic dose, RR 1.02 (95%CI 0.53 to 1.96); RD 0.1% (95%CI -3.3% to 6.7%); Low certainty ⊕⊕◯◯
- Anticoagulants in full dose probably reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.59 (95%CI 0.44 to 0.79); RD -2.9% (95%CI -3.9% to -1.5%); Moderate certainty ⊕⊕⊕◯
- Anticoagulants in intermediate dose or full dose probably increase major bleeding in comparison with prophylactic dose, RR 1.72 (95%CI 1.14 to 2.61); RD 1.4% (95%CI 0.3% to 3.1%); Moderate 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



Although the subgroup of noncritical patients reported by Zarychanski et al showed a trend toward less mortality in comparison with severe patients, we did not report results according to severity because we consider that the mentioned differential effect is implausible.

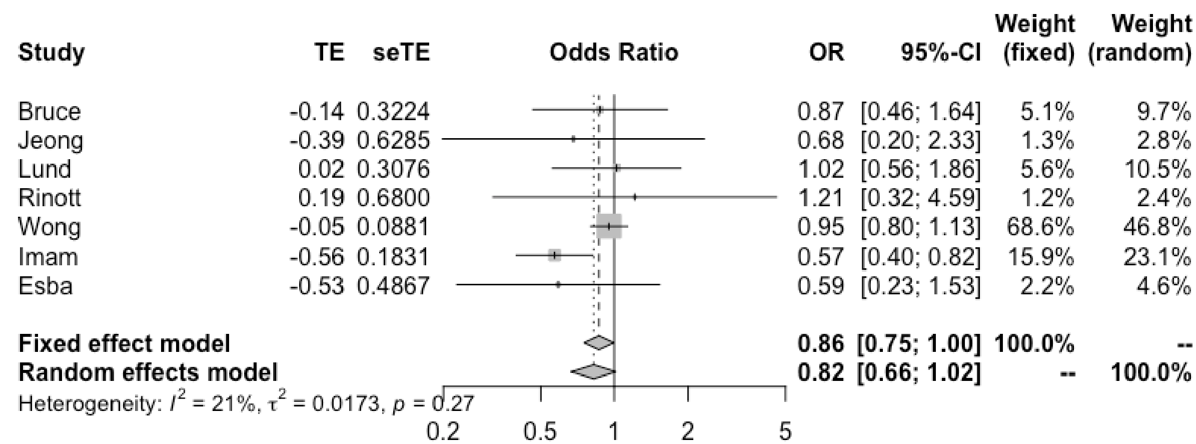
NSAIDs

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

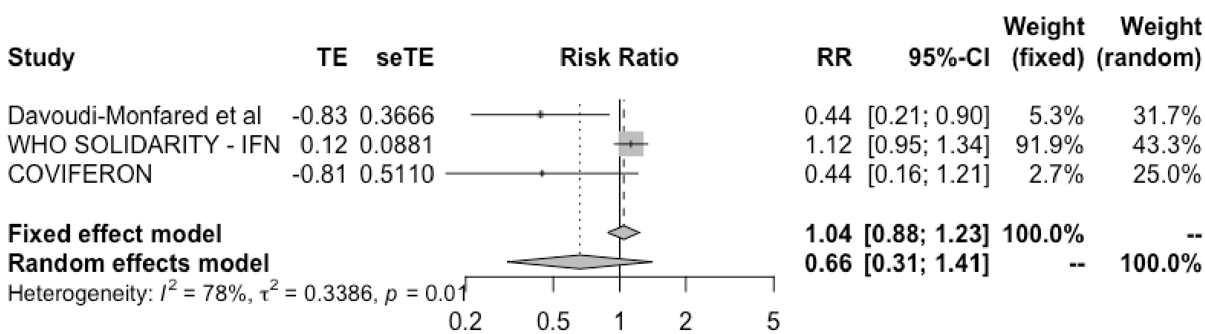
See Summary of findings Table 9, Appendix 1

We identified five RCTs including 4,487 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 2,050 patients assigned to intervention and 2,050 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 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to 3.7%); Moderate certainty ⊕⊕⊕◯ (Figure 18)

- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕◯
- It is uncertain if interferon beta-1a (subcutaneous) affects symptom resolution or improvement; HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕◯◯◯
- Interferon beta-1a (inhaled) may increase symptom resolution or improvement, HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯

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



Bamlanivimab +/- etesevimab (monoclonal antibody)

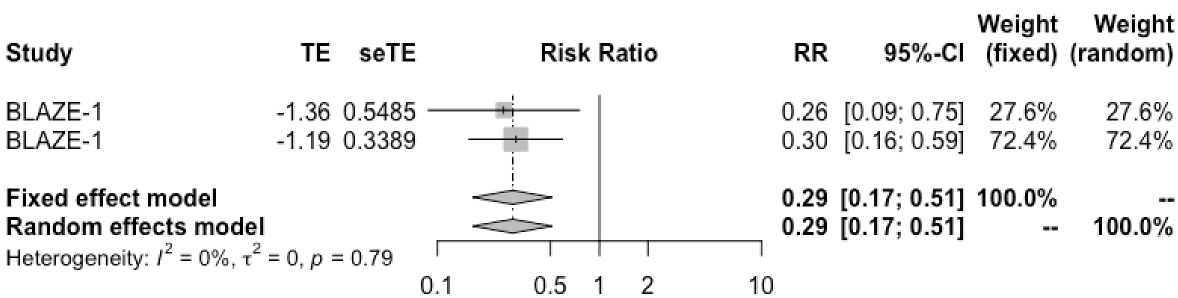
See Summary of findings Table 10, Appendix 1

We identified seven RCTs including 5,147 patients in which bamlanivimab was compared against standard of care. Three 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 increase severe adverse events; RR 1.16 (95%CI 0.76 to 1.78); RD 1.6% (95%CI -0.2% to -7.9%); Low certainty ⊕⊕○○
- Bamlanivimab probably reduces hospitalizations in patients with non-severe disease; RR 0.29 (95%CI 0.17 to 0.51); RD -5.2% (95%CI -6.1% to -3.6%); 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

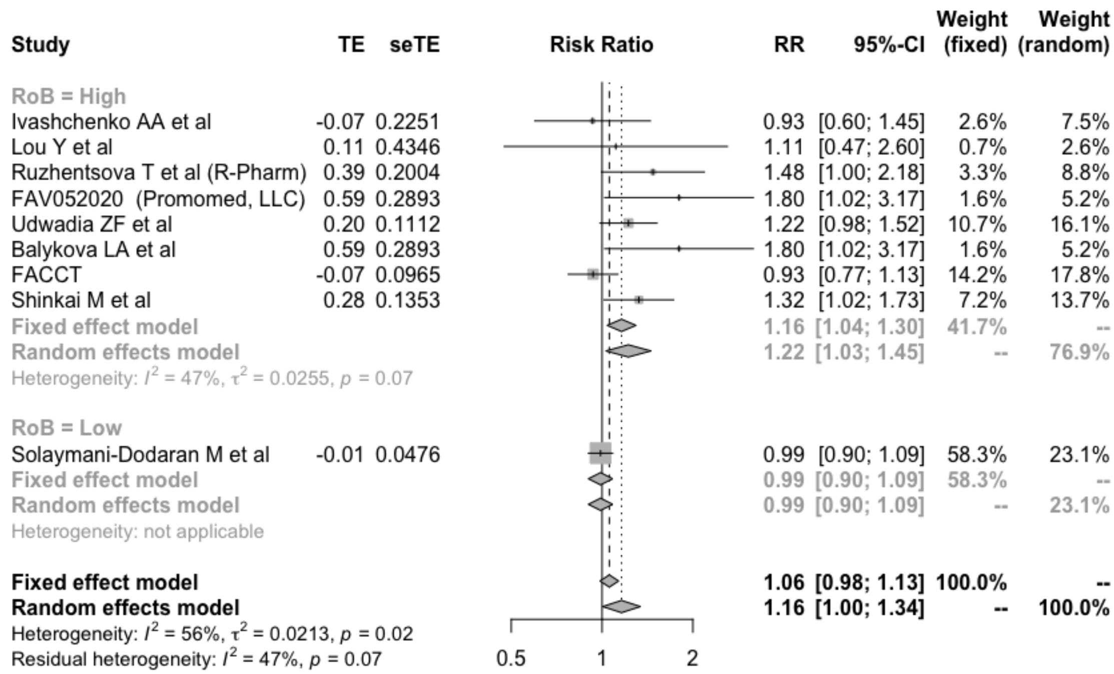
See Summary of findings Table 11, Appendix 1

We identified 15 RCTs including 2,184 patients in which favipiravir was compared against standard of care or other treatments. Seven studies reported on favipiravir with or without HCQ versus standard of care, two studies reported on favipiravir vs HCQ or CQ, one 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 not reduce mortality; RR 1.09 (95%CI 0.72 to 1.64); RD 1.4% (95%CI -4.5% to 10.2%); Low certainty ⊕⊕○○
- Favipiravir may not reduce mechanical ventilation requirements; RR 1.24 (95%CI 0.72 to 2.12); RD 4.2% (95%CI -4.8% to 19.5%); Low certainty ⊕⊕○○

- Favipiravir probably does not increase symptom resolution or improvement, RR 0.99 (95%CI 0.9 to 1.09); RD -0.6% (95%CI -6% to 5.6%); Moderate certainty ⊕⊕⊕◯ (Figure 20) (based on low risk of bias studies)
- It is uncertain if favipiravir increases the risk of severe adverse events; RR 0.64 (95%CI 0.29 to 1.41); RD -3.7% (95%CI -7.2% to 4.2%); Very low certainty ⊕◯◯◯
- It is uncertain if favipiravir affects hospitalizations in patients with non-severe disease; RR 0.75 (95%CI 0.13 to 4.36); RD -1.8% (95%CI -6.4% to 24.9%); Very low certainty ⊕◯◯◯

Figure 20. Symptom resolution at 7-15 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 32 RCTs including 5,592 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 21.7%. Most studies did not report on clinical important outcomes and most of the ones that did have important methodological limitations including inappropriate randomization process and lack or unclear report of allocation concealment. Our results showed:

- Ivermectin may not significantly reduce mortality, RR 0.96 (95%CI 0.58 to 1.59); RD -0.6% (95%CI -6.7% to 9.4%); Low certainty ⊕⊕◯◯ (Figure 21) (based on low risk of bias studies)
- Ivermectin may not reduce mechanical ventilation requirements, RR 1.05 (95%CI 0.64 to 1.72); RD 0.9% (95%CI -6.2% to 12.5%); Low certainty ⊕⊕◯◯
- Ivermectin probably does not improve symptom resolution or improvement, RR 1.02 (95%CI 0.96 to 1.1); RD 1.2% (95%CI -2.4% to 6.1%); Moderate certainty ⊕⊕⊕◯ (Figure 22) (based on low risk of bias studies)
- It is uncertain if ivermectin affects symptomatic infection, RR 0.22 (95%CI 0.09 to 0.53); RD -13.6% (95%CI -15.8% to -8.2%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects severe adverse events, RR 1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.2%); Very low certainty ⊕◯◯◯
- Ivermectin may reduce hospitalizations in non-severe patients, RR 0.62 (95%CI 0.36 to 1.07); RD -3.9% (95%CI -6.5% to 0.6%); Low certainty ⊕⊕◯◯

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

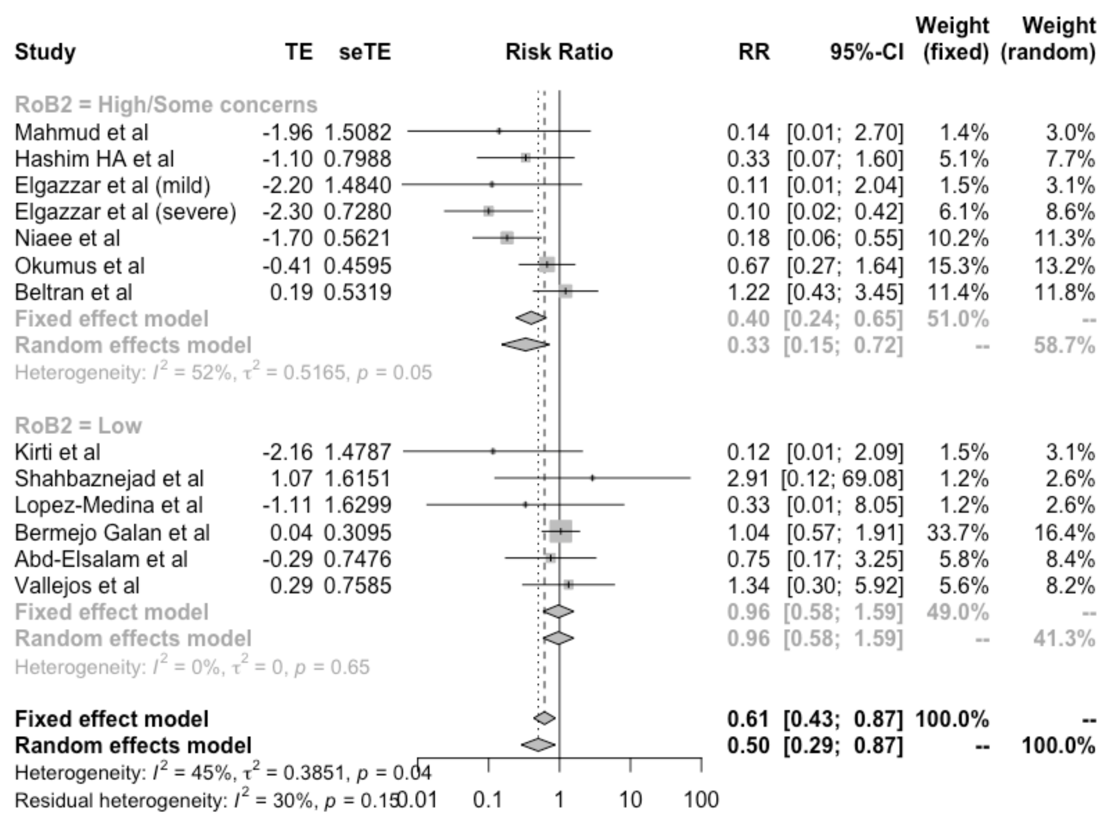
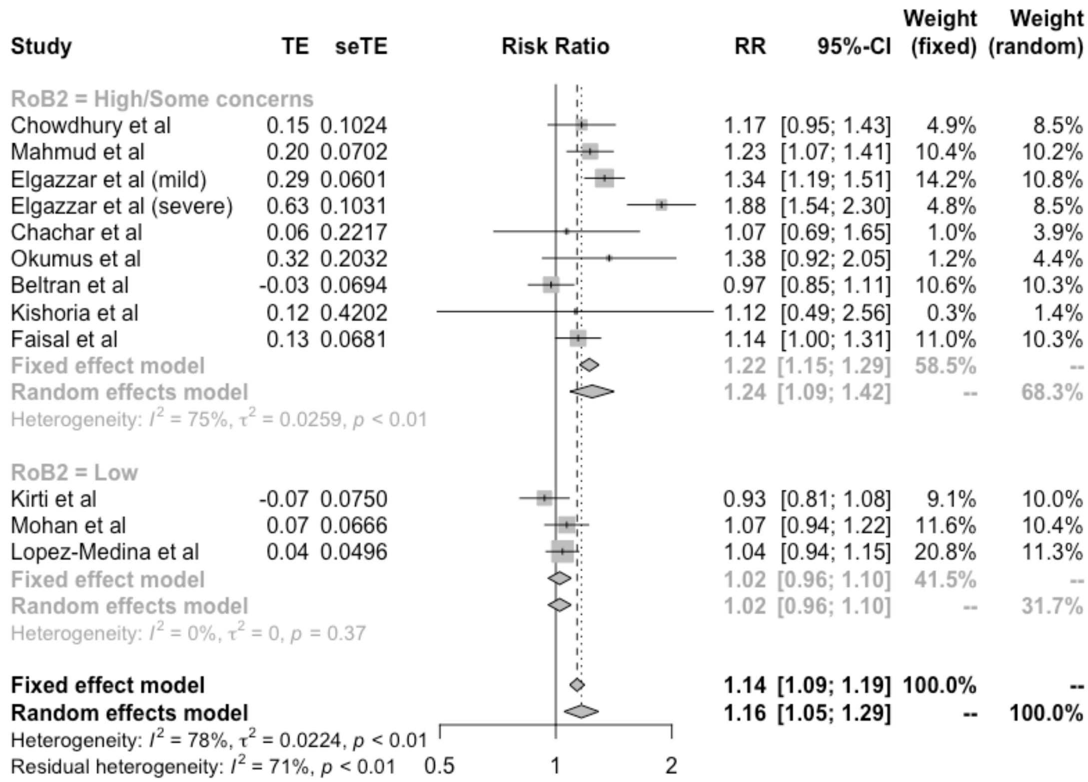


Figure 22. Symptom resolution or improvement in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



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

Baricitinib

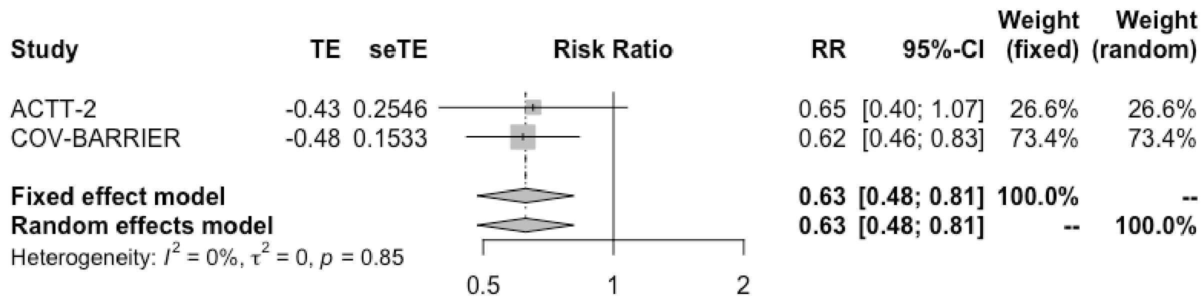
See Summary of findings Table 13, Appendix 1

We identified two RCTs including 2,558 patients in which baricitinib was compared against standard of care. Both studies included moderate to severe hospitalized patients. Critical patients were excluded. Our results showed:

- Baricitinib may reduce mortality, RR 0.63 (95%CI 0.48 to 0.81); RD -5.9% (95%CI -8.3% to -3%); Moderate certainty ⨁⨁⨁◯ (Figure 23)

- Baricitinib may reduce mechanical ventilation, RR 0.66 (95%CI 0.46 to 0.93); RD -5.9% (95%CI -9.2% to -1.2%); Low certainty ⊕⊕○○
- Baricitinib probably increases time to symptom resolution, RR 1.25 (95%CI 1.11 to 1.41); RD 15.1% (95%CI 6.6% to 24.8%); Moderate certainty ⊕⊕⊕○
- Baricitinib may not increase severe adverse events, RR 0.77 (95%CI 0.63 to 0.95); RD -2.3% (95%CI -3.7% to -0.5%); Low certainty ⊕⊕○○

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



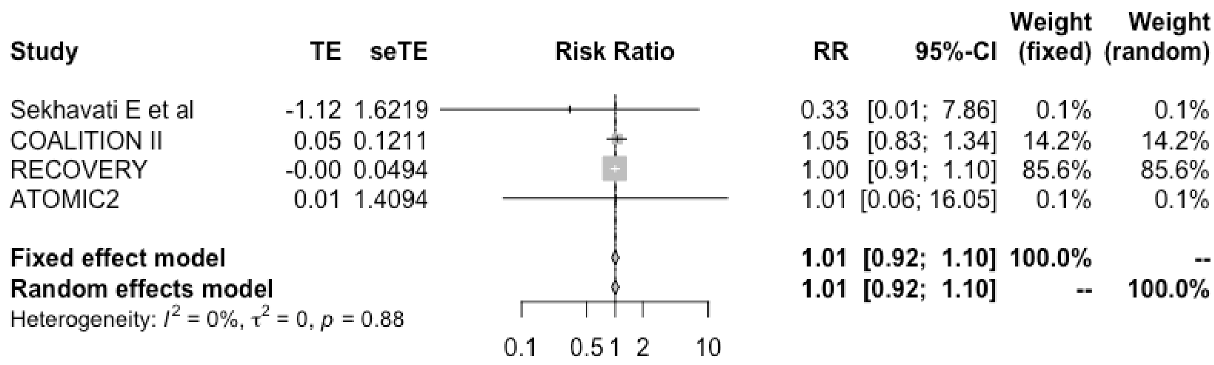
Azithromycin

[***See Summary of findings Table 14, Appendix 1***]

We identified nine RCTs including 10,209 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 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); 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 -3.6% to 6.4%); Low certainty ⊕⊕○○

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

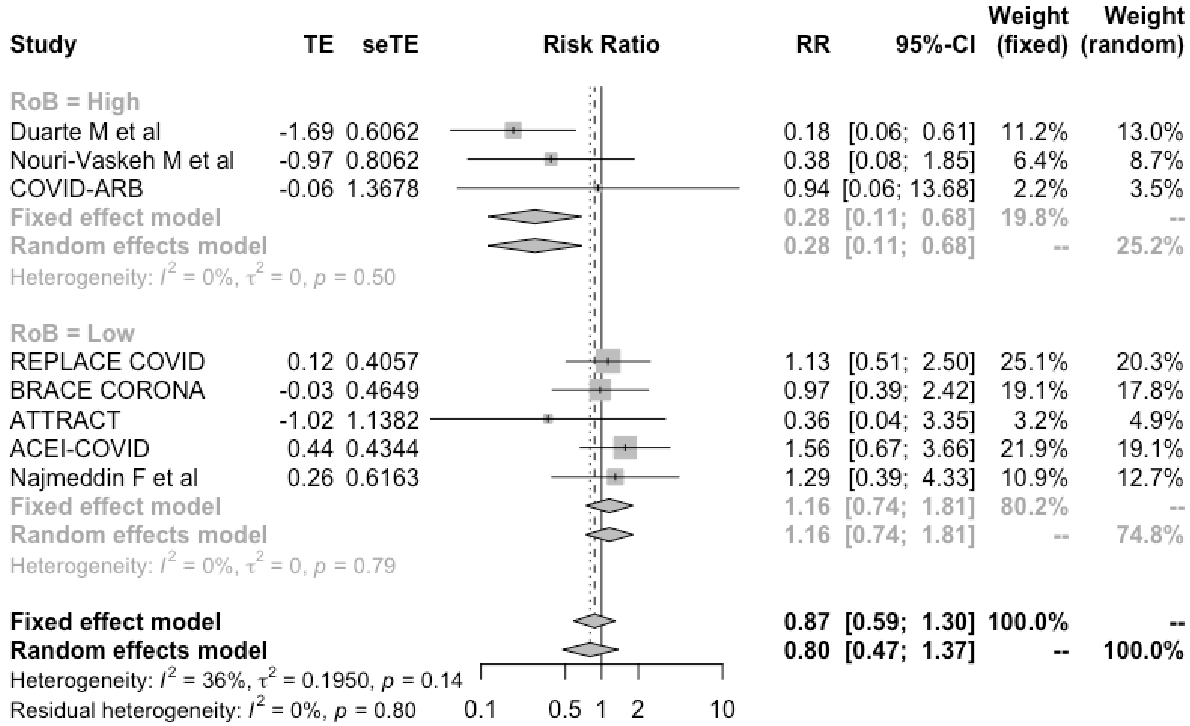


ACEI/ARB initiation or continuation

We identified nine RCTs including 1,547 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 1.16 (95%CI 0.74 to 1.81); RD 2.6% (95%CI -4.2% to 13%); Low certainty ⊕⊕◯◯ (Figure 25) (based on low risk of bias studies)
- ACEI/ARB discontinuation may reduce mechanical ventilation requirements, RR 0.92 (95%CI 0.67 to 1.25); RD -1.4% (95%CI -5.7% to 4.3%); Low certainty ⊕⊕◯◯

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



Colchicine

See Summary of findings Table 15, Appendix 1

We identified five RCTs including 16,105 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 1 (95%CI 0.93 to 1.08); RD 0% (95%CI -1.1% to 1.3%); Moderate certainty ⊕⊕⊕◯ (Figure 26)
- Colchicine probably does not reduce mechanical ventilation requirements, RR 1.02 (95%CI 0.92 to 1.13); RD 0.3% (95%CI -1.4% to 2.2%); Moderate certainty ⊕⊕⊕◯ (Figure 27)

- Colchicine probably does not increase symptom resolution or improvement, RR 0.99 (95%CI 0.96 to 1.01); RD -0.7% (95%CI -2.1% to -0.7%); High certainty ⊕⊕⊕⊕
- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 1); RD -2.2% (95%CI -4% to 0%); High certainty ⊕⊕⊕⊕
- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕◯◯◯
- Colchicine may reduce hospitalizations in patients with recent onset disease, RR 0.8 (95%CI 0.62 to 1.03); RD -1.5% (95%CI -2.8% to 0.2%); Low certainty ⊕◯◯◯

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

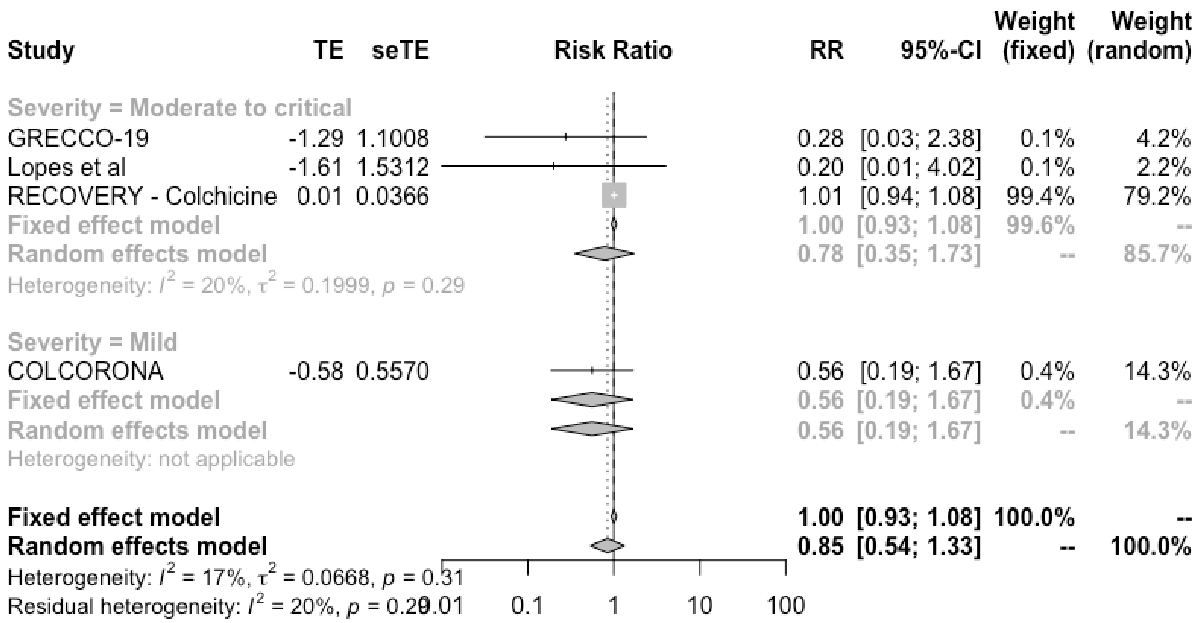
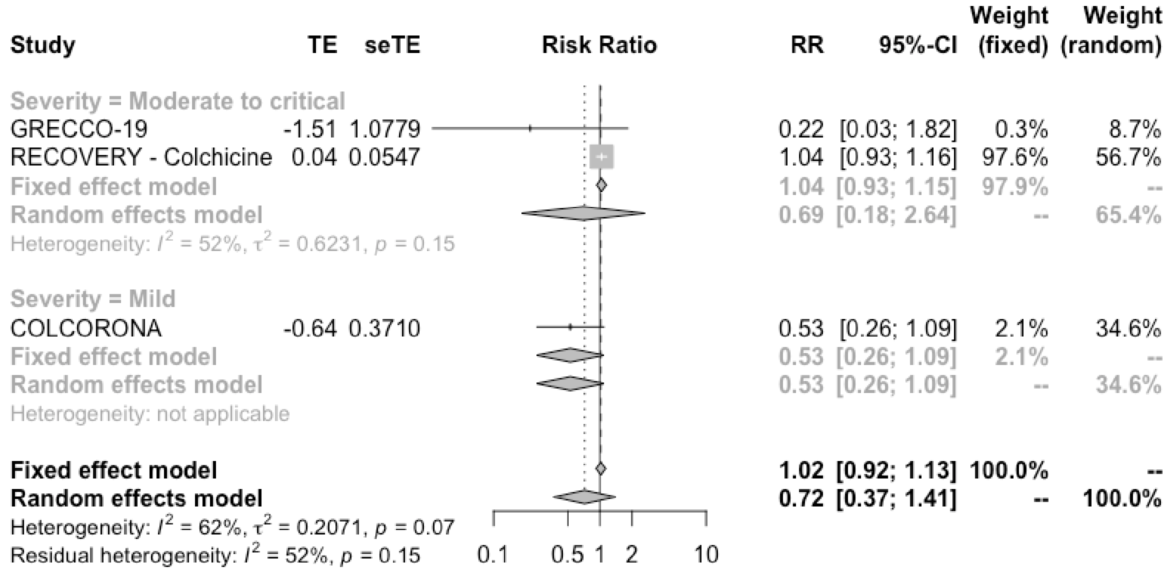


Figure 27. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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 as the number of events was low.

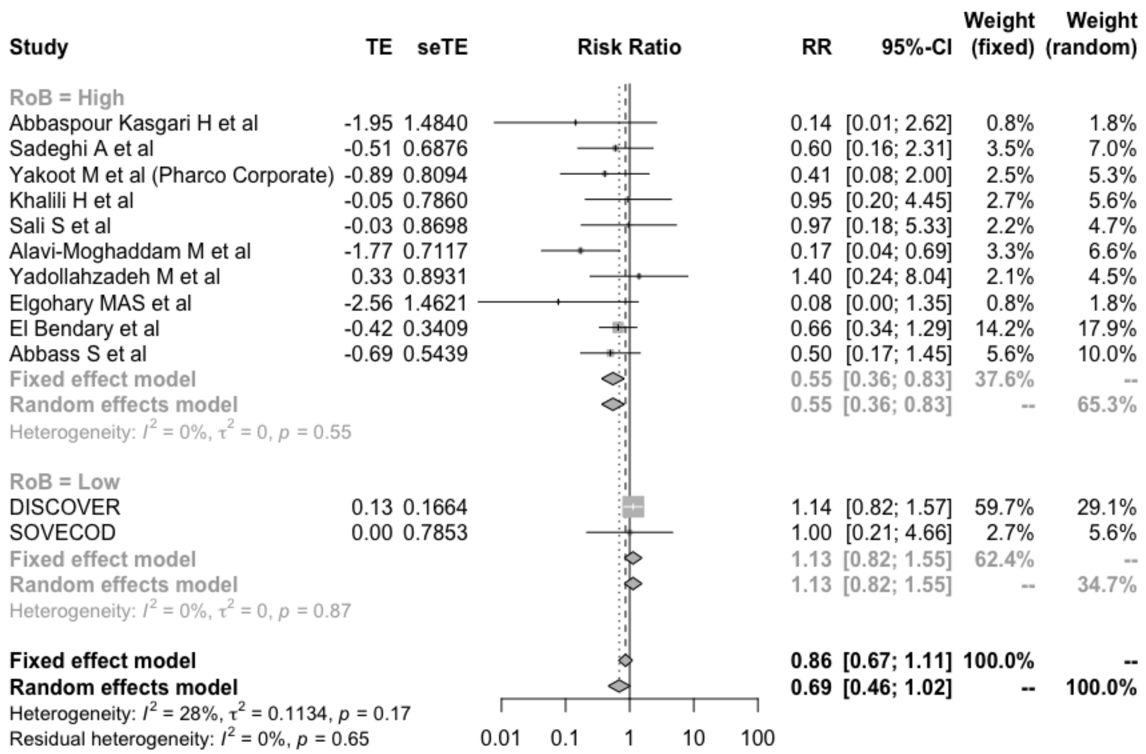
Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir

See Summary of findings Table 16, Appendix 1

We identified 13 RCTs including 2,270 patients in which sofosbuvir alone or in combination with daclatasvir or ledipasvir was compared against standard of care or other treatments. One study compared sofosbuvir alone vs. standard of care, one study compared sofosbuvir + ravidasvir vs. standard of care, one study compared sofosbuvir alone vs. lopinavir-ritonavir, four studies compared sofosbuvir + daclatasvir vs. standard of care, two studies compared sofosbuvir + daclatasvir vs. lopinavir-ritonavir, and two 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 not reduce mortality, RR 1.13 (95%CI 0.82 to 1.55); RD 2% (95%CI -2.9% to 8.8%); Low certainty ⊕⊕◯◯ (Figure 28) (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mechanical ventilation requirements, RR 1.04 (95%CI 0.29 to 3.7); RD 0.7% (95%CI -12.3% to 46.7%); Very low certainty ⊕◯◯◯ (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir probably does not improve time to symptom resolution, RR 0.97 (95%CI 0.9 to 1.06); RD -1.8% (95%CI -6% to 3.6%); Moderate certainty ⊕⊕⊕◯ (based on low risk of bias studies)

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



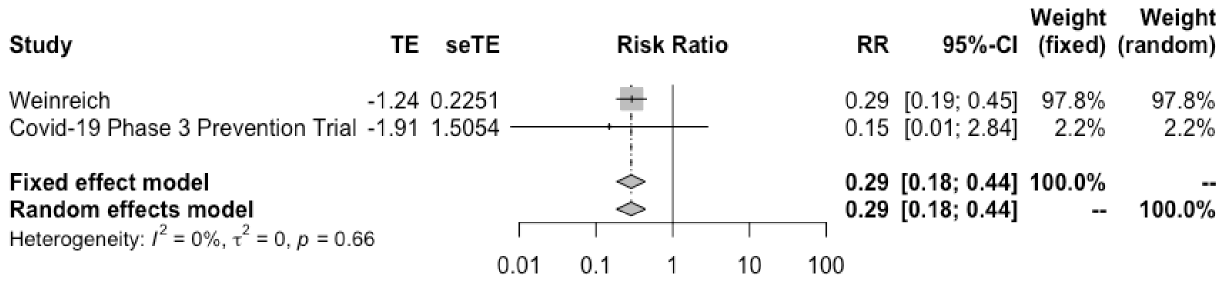
REGEN-COV (casirivimab and imdevimab)

See Summary of findings Table 17, Appendix 1

We identified five RCTs including 17,609 patients in which REGEN-COV (casirivimab and imdevimab) was compared against standard of care in patients with recent onset COVID-19. RECOVERY trial was the biggest, included severe to critical patients and reported differential effect in seronegative patients at baseline. The other three studies included mild patients with recent onset disease and exposed individuals with negative PCR. Our results showed:

- Overall REGEN-COV probably does not significantly decrease mortality, RR 0.94 (95%CI 0.87 to 1.02); RD -1% (95%CI -2.1% to 0.3%); Moderate certainty ⊕⊕⊕◯
- In seronegative patients REGEN-COV probably decreases mortality, RR 0.8 (95%CI 0.7 to 0.91); RD -3.2% (95%CI -4.8% to -1.4%); Moderate certainty ⊕⊕⊕◯
- Overall REGEN-COV probably does not significantly decrease mechanical ventilation, RR 0.96 (95%CI 0.89 to 1.03); RD -0.7% (95%CI -1.9% to -0.5%); Moderate certainty ⊕⊕⊕◯
- In seronegative patients REGEN-COV probably reduces mechanical ventilation, RR 0.83 (95%CI 0.75 to 0.92); RD -2.9% (95%CI -4.3% to -1.4%); Moderate certainty ⊕⊕⊕◯
- Overall REGEN-COV probably does not increase symptom resolution, RR 1.06 (95%CI 0.96 to 1.16); RD 3.6% (95%CI -2.4% to 9.7%); Moderate certainty ⊕⊕⊕◯
- In seronegative patients REGEN-COV probably increases symptom resolution, RR 1.12 (95%CI 1.01 to 1.25); RD 7.2% (95%CI 0.6% to 15.1%); Moderate certainty ⊕⊕⊕◯
- REGEN-COV reduces symptomatic infections in exposed individuals, RR 0.49 (95%CI 0.35 to 0.67); RD -8.9% (95%CI -11.3% to -5.7%); High certainty ⊕⊕⊕⊕
- REGEN-COV probably does not increases severe adverse events, RR 0.63 (95%CI 0.48 to 0.81); RD -3.8% (95%CI -5.3% to -1.9%); Moderate certainty ⊕⊕⊕◯
- REGEN-COV probably reduces hospitalization, RR 0.29 (95%CI 0.18 to 0.44); RD -5.3% (95%CI -6.1% to -4.1%); Moderate certainty ⊕⊕⊕◯ (Figure 29)

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



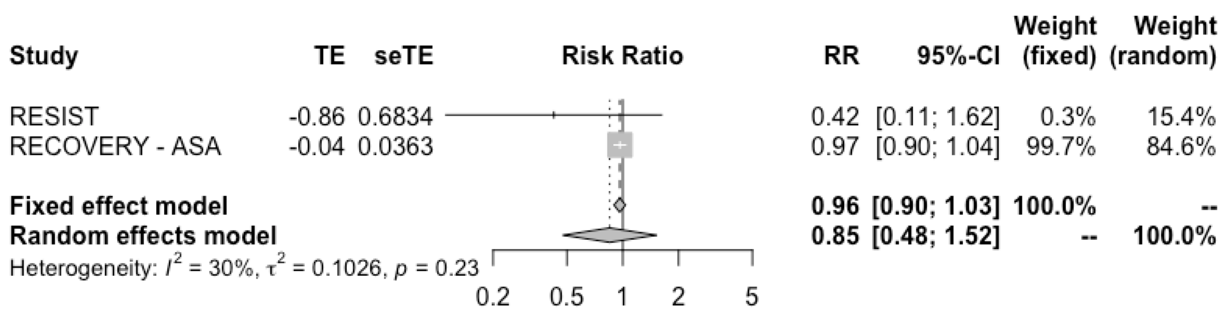
In addition, one study that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab in non-severe patients with risk factors for severity reported no important differences in hospitalizations.

Aspirin

We identified two RCTs including 15,332 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 0.96 (95%CI 0.90 to 1.03); RD -0.6% (95%CI -1.6% to 0.5%); Moderate certainty ⊕⊕⊕◯ (Figure 30)
- Aspirin probably does not reduce mechanical ventilation, RR 0.95 (95%CI 0.87 to 1.05); RD -0.8% (95%CI -2.2% to 0.9%); Moderate certainty ⊕⊕⊕◯
- Aspirin probably does not increase symptom resolution or improvement, RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕◯

Figure 30. Mortality in randomized studies comparing aspirin vs standard of care in patients with COVID-19



Sotrovimab

We identified one RCT including 583 patients with recent onset mild COVID-19 and risk factors for severe disease, in which sotrovimab was compared against standard of care. Our results showed:

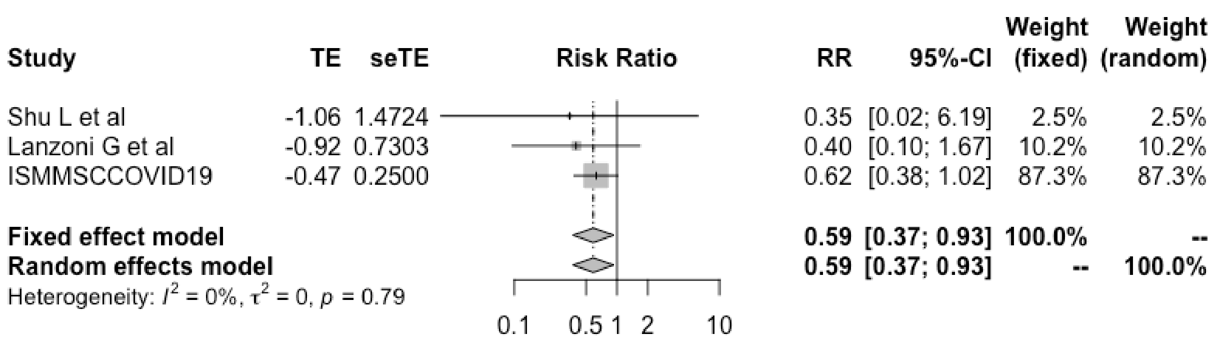
- Sotrovimab probably reduces hospitalizations, RR 0.14 (95%CI 0.04 to 0.48); RD -6.3% (95%CI -7.1% to -3.8%); Moderate certainty ⊕⊕⊕◯
- Severe adverse events, RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕◯◯

Mesenchymal stem-cell transplantation

We identified four RCTs including 205 patients with severe to critical COVID-19, in which mesenchymal stem-cell transplantation was compared against standard of care. Only three of those studies including 105 patients reported on mortality outcome. Our results showed:

- Mesenchymal stem-cell transplantation may reduce mortality, RR 0.59 (95%CI 0.37 to 0.93); RD -6.2% (95%CI -9.8% to -1%); Low certainty ⊕⊕◯◯ (Figure 31)

Figure 31. Mortality in randomized studies comparing mesenchymal stem-cell transplantation vs standard of care in patients with COVID-19

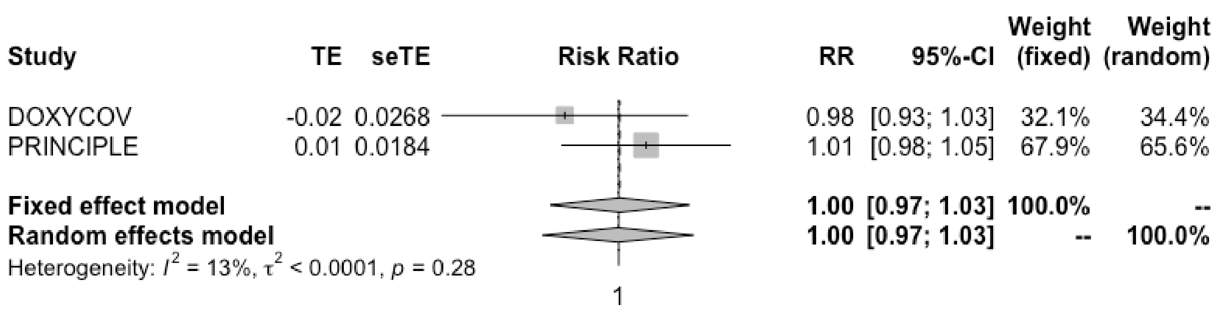


Doxycycline

We identified two RCTs including 1,015 patients with mild COVID-19, in which doxycycline was compared against standard of care. Our results showed:

- 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 32)
- Doxycycline may not reduce hospitalizations, RR 1.13 (95%CI 0.73 to 1.74); RD 0.5% (95%CI -1.4% to 2.6%); Low certainty ⊕⊕◯◯

Figure 32. Symptom resolution or improvement in randomized studies comparing doxycycline vs standard of care in patients with COVID-19



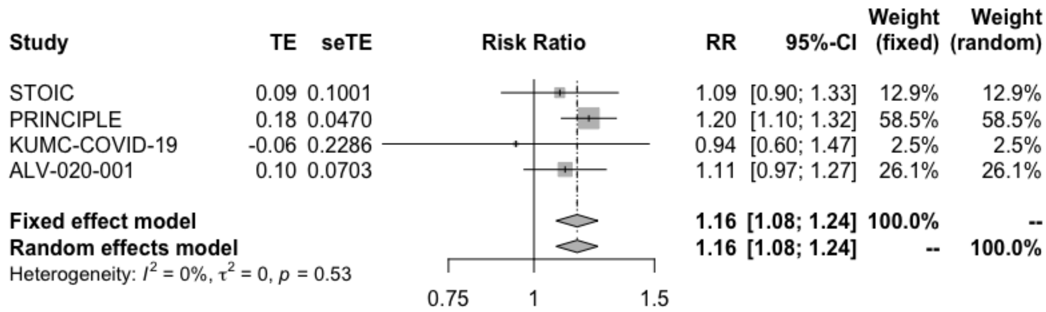
Inhaled corticosteroids

See Summary of findings Table 18, Appendix 1

We identified four RCTs including 2,467 patients with mild COVID-19, in which inhaled coticosteroids were compared against standard of care. Our results showed:

- It is uncertain if inhaled corticosteroids reduce or increase mortality, RR 0.74 (95%CI 0.28 to 1.99); RD -4.1% (95%CI -11.5% to 15.9%); Very low certainty ⊕◯◯◯
- It is uncertain if inhaled corticosteroids reduce or increase mechanical ventilation, RR 0.94 (95%CI 0.44 to 1.98); RD -1% (95%CI -9.6% to 17%); Very low certainty ⊕◯◯◯
- Inhaled corticosteroids probably increase symptom resolution or improvement, RR 1.16 (95%CI 1.08 to 1.24); RD 9.6% (95%CI 4.8% to 14.5%); Moderate certainty ⊕⊕⊕◯ (Figure 33)
- Inhaled corticosteroids may reduce hospitalizations, RR 0.82 (95%CI 0.62 to 1.08); RD -1.3% (95%CI -2.8% to 0.6%); Low certainty ⊕⊕◯◯

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



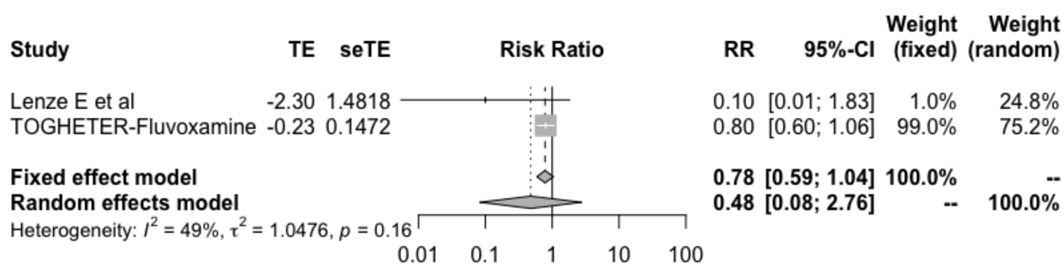
Fluvoxamine

See Summary of findings Table 19, Appendix 1

We identified two RCTs including 1,624 patients with COVID-19, in which inhaled fluvoxamine was compared against standard of care. Our results showed:

- It is uncertain if fluvoxamine reduces or increase mortality, RR 0.70 (95%CI 0.38 to 1.30); RD -4.8% (95%CI -9.9% to 4.8%); Very low certainty ⊕◯◯◯
- Fluvoxamine probably reduces hospitalizations, RR 0.78 (95%CI 0.59 to 1.04); RD -1.6% (95%CI -3% to 0.3%); Moderate certainty ⊕⊕⊕◯ (Figure 34)
- Fluvoxamine may not increase severe adverse events, RR 0.74 (95%CI 0.49 to 1.13); RD -2.7% (95%CI -5.2% to 1.3%); Low certainty ⊕⊕◯◯

Figure 34. Hospitalizations in randomized studies comparing fluvoxamine vs standard of care in patients with COVID-19



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;[13] preprint; 2020	Patients with mild COVID-19 infection. 10 assigned to 99mTc-MDP 5/ml once a day for 7 days and 11 assigned to standard of care.	Median age 61 ± 20, male 42.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Adalimumab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Fakharian A et al trial;[14] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 34 assigned to adalimumab 40 mg once and 34 assigned to SOC	Mean age 54.6 ± 12, male 58.8%, hypertension 29.4%, diabetes 27.9%, COPD 1.5%, CHD 4.4%, CKD 1.5%, cancer 1.5%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ammonium chloride Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Siami et al;[15] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 60 assigned to ammonium chloride 125 mg and 60 assigned to SOC	NR	Corticosteroids 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** Very low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Anakinra **Anakinra may not improve time to symptom resolution. Further research is needed to confirm or discard these findings**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CORIMUNO-ANA-1 trial;[16] Bureau et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 59 assigned to anakinra 400 mg a day for 3 days followed by 200 mg for 1 day followed by 100 mg for 1 day and 55 assigned to SOC	Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD 31.6%, cancer 9.6%,	Corticosteroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%, tocilizumab 0.8%, azithromycin 24.6%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** 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
SAVE-MORE trial;[17] Kyriazopoulou et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 405 assigned to Anakinra 100 mg SC a day for 7 to 10 days and 189 assigned to SOC	Mean age 61.9 ± 12.1, male 57.9%, diabetes 15.8%, COPD 4%, asthma %, CHD 3%, CKD 1.7%	Corticosteroids 86.2%, remdesivir 71.9%, azithromycin 18.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

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

Continuing or initiating ACEIs or ARBs may not reduce mortality. Further research is needed to confirm or discard these findings

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
REPLACE COVID trial;[18] 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 1.16 (95%CI 0.74 to 1.81); RD 2.6% (95%CI -4.2% to 13%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.92 (95%CI 0.67 to 1.25); RD -1.4% (95%CI -5.7% to 4.3%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
BRACE CORONA trial;[19] Lopes et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB	Median age 55.5 ± 19, male 59.6%, hypertension 100%, diabetes 31.9%, COPD %, asthma 3.9%, CHD 4.6%, CKD 1.4%, cancer 1.5%,	Corticosteroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.	

ACEI-COVID trial;[20] Bauer et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 100 assigned to continuation of ACEI/ARB and 104 assigned to discontinuation of ACEI/ARB	Mean age 72 ± 11, male 63%, hypertension 98%, diabetes 33%, CHD 22%	Remdesivir 6.8%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ATTRACT trial;[21] Tornling et al; Preprint; 2020	Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200 mg a day for 7 days and 55 assigned to SOC	Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%	Corticosteroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Nouri-Vaskeh et al;[22] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan 50 mg a day for 14 days and 39 assigned to Amlodipine 5 mg a day for 14 days	Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
SURG-2020-28683 trial;[23] Puskarich et al; Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to losartan 25 mg a day for 10 days and 59 assigned to SOC	Age (35-54) 46%, male 51.4%, hypertension 7.7%, diabetes 6%, COPD %, asthma 10.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

COVID-ARB trial;[24] Geriak et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 16 assigned to losartan 25 mg a day for 10 days and 15 assigned to SOC	Median age 53, male %, hypertension 38.7%, diabetes 25.8%, CHD 3.2%, obesity 41.9%	Corticosteroids 22.6%, remdesivir 29%, hydroxychloroquine 9.7%, , azithromycin 16.1%, convalescent plasma 6.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Duarte et al;[25] peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 71 assigned to Telmisartan 80 mg twice daily and 70 assigned to SOC	Mean age 66 ± 17, male 53.2%, hypertension 44.3%, diabetes 19%, chronic lung disease 11.4%, asthma 1.3%, CHD NR%, CKD 3.2%, cerebrovascular disease 6.9%, obesity 15.2%	Corticosteroids 50.6%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. Significant number of exclusions post randomization. Stop early for benefit in the context of multiple interim analysis.	
Najmeddin et al;[26] peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to continuation of ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB	Mean age 66.3 ± 9.9, male 46.9%, diabetes 50%, COPD 1.6%, CHD 25%, CKD 1.6%, cancer 4.7%,	Corticosteroids 42.2%, remdesivir 10.9%, , azithromycin 9.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes: 10.9% lost to follow-up	

Anticoagulants

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
HESACOVID trial;[27] 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%	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 0.97 (95%CI 0.79 to 1.19); RD -0.5% (95%CI -3.4% to 3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Venous thromboembolic events (intermediate dose):** RR 1.02 (95%CI 0.53 to 1.96); RD 0.1% (95%CI -3.3% to 6.7%); Low ⊕⊕◯◯
REMAP-CAP, ACTIV-4a, ATTACC trial;[28] 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%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
INSPIRATION trial;[29] Sadeghipour et al; peer reviewed;	Patients with moderate to critical COVID-19 infection.	Median age 62 ± 21, male 57.8%, hypertension 44.3%,	Corticosteroids 93.2%, remdesivir 60.1%, lopinavir-ritonavir 1%,	Low for mortality and mechanical ventilation; Low for symptom	

2021	276 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 286 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	diabetes 27.7%, COPD 6.9%, CHD 13.9%, CKD %, cerebrovascular disease 3%	tocilizumab 13.2%	resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	**Venous thromboembolic events (therapeutic dose):** RR 0.59 (95%CI 0.44 to 0.79); RD -2.9% (95%CI -3.9% to -1.5%); Moderate ⨁⨁⨁◯ **Major bleeding:** RR 1.72 (95%CI 1.14 to 2.61); RD 1.4% (95%CI 0.3% to 3.1%); Moderate ⨁⨁⨁◯ **Hospitalization:** No information
Perepu et al;[30] 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;[31] 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%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
ACTION trial;[32] Lopes et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 311 assigned	Mean age 56.6 ± 14.3, male 60%, hypertension 49.1%, diabetes 24.4%,	Corticosteroids 83%	Low for mortality and mechanical ventilation; low for symptom	

	to enoxaparin 1 mg/kg twice a day or rivaroxaban 20 mg a day and 304 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	COPD 3.1%, asthma 4.7%, CHD 4.6%, cancer 2.6%,		resolution, infection, and adverse events Notes: Although patients and carers were aware of the intervention arm assigned, outcome assessors were blinded.	
RAPID trial;[33] Sholzberg et al; preprint; 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%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
Aprepitant **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Mehboob et al;[34]	Patients with mild to	Mean age 54.2 ± 10.91,	NR	High for mortality and	**Mortality:** No

preprint; 2020	critical COVID-19 infection. 10 assigned to aprepitant 80 mg once a day for 3-5 days and 8 assigned to standard of care	male 61.1%,		invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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

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;[35] Tieu et al; Preprint; 2020	Patients with mild to moderate COVID-19. 39 assigned to artemisinin 500 mg for 5 days and 21 assigned to SOC	Mean age 43.3 ± 11.9, male 63.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

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

Aspirin

Aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
RESIST trial;[36] Ghati et al; preprint; 2021	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 0.96 (95%CI 0.90 to 1.03); RD -0.6% (95%CI -1.6% to 0.5%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.95 (95%CI 0.87 to 1.05); RD -0.8% (95%CI -2.2% to 0.9%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%);
RECOVERY - ASA trial;[37] Horby et al; preprint; 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.	Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Auxora

Uncertainty in potential benefits and harms. Further research 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					
Miller et al;[38] peer-reviewed; 2020	Patients with severe COVID-19 infection. 17 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 nine assigned to standard of care	Mean age 60 ± 12, male 46.1%, hypertension 46.1%, diabetes 38.4%,	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. Analysis performed on a subgroup (patients that required high-flow nasal cannula (HFNC) were excluded from primary analysis).	**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

Aviptadil Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
COVID-AIV trial[39] Jihad et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 136 assigned to aviptadil three infusions of 50, 100 and 150pmol/kg/hr and 67 assigned to SOC	Mean age 61 ± NR, male 69%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Azithromycin **Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Sekhavati et al;[40] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to azithromycin 500 mg twice daily and 55 assigned to standard of care	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to
Guvenmez et al;[41] 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.	
COALITION II trial;[42] 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	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, coronary heart disease 5.8%,	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	

	standard of care	chronic kidney disease 11%, cerebrovascular disease 3.8%, immunosuppression %, cancer 3.5%, obesity %		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	19.9%); Very low certainty ⨁◯◯◯ **Hospitalization:** RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -3.6% to 6.4%); Low certainty ⨁⨁◯◯
RECOVERY trial[43] 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;[44] 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.	
PRINCIPLE trial;[45] Butler et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 500 assigned to azithromycin 500 mg a day for 3 days and 629 assigned to SOC	Mean age 60.7 ± 7.8, male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,	NR	Some concerns for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have	

				introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	
ATOMIC2 trial;[46] Hinks et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 145 assigned to azithromycin 500 mg a day for 14 days and 147 assigned to SOC	Mean age 45.9 ± 14.8, male 51.5%, hypertension 17.6%, diabetes 8.5%, COPD 4.1%, asthma 18%, CHD 4.1%, cancer 0.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTION trial;[47] Oldenburg et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 131 assigned to azithromycin 1.2 g once and 70 assigned to SOC	Median age 43, male 44%, hypertension 12.2%, diabetes 3.8%, COPD 1.5%, asthma 12%, CKD 1%, cerebrovascular disease 1%, cancer 0.4%,	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	

Azvudine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Ren et al;[48] peer-reviewed; 2020	Patients with mild to moderate COVID-19	Median age 52 ± 59, male 60%, hypertension	Antivirals 100%, antibiotics 40%	High for mortality and invasive mechanical	**Mortality:** No information

	infection. 10 assigned to azvudine 5 mg once a day and 10 assigned to standard of care	5%, diabetes 5%, coronary heart disease 5%		ventilation; high for symptom resolution, 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 **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;[49] 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, 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;[50] 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 ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.56
ACTIV-3/TICO trial;[51] Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000 mg once and 151 assigned to SOC	Median age 71 ± 22, male 66%, hypertension 49%, diabetes 29%, COPD %, asthma 9%, CHD 4%, CKD 11%, obesity 52%	Corticosteroids 49%, remdesivir 95%,	Low for mortality and adverse events; high for symptom resolution. Notes: Significant loss to follow-up for symptom improvement/resolution outcome.	

Gottlieb et al;[52] 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	(95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Moderate certainty ⊕⊕⊕◯ **Adverse events:** RR 1.16 (95%CI 0.76 to 1.78); RD 1.6% (95%CI -0.2% to -7.9%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.29 (95%CI 0.17 to 0.51); RD -5.2% (95%CI -6.1% to -3.6%); Low certainty ⊕⊕◯◯
BLAZE-2 trial;[53] Cohen et al; peer reviewed; 2021	Patients exposed to SARS-CoV2. 484 assigned to bamlanivimab 4200 mg once and 482 assigned to SOC	Median age 53	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
BLAZE-1 trial;[54] 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;[55] 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;[56] McCreary et al; preprint; 2021	Patients with mild COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2 (Regeneron) and 1013 assigned to	Mean age 56 ± 16, male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD 6.5%, immunosuppresive therapy 27%, obesity	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	bamlanivimab +/- etesevimab	48%			
Baricitinib **Baricitinib probably reduces mortality and time to symptom resolution. Certainty of the evidence was moderate because of 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 (standard of care) and GRADE certainty of the evidence**
RCT					
ACTT-2 trial;[57] 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 0.63 (95%CI 0.48 to 0.81); RD -5.9% (95%CI -8.3% to -3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.66 (95%CI 0.46 to 0.93); RD -5.9% (95%CI -9.2% to -1.2%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.25 (95%CI 1.11 to 1.41); RD 15.1% (95%CI 6.6% to 24.8%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR

					0.77 (95%CI 0.63 to 0.95); RD -2.3% (95%CI -3.7% to -0.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
COV-BARRIER trial;[58] 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	

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;[59] preprint; 2020	Patients with severe COVID-19. 30 assigned to BCG 0.1 ml once and 30 assigned to standard of care	Mean age 45.2 ± 36.5, male 60%, obesity 23%	Remdesivir 6.6%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information **Hospitalization:** No information

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;[60] 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

Bromhexine hydrochloride

Uncertainty in potential benefits and harms. Further research 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;[61] peer-reviewed; 2020	Patients with severe to critical COVID-19. 12	Median age 52 ± 15.5, male 77.8%,	Corticosteroids 22.2%, interferon 77.7%	High for mortality and invasive mechanical	**Mortality:** Very low certainty ⨁◯◯◯

	assigned to bromhexine hydrochloride 32 mf three times a day for 14 days and 6 assigned to standard of care	hypertension 33.3%, diabetes 11.1%		ventilation; high for symptom resolution, infection, and 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):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Ansarin et al;[62] 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.	
Mikhaylov et al;[63] Preprint; 2021	Patients exposed to COVID-19 infection. 25 assigned to bromhexine 12 mg a day and 25 assigned to SOC	Mean age 40.6 ± 7.6, male 42%, comorbidity 6%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tolouian et al;[64] Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 48 assigned to bromhexine 32 mg a	Mean age 52 ± 16, male 46%, hypertension 39%, diabetes 33%, COPD 7%, asthma 6%, CHD 9%, CKD 5%,	Lopinavir-ritonavir 100%, interferon 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	

	day for 14 days and 52 assigned to SOC	cerebrovascular disease 2%, cancer 6%,		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Camostat mesilate **Uncertainty in potential benefits and harms. Further research 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;[65] 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 ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

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;[66] Cariccchio 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 ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Three C trial;[67] Cremer et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 29 assigned to canakinumab 300 to 600 mg once and 16 assigned to SOC	Mean age 68.8 ± 13.2, male 73.3%, hypertension 71.1%, diabetes 46.7%, COPD 17.8% CHD 22.2%, CKD 33.3%, cerebrovascular disease 4.4%	Steroids 46.7%, remdesivir 46.7%, convalescent plasma 9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

CERC-002 (monoclonal antibody) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Perlin et al;[68] 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.	**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

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;[69] Peer reviewed; 2020	Patients with mild COVID-19. 30 assigned to chloroquine nasal drops 0.03% six times a day for 10 days and 30 assigned to SOC	Mean age 34.9 ± 10.35, male 78.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[70] Cruz et al; preprint; 2020	Patients with mild to moderate COVID-19. 10 assigned to CIGB-325 2.5 mg/kg/day during 5-consecutive days) and 10 assigned to standard of care	Mean age 45.3 ± 12, male 70%, hypertension 25%, diabetes 0%, cancer 5%, obesity 25%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Clarithromycin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Rashad et al;[44] preprint; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to clarithromycin 1000 mg a day for 7 days and 99 assigned to SOC	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[71] 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 ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Colchicine

Colchicine may reduce mortality and mechanical ventilation requirements; 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 (standard of care) and GRADE certainty of the evidence
RCT					
GRECCO-19 trial;[72] Deftereos et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 50 assigned to colchicine 1.5 mg once followed by 0.5 mg twice daily until hospital discharge or 21 days and 55 assigned to 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 1 (95%CI 0.93 to 1.08); RD 0% (95%CI -1.1% to 1.3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.02 (95%CI 0.92 to 1.13); RD 0.3% (95%CI -1.4% to -2.2%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 0.99 (95%CI 0.96 to 1.01); RD -0.7% (95%CI -2.1% to -0.7%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.61 to 1); RD -2.2% (95%CI
Lopes et al;[73] 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.	
Salehzadeh et al;[74] preprint; 2020	Patients with moderate to critical COVID-19. 50 assigned to colchicine	Mean age 56, male 41%, hypertension 11%, diabetes 11%, chronic lung disease 4%,	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	1 mg a day for 6 days and 50 assigned to standard of care	coronary heart disease 15%, chronic kidney disease 5%		infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	-4% to 0%); High certainty ⊕⊕⊕⊕ **Pulmonary embolism:** RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.8 (95%CI 0.62 to 1.03); RD -1.5% (95%CI -2.8% to 0.2%); Low certainty ⊕⊕◯◯
Tardif et al;[75] peer-reviewed; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe disease. 2235 assigned to colchicine 1 mg a day for 3 days followed by 0.5 mg for a total of 27 days and 2253 assigned to SOC	Mean age 54.3, male 46%, hypertension 36.3%, diabetes 19.9%, COPD 26.5%, CHD 5.4%, obesity 45.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
RECOVERY - Colchicine trial;[76] Horby et al; preprint; 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.	

Colchicine + rosuvastatin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Gaitan-Duarte et al;[77] preprint; 2021	Patients with moderate to severe COVID-19 infection. 153 assigned to colchicine + rosuvastatin 1 mg + 40 mg a day for 14 days and 161 assigned to SOC	Mean age 55.4 ± 12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%	Corticosteroids 98%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Convalescent plasma

Convalescent plasma does not reduce mortality nor mechanical ventilation requirements nor improves time to symptom resolution. Convalescent plasma probably increases 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;[78] 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 1 (95%CI 0.94 to 1.06); RD 0% (95%CI -1% to 1%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 1.05 (95% CI 0.94 to 1.17); RD 0.8% (95%CI -1% to 2.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 0.99 (95% CI 0.94 to 1.05); RD -0.6% (95%CI -3.6% to 3%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.38 (95% CI 1.07 to 1.78); RD 3.9% (95%CI 0.7% to 8%);
CONCOVID trial; Gharbharan et al;[79] preprint; 2020	Patients with moderate to critical COVID-19 infection. 43 assigned to convalescent plasma 300 ml once or twice and 43 assigned to standard of care	Median age 62 ± 18, male 72%, hypertension 26%, diabetes 24.4%, chronic lung disease 26.7%, coronary heart disease 23.2%, chronic kidney disease 8.1%, immunosuppression 12.8%, cancer 9.3%	NR	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Avendaño-Solá et al;[80] preprint; 2020	Patients with severe COVID-19. 38 assigned to convalescent plasma 250-300 ml once and	Mean age 60.8 ± 15.5, male 54.3%, hypertension 39.5%, diabetes 20.9%, chronic lung disease 12.3%,	Corticosteroids 56.8%, remdesivir 4.94%, hydroxychloroquine 86.4%, lopinavir-ritonavir 41.9%,	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse	

	43 assigned to standard of care	asthma NR%, coronary heart disease 18.5%, chronic kidney disease 4.9%	tocilizumab 28.4%, azithromycin 61.7%	events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.90 (95% CI 0.64 to 1.26); RD -0.7% (95%CI -2.7% to 1.9%); Low certainty ⊕⊕◯◯
PLACID trial;[81] 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;[82] 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;[83] 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;[84] 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;[85] 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;[86] Ray et al; preprint; 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%,	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.	
RECOVERY-Plasma trial;[87] 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	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	

	5763 assigned to SOC			events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Baklaushev et al;[88] 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;[89] 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	Patients with severe to	Mean age 58 ± 25, male	Corticosteroids 82.6%	High for mortality and	

al;[90] preprint; 2021	critical COVID-19 infection. 130 assigned to CP 200 ml a day for 2 days and 60 assigned to IVIG	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%		mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Pouladzadeh et al;[91] 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;[92] 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;[93] 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;[94] Koerper et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to CP 850 ml in three infusions and 52 assigned to SOC	Mean age 60 ± 13, male 73.3%, hypertension 56.2%, diabetes 31.4%, COPD 16.2%, CHD 21.9%, cancer 4.7%, obesity 54.2%	Corticosteroids 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP trial;[95] 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;[96] 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;[97] Sekine et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 80 assigned	Median age 60.5 ± 20, male 58.1%, hypertension 61.3%,	Corticosteroids 98.8%	Low for mortality and mechanical ventilation; high for symptom	

	to CP 300 ml twice and 80 assigned to SOC	diabetes 39.4%, COPD 13.8%, CHD 21.9%, obesity 56.9%		resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVIDIT trial;[98] Kirenga et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 69 assigned to CP 150 -300 ml twice and 67 assigned to SOC	Mean age 50 ± 23.5, male 71.3%, hypertension 36%, diabetes 32%, asthma 3.7%, obesity 33.3%	Corticosteroids 58.8%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
C3PO trial;[99] Korley et al; peer reviewed; 2021	Patients with early mild to moderate COVID-19 infection with risk factors for severe disease. 257 assigned to CP 250 ml and 254 assigned to SOC	Median age 54 ± 21, male 46%, hypertension 42.3%, diabetes 27.8%, COPD 6.1%, CHD 10%, CKD 5.3%, cancer 0.8%, obesity %	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
DAWn-Plasma trial;[100] Devos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 320 assigned to CP 200 to 250 ml once or twice and 163 assigned to SOC	Mean age 62 ± 14, male 68.7%, hypertension %, diabetes 29.6%, COPD 9.4%, asthma 10.1%, CHD 14.1%, CKD 13.4%,	Corticosteroids 66.4%, remdesivir 14.8%, hydroxychloroquine 1.4%, lopinavir-ritonavir 0.4%, tocilizumab 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.	
Balcells et al;[101] peer reviewed; 2020	Patients with moderate to severe COVID-19. 28 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)	Mean age 65.8 ± 65, male 50%, hypertension 67.2%, 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%	Corticosteroids 51.7%, hydroxychloroquine 12%, lopinavir-ritonavir 1.7%, tocilizumab 3.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information
Non-RCT					
Joyner et al;[102] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 20000 received CP	Median age 62.3 ± 79.3, male 60.8%	NR	Low for specific transfusion related adverse events	**Adverse events:** Transfusion related circulatory overload 0.18%; Transfusion related lung injury 0.10%; Severe allergic transfusion reaction 0.10%

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

Darunavir-cobicistat Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DC-COVID-19 trial;[104] 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

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;[105] preprint; 2021	Patients exposed to COVID-19 infection. 116 assigned to DSMO three applications a day for one month and 116 assigned to SOC	Mean age 37.2 ± 8.7	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** No information

Doxycycline

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

Study; publication status	Patients and 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;[106] 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	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1

				symptoms and adverse events outcomes results.	(95%CI 0.97 to 1.03); RD 0% (95%CI -1.8% to 1.8%); High certainty ⊕⊕⊕⊕
PRINCIPLE trial;[107] 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):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR 1.13 (95%CI 0.73 to 1.74); RD 0.5% (95%CI -1.4% to 2.6%); Low certainty ⊕⊕◯◯

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;[108] 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	Patients with mild to	Mean age 41.9 ± 12.4,	NR	High for mortality and	

AndroCoV trial;[109] Cadegiani et al; Peer reviewed; 2020	moderate COVID-19. 43 assigned to dutasteride 0.5 mg a day for 30 days and 44 assigned to SOC	male 100%, hypertension 21.8%, diabetes 9.2%, COPD 0%, asthma 1.1%, CHD 1.1%, cancer 0%, obesity 10.3%		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 ⊕◯◯◯

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;[110] Delgado-Enciso et al; preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to electrolyzed saline nebulizations 4 times a day for 10 days and 39 assigned to standard of care	Mean age 47 ± 14.6, male 53.5%, hypertension 18.9%, diabetes 11.9%	Corticosteroids 3.65%, remdesivir %, hydroxychloroquine 7.5%, ivermectin 9.4%, ATB 30.6%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:**

					Very low certainty ⊕◯◯◯

Emtricitabine/tenofovir Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Gaitan-Duarte et al;[111] preprint; 2021	Patients with moderate to severe COVID-19 infection. 160 assigned to emtricitabine/ tenofovir 200/300 mg once a day for 10 days and 161 assigned to SOC	Mean age 55.4 ± 12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%	Corticosteroids 98%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**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

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;[112] Preprint; 2020	Patients with moderate to severe COVID-19. assigned to enisamium 500 mg 4 times a day for 7 days or SOC. Number of patients in each arm not reported.	NR	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 ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Famotidine Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
Non-RCT					
Samimagham et al;[113] preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to famotidine 160 mg for up to 14 days and 10 assigned to SOC	Mean age 47.5 ± 13, male 60%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Favipiravir

Favipiravir may not reduce mortality nor mechanical ventilation requirements and it probably 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					
Chen et al; preprint;[114] 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 0.72 to 1.64); RD 1.4% (95%CI -4.5% to 10.2%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.24 (95%CI 0.72 to 2.12); RD 4.2% (95%CI -4.8% to 19.5%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 0.99 (95%CI 0.9 to 1.09); RD -0.6% (95%CI -6% to 5.6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:**
Ivashchenko et al[115] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 20 assigned to favipiravir 1600 mg once followed by 600 mg twice a day for 12 days, 20 assigned to favipiravir and 20 assigned to standard of care	Mean age not reported	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Lou et al;[49] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7,	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	

	9 assigned to favipiravir and 10 assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Doi et al;[116] 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) 1800 mg on day 6 followed by 800 mg twice daily for 10 days	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 probably inappropriate.	
Dabbous et al;[117] preprint; 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;[118] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600	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	

	mg twice a day for 7 days, 7 assigned to TCZ 400 mg once or twice and 5 assigned to favipiravir + TCZ			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khamis et al;[119] 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;[120] 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;[121] 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;[122] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 100 assigned to favipiravir 3200 mf once followed by 1200 mg a day for 14 days and 100 assigned to SOC	Mean age 49.7 ± 13, male 50%, hypertension 28.5%, diabetes 9%, COPD 5%, asthma %, CHD 6%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Solaymani-Dodaran et al;[123] 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;[124] peer reviewed; 2021	Patients with COVID-19 infection who were discharged from hospital. 36 assigned to Favipiravir 3200 mg once followed by	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	

	1200 mg a day for 7 days and 19 assigned to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
FACCT trial;[125] 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;[126] 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 commorbiditie 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.	

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;[127] peer-reviewed; 2020	Patients with moderate to severe	Mean age 57.7 ± 8.4, male 59%, hypertension	NR	High for mortality and invasive mechanical	**Mortality:** No information

	COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to HCQ	NR%, diabetes 27.8%, chronic lung disease 1.9%		ventilation; high for symptom resolution, 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 **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

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;[128] 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	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

				probably inappropriate.	**improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information **Hospitalization:** No information
Fluvoxamine **Fluvoxamine probably reduces hospitalizations and may not 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					
Lenze et al;[129] 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 ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis**
TOGETHER-Fluvoxamine trial;[130] Reis et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 739 assigned to fluvoxamine	Median age 50 ± 18, male 42.5%, hypertension 13.2%, diabetes 16.5%, COPD	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	

	100 mg a day for 10 days and 733 assigned to SOC	0.6%, asthma 1.8%, CHD 1.1%, CKD 0.3%, obesity 0.2%		and adverse events	**studies):** No information **Adverse events:** RR 0.74 (95%CI 0.49 to 1.13); RD -2.7% (95%CI -5.2% to 1.3%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.78 (95%CI 0.59 to 1.04); RD -1.6% (95%CI -3% to 0.3%); Moderate certainty ⊕⊕⊕◯
Fostamatinib **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Strich et al;[131] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to fostamatinib 300 mg a day for 14 days and 29 assigned to SOC	Mean age 55.6 ± 13.7, male 79.7%, hypertension 54.2%, diabetes 37.3%, asthma 11.9%, CHD 13.6%, obesity 57.6%	Corticosteroids 100%, remdesivir 100%, convalescent plasma 42.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis**

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

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;[132] 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

Hydroxychloroquine and chloroquine

HCQ/CQ probably does not reduce mortality, invasive mechanical ventilation nor significantly improves time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19, it may reduce the risk of infection. However, certainty of the evidence is low because of risk of bias and imprecision.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CloroCOVID19 trial;[133] 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 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.93 to 1.24); RD 1.2% (95%CI -1.2% to 4.2%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.94 to 1.1); RD 1.2% (95%CI -3.6% to 6.1%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.85 (95%CI 0.72 to 1.01); RD -2.6% (95%CI -4.9% to 0.2%); Low certainty ⊕⊕◯◯
Huang et al;[134] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to chloroquine 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RECOVERY - Hydroxychloroquine trial;[135] Horby et al; preprint; 2020	Patients with Mild to critical COVID-19 infection. 1561 assigned to hydroxychloroquine 800 mg once followed	Mean age 65.3 ± 15.3, male %, diabetes 26.9%, chronic lung disease 21.9%, asthma NR%, coronary heart disease 25.4%, chronic kidney	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events	

	by 400 mg twice a day for 9 days and 3155 assigned to standard of care	disease 7.8%, HIV 0.4%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Severe Adverse events:** RR 0.94 (95%CI 0.66 to 1.34); RD -0.6% (95%CI -3.5% to 3.5%); Low certainty ⨁⨁◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯
BCN PEP CoV-2 trial;[136] Mitja et al; preprint; 2020	Patients exposed to COVID-19. 1116 assigned to hydroxychloroquine 800 mg once followed by 400 mg x once a day for 6 days and 1198 assigned to standard of care	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, coronary heart disease 13.3%, Nervous system disease 4.1%	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant number of patients excluded from analysis.	
COVID-19 PEP trial;[137] Boulware et al; peer-reviewed; 2020	Patients exposed to COVID-19. 414 assigned to hydroxychloroquine 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	Median age 40 ± 6.5, male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma 7.6%, comorbidities 27.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Significant loss of information that might have affected the study's results.	
Cavalcanti et al trial;[138] Cavalcanti et al; peer-reviewed;	Patients with moderate to severe COVID-19 infection.	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%,	Corticosteroids 1.5%, ACE inhibitors 1.2%, ARBs 17.4%, NSAID	Low for mortality and invasive mechanical ventilation; high for	

2020	159 assigned to hydroxychloroquine 400 mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to standard of care	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%	4.4%	symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Kamran SM et al trial;[139] Kamran et al; preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to hydroxychloroquine 400 mg twice a day once then 200 mg twice a day for 4 days and 151 assigned to standard of care	Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%	NR	High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PET trial;[140] Skipper et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 212 assigned to hydroxychloroquine 1400 mg once followed by 600 mg once a day for 5 days and 211 assigned to standard of care	Median age 40 ± 9, male 44%, hypertension 11%, diabetes 4%, chronic lung disease %, asthma 11%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
BCN PEP CoV-2 trial;[141] Mitja et al; preprint; 2020	Patients with mild COVID-19 infection. 136 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 6 days and 157 assigned to standard of care	Mean age 41.6 ± 12.6, male 49%, comorbidities 53.2%	NR	High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Tang et al; peer-reviewed;[142] 2020	Patients with mild to moderate COVID-19 infection. 75 assigned to hydroxychloroquine 1200 mg daily for three days followed by 800 mg daily to complete 7 days and 75 assigned to standard of care	Mean age 46.1 ± 14.7, male 54.7%, hypertension 6%, diabetes 14%, other comorbidities 31%	Corticosteroids 7%, lopinavir-ritonavir 17%, umifenovir 47%, oseltamivir 11%, entecavir 1%, ATB 39%, ribavirin 47%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcome results.	
Chen et al;[143] 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;[144] 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;[145] preprint; 2020	Patients with mild to severe COVID-19	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and invasive mechanical	

	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			ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HC-nCoV trial;[146] Jun et al; peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 15 assigned to hydroxychloroquine 400 mg once a day for 5 days and 15 assigned to standard of care	Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%, chronic lung disease 3.3%	Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Abd-Elsalam et al;[147] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg tablets twice daily for 15 days and 97 assigned to standard of care	Mean age 40.7 ± 19.3, male 58.8%, chronic kidney disease 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PREP trial;[148] Rajasingham et al; peer-reviewed; 2020	Patients exposed to COVID-19. 989 assigned to hydroxychloroquine 400 mg twice in one	Median age 41 ± 15, male 49%, hypertension 14%, asthma 10%	NR	Low for infection, and adverse events	

	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				
TEACH trial;[149] Ulrich et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 67 assigned to hydroxychloroquine 800 mg on day 1 followed by 200 mg twice a day for 2 to 5 days and 61 assigned to standard of care	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart disease 26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%	Corticosteroids 10.2%, remdesivir 0.8%, lopinavir-ritonavir 0.8%, azithromycin 23.4%, convalescent plasma 13.3%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
PrEP_COVID trial;[150] Grau-Pujol et al; preprint; 2020	Patients exposed to COVID-19. 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;[151] Abella et al; peer-reviewed; 2020	Patients exposed to COVID-19. 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 trial;[152] Pan et al;	Patients with moderate to critical COVID-19. 947	Age < 70 years 61%, male 62%, diabetes 25%, COPD 6%, asthma 5%,	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some	

preprint; 2020	assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 10 days and 906 assigned to standard of care	coronary heart disease 21%, chronic kidney disease %		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;[127] 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;[153] Abstract; 2020	Patients exposed to COVID-19. 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;[154] 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	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	

	twice a day for 5 days and 237 assigned to standard of care				
HAHPS trial;[155] 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;[156] 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;[157] 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;[158] 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	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	

	CQ			study. Concealment of allocation is probably inappropriate.	
HYDRA trial;[159] Hernandez-Cardenas et al; Preprint; 2020	Patients with severe to critical COVID-19. 106 assigned to HCQ 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;[160] Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to HCQ 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;[161] 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.	
Beltran et al;[162] Preprint; 2020	Patients with moderate to severe COVID-19. 33 assigned to HCQ 800 mg once followed by 400 mg a day for 5	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	days and 37 assigned to SOC	5.3%		Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
PATCH 1 trial;[163] Amaravadi et al; Preprint; 2020	Patients with mild COVID-19 infection. 17 assigned to HCQ 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;[164] 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	
Seet et al;[165] peer reviewed; 2021	Patients exposed to COVID-19 infection. 432 assigned to HCQ 400 mg once followed by 200 mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOGETHER trial;[166] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to HCQ 800 mg once	Mean age 53, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	

	followed by 400 mg a day for 9 days and 227 assigned to SOC	CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%		and adverse events	
CLOROTRIAL trial;[167] Réa-Neto et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to HCQ 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;[168] Syed et al; preprint; 2021	Health care workers exposed to COVID-19 infection. 154 assigned to HCQ 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;[169] Sivapalan et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 61 assigned to HCQ + AZT 400 mg plus 500 to 250 mg a day and 56 assigned to SOC	Median age 65 ± 25, male 56%, hypertension 38%, diabetes 24%, COPD 9%, asthma 22%, CHD 7%, CKD 7%	Corticosteroids 32%, remdesivir 25%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
HONEST trial;[170] Byakika-Kibwika et al; preprint; 2021	Patients with moderate COVID-19 infection. 55 assigned to HCQ 800 mg once followed by 400 mg a day for 5 days and 50	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	

	assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SEV-COVID trial;[171] Singh et al; preprint; 2021	Patients with severe COVID-19 infection. 20 assigned to ribavirin + HCQ (dosage not reported) and 21 assigned to SOC	Mean age 53.3 ±, male 77.2%, hypertension 34%, diabetes 27.2%, COPD 13.6%, asthma 2.2%, CHD 20.4%, cancer 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.	
ALBERTA HOPE-Covid19 trial;[172] Schwartz et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 111 assigned to HCQ 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 ;[173] Naggie et al ; preprint ; 2021	Patients with exposed to COVID-19 infection. 683 assigned to HCQ 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;[174] peer reviewed; 2021	Patients with mild COVID-19 infection. 42 assigned to HCQ + azithromycin 400/500 mg a day for 7 days and 42 assigned	Mean age 36.5 ± 9.6, male 40.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

	to SOC				

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;[175] preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric oxygen two sessions a day for 4 days and 9 assigned to SOC	Median age 65.4 ± 7.8, male 60%, hypertension 72%, diabetes 60%, COPD %, asthma 8%, CHD 24%, cancer 4%, obesity 8%	Corticosteroids 92%, tocilizumab 24%, convalescent plasma 80%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding and concealment are probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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

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

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

Ali et al;[176] 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 ⊕◯◯◯ **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
Parikh et al;[177] preprint; 2021	Patients with moderate to severe COVID-19 infection. 30 assigned to C-IVIG 30ml 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.	

Icatibant / iC1e/K

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mansour et al;[178] preprint; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to icatibant 30 mg every 8 hours for 4 days, and 10 assigned to iC1e/K	Mean age 51.6 ± 11.5, male 53.3%, hypertension 50%, diabetes 46.7%, asthma 3.3%, obesity 43.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

				study which might have introduced bias to symptoms and adverse events outcomes results.	**improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **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;[179] kosmopoulos et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 46 assigned to icosapent ethyl 8 g a day for three days followed 4 g a day for 11 days and 49 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information **Hospitalization:** No information

IFX-1 Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and 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;[180] peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1 800 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:** 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

Imatinib Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and 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;[181] Aman et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 197 assigned to imatinib 800 mg once followed by 400 mg a day for 10 days and 188 assigned to SOC	Median age 64 ± 17, male 69%, hypertension 37.6%, diabetes 25%, COPD 18.4%, asthma 18%, CHD 22%, obesity 38%	Corticosteroids 72%, remdesivir 21%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.05 (95%CI 0.84 to 1.32); RD 0.5% (95%CI -1.6% to 3.3%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information

Indomethacin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Ravichandran et al;[182] preprint; 2021	Patients with moderate COVID-19 infection. 102 assigned to indomethacin 75 mg a day and 108 assigned to SOC	Mean age 47 ± 16, male 56.2%, hypertension 19%, diabetes 29%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

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;[183] Fisher et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 29 assigned to infliximab and 34 assigned to SOC	Median age 64.5 ± 20, male 61.8%	Corticosteroids 94.3%, remdesivir 61.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably 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

INM005 (polyclonal fragments of equine antibodies) INM005 may not improve symptom resolution and may not 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					
Lopardo et al;[184] peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005 4 mg/kg in two doses on days 1 and 3 and 123 assigned to SOC	Mean age 53.8 ± 12.5, male 65.1%, comorbidities 80%	Corticosteroids 57.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 1.06 (95%CI 0.96 to 1.66); RD 3.6% (95%CI -2.4% to 10.3%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information

Interferon alpha-2b and interferon gamma

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ESPERANZA trial;[185] Esquivel-Moynelo et al; preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to interferon alpha-2b plus interferon gamma twice a week for two weeks (standard care) and 33 assigned to interferon alpha-2b three times a week (IM)	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%, coronary heart disease 6.3%, any comorbidities 50.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, antibiotics 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Interferon beta-1a

IFN beta-1a probably does not reduce mortality nor invasive mechanical ventilation requirements. Inhaled interferon beta-1a may improve time to symptom resolution.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Davoudi-Monfared et al;[186] preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three times a week and 39 assigned to standard of care	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	Corticosteroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to 3.7%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No
WHO SOLIDARITY;[152] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2050 assigned to interferon beta-1a three doses over six days of 44 µg and 2050 assigned to standard of care	Age < 70 years 61%, male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%,	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	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.	
COVIFERON trial;[187] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days	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	

	1, 3 and 6, 20 assigned to interferon beta-1b 0.25 mg on days 1, 3 and 6 and 20 assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	information
Darazam et al;[188] Preprint; 2020	Patients with severe to critical COVID-19. 85 assigned to interferon beta-1a 88 micrograms on days 1, 3 and 6 and 83 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6	Mean age 59.8 ± 16.5, male 61.9%, hypertension 37.3%, diabetes 26.8%, COPD 1.2%, asthma 1.8%, CHD 18.7%, CKD 8.3%, cerebrovascular disease 5.4%, cancer 0.6%	Corticosteroids 1.1%, 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.	
Monk P et al;[189] et al; peer-reviewed; 2020	Patients with mild to severe COVID-19. 48 assigned to interferon beta-1a nebulized once a day for 15 days and 50 assigned to standard of care	Mean age 57.1 ± 13.2, male 59.2%, hypertension 54.7%, diabetes 22.6%, COPD 44.2%, asthma %, coronary heart disease 24.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

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

Interferon beta-1b

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Rahmani et al;[190] peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to standard of care	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%	Corticosteroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
COVIFERON trial;[187] 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.	

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;[191] Peer reviewed; 2021	Patients with moderate COVID-19 infection. 18 assigned to interferon gamma 500000 IU a day for 5 days and 18 assigned to SOC	Mean age 63 ± 12, male 44%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Interferon kappa plus TFF2 Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Fu et al;[192] peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2 mg once a day for six days and 40 assigned to standard of care	Mean age 35.2 ± 11.2, male 63.7%, hypertension 5%, diabetes 3.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

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;[193] Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin + iota-carrageenan 12 mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC	Median age 38 ± 12.5, male 42.7%, hypertension 9%, diabetes, 7.3%, CKD 2.1%, obesity 11.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
CARR-COV-02 trial;[194] Figueroa et al; preprint; 2021	Patients exposed to COVID-19 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.	

Itolizumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ITOLI-C19-02-I-00 trial;[195] Kumar et al; preprint; 2020	Patients with severe COVID-19. 20 assigned to itolizumab 1.6 mg/kg once followed by 0.8 mg/kg weekly and 10 assigned to standard of care	Mean age 49 ± 13, male 86.6%, hypertension 20%,	Nr	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ivermectin

Ivermectin may not reduce mortality and probably does not improve time to symptom resolution. It is uncertain if it affects mechanical ventilation requirements, symptomatic infection as prophylaxis or 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					
Zagazig University trial;[196] Shouman et al; peer-reviewed; 2020	Patients exposed to COVID-19. 203 assigned to ivermectin 15 to 24 mg and 101 assigned to standard of care	Mean age 38.72 ± 15.94, male 51.3%, hypertension 10.2%, diabetes 8.1%, CKD 1%, asthma 2.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.96 (95%CI 0.58 to 1.59); RD -0.6% (95%CI -6.7% to 9.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.05 (95%CI 0.64 to 1.72); RD 0.9% (95%CI -6.2% to 12.5%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.96 to 1.1); RD 1.2% (95%CI -2.4% to 6.1%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.22 (95%CI 0.09 to 0.53); RD -13.6% (95%CI -15.8% to -8.2%); Very low certainty ⊕◯◯◯ **Adverse events:** RR
Chowdhury et al;[197] preprint; 2020	Patients with mild to moderate COVID-19. 60 assigned to ivermectin plus doxycycline 200 μgm/kg single dose + 100 mg BID for 10days and 56 assigned to hydroxychloroquine plus azithromycin	Mean age 33.9 ± 14.1, male 72.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Podder et al;[198] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 μgm/kg once and 30 assigned to standard of	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	

	care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.2%); Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.62 (95%CI 0.36 to 1.07); RD -3.9% (95%CI -6.5% to 0.6%); Low certainty ⊕⊕◯◯
Hashim et al;[199] preprint; 2020	Patients with mild to critical COVID-19. 70 assigned to ivermectin plus doxycycline 200 µgm/kg two or three doses + 100 mg twice a day for 5 to 10 days and 70 assigned to standard of care	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.	
Mahmud et al;[200] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 183 assigned to ivermectin plus doxycycline 12 mg once + 100 mg twice a day for 5 days and 180 assigned to standard of care	Mean age 39.6 ± 13.2, male 58.8%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events. Notes: 8% of patients were lost to follow-up.	
Elgazzar et al (mild);[201] preprint (retracted); 2020	Patients with mild to moderate COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 55.2 ± 19.8, male 69.5%, hypertension 11.5%, diabetes 14.5%, COPD %, asthma 5.5%, coronary heart disease 4%, chronic kidney disease %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elgazzar et al (severe);[201] preprint	Patients with severe COVID-19. 100	Mean age 58.9 ± 19.5, male 71%, hypertension	NR	High for mortality and mechanical ventilation;	

(retracted); 2020	assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	16%, diabetes 20%, COPD %, asthma 13%, coronary heart disease 7.5%		high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elgazzar et al (prophylaxis);[201] preprint (retracted); 2020	Patients exposed to COVID-19. 100 assigned to ivermectin 400 µgm/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;[202] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 20 assigned to ivermectin 0.6 mg/kg for 5 days and 12 assigned to standard of care	Mean age 40.2 ± 12, male 55.5%, hypertension 13.3%, diabetes 15.5%, COPD 11.1%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Niaee et al;[203] 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;[204] 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;[205] 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;[206] 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;[207] 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;[208] 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;[193] Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 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;[209] 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;[210] 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;[211] Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to ivermectin 0.2 mg/kg once or	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection,	

	SOC			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;[212] peer-reviewed; 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;[213] 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;[214] peer-reviewed; 2021	Patients with severe COVID-19. 30 assigned to ivermectin 0.2 mg/kg for 5 days and 30 assigned to	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

	SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Beltran et al;[162] Preprint; 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;[215] 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;[164] 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;[216] peer-reviewed; 2021	Patients with moderate to critical COVID-19 infection. 27 assigned to ivermectin 100 to 400 mcg/kg and 4 assigned to SOC	Mean age 49.4 ± 14.6, male 45.2%	Corticosteroids 32.3%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to	

				symptoms and adverse events outcomes results.	
Kishoria et al;[217] 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;[165] peer-reviewed; 2021	Patients exposed to COVID-19 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;[218] 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;[219] preprint; 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;[220] 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;[221] 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	

Ivermectin (inhaled)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Aref et al;[222] peer reviewed; 2021	Patients with mild COVID-19 infection. 57 assigned to inhaled (inh) ivermectin and	Mean age 45 ± 19, male 71.9%, hypertension 17.5%, diabetes 12.3%, COPD 0.9%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection,	**Mortality:** No information

	57 assigned to SOC	cerebrovascular disease 3.5%		and adverse events Notes: Non-blinded study. Randomization and concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Intravenous immunoglobulin (IVIG)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Sakoulas et al;[223] 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No

				inappropriate.	information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Gharebaghi et al;[224] preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to IVIG 5 g a day for 3 days and 29 assigned to standard of care	Mean age 56 ± 16, male 69.5%, hypertension 22%, diabetes 27.1%, chronic lung disease 3.3%,	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
Tabarsi et al;[225] peer-reviewed; 2020	Patients with severe COVID-19. 52 assigned to IVIG 400 mg/Kg daily for three doses and 32 assigned to standard of care	Mean age 53 ± 13, male 77.4%, hypertension 20.2%, diabetes 21.4%, COPD 1.2%, asthma %, coronary heart disease %, chronic kidney disease 4.7%, cancer 1.2%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Raman et al;[226] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to IVIG 0.4 g/kg for 5 days and 50 assigned to SOC	Mean age 48.7 ± 12, male 33%, hypertension 31%, obesity 16%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

KB109 (microbiome modificator) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Haran et al;[227] 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;[228] peer reviewed; 2021	Patients with severe COVID-19 infection. 45 assigned to L-arginine 1.66 g twice a day during hospitalization and 45 assigned to SOC	Mean age 61.6, male 81.2%, hypertension 36.7%, diabetes 10%, CHD 14.5%, obesity 10%	Corticosteroids 100%, remdesivir 27.8%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
***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;[229] Endam et al; preprint; 2021	Patients with mild recently diagnosed COVID-19 infection. 12 assigned to *Lactococcus lactis* (intranasal) two nasal irrigations a day and 11 assigned to SOC	Mean age 30.4 ± 9.1, male 30%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty

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

Leflunomide

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hu et al;[230] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50 mg every 12 h (three doses) followed by 20 mg a day for 10 days and 5 assigned to standard of care	Mean age 52.5 ± 11.5, male 30%, hypertension 60%, chronic lung disease 10%	Umifenovir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Wang et al;[231] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day	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	Corticosteroids 34.1%, hydroxychloroquine 56.8%, lopinavir-ritonavir 11.4%, umifenovir 75%, IVIG 20.4%, ATB 63.6%,	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	

	followed by 20 mg a day for 8 days and 24 assigned to standard of care	2.3%	IFN 100%	Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Hospitalization:** No information

Lenzilumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and 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;[232] Temesgen et al; preprint; 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%, diabetes 53.4%, COPD 7.3%, asthma 10.6%, CHD 13.6%, CKD 14%,	Corticosteroids 93.7%, remdesivir 72.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.7 (95%CI 0.42 to 1.15); RD -4.8% (95%CI -9.3% to 2.4%); Low certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.71 (95%CI 0.48 to 1.04); RD -5% (95%CI -9% to 0.7%); Low certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.82 (95%CI 0.62 to 1.07); RD -1.8%

					(95%CI -3.9% to 0.7%); Low certainty ⨁⨁⨁◯ **Hospitalization:** No information

Levamisole

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Roostaei et al;[233] 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

Lincomycin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Guvenmez et al;[41] 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

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;[234] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to lopinavir-ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Corticosteroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -1.3% to 1.8%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⨁⨁⨁⨁ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Severe Adverse events:** RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -
ELACOI trial;[235] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, intravenous immunoglobulin 6.3%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY - Lopinavir-ritonavir trial;[236] Horby et al; other; 2020	Patients with mild to critical COVID-19 infection. 1616 assigned to lopinavir-	Mean age 66.2 ± 15.9, male 60.5%, diabetes 27.5%, chronic lung disease 23.5%, coronary	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom	

	ritonavir 400/100 mg twice a day for 10 days and 3424 assigned to standard of care	heart disease 26%		resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	6.5% to -0.2%); Low certainty ⨁⨁◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯
Huang et al; peer-reviewed;[134] 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;[237] 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;[238] 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 g IV	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	loading dose followed by orally 400-600 mg every 8 hours for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir			infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
WHO SOLIDARITY - trial;[152] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 1399 assigned to lopinavir-ritonavir 200/50 mg twice a day for 14 days and 1372 assigned to standard of care	Age 61% < 70 years, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	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.	
Sali et al;[239] 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;[240] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to HCQ	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	

	200 mg a day and 119 to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Kasgari et al;[241] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Yadollahzadeh et al;[242] 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;[166] 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	
SEV-COVID trial;[171] Singh et al;	Patients with severe COVID-19 infection.	Mean age 53.3 ±, male 77.2%, hypertension	NR	High for mortality and mechanical ventilation;	

preprint; 2021	20 assigned to ribavirin + lopinavir-ritonavir (dosage not reported) and 21 assigned to SOC	34%, diabetes 27.2%, COPD 13.6%, asthma 2.2%, CHD 20.4%, cancer 0%,		high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COPEP trial;[243] Labhardt et al; preprint; 2021	Patients exposed to COVID-19 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.	

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;[244] Papachristofilou et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 11 assigned to low-dose radiation therapy 0.5 to 1.0 Gy and 11 assigned to SOC	Mean age 75, male 77.3%, diabetes 54.6%, COPD 22.7%, asthma %, CHD 40.9%, cancer 18.2%,	Corticosteroids 100%, remdesivir 50%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty

					⊕○○○ **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;[245] Cremer et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 21 assigned to mavrilimumab 6 mg/kg once and 19 assigned to SOC	Mean age 56.7 ± 23.8, male 65%, hypertension 55%, diabetes 43%, COPD 8%, CKD 8%, cerebrovascular disease 3%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom resolution or improvement:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

					Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Melatonin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Farnoosh et al;[246] 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:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Davoodian et al;[247] preprint; 2021	Patients with severe COVID-19 infection. 41 assigned to melatonin 6 mg a day for 14 days and 39 assigned to SOC	Median age 56 ± 40, male 56.8%, hypertension 18.5%, diabetes 14.8%, CHD 19.8%, CKD 3.7%	Corticosteroids 12.3%, hydroxychloroquine 69%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Alizadeh et al;[248] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 14 assigned to melatonin 6 mg a day for 14 days and 17 assigned to SOC	Mean age 36 ± 8.2, male 64.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study. Concealment of allocation probably inappropriate.	
Mousavi et al;[249] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 48 assigned to melatonin 3 mg a day for 10 days and 48 assigned to SOC	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 Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Mesenchymal stem-cell transplantation

Mesenchymal stem-cell transplantation may reduce mortality.

Study; publication status	Patients and 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;[251] 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 0.59 (95%CI 0.37 to 0.93); RD -6.2% (95%CI -9.8% to -1%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection**
Shi et al;[252] preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem cell	Mean age 60.3 ± 8.4, male 56%, hypertension 27%, diabetes 17%, COPD 2%	Corticosteroids 22%	Low for mortality and mechanical ventilation	

	three infusions with 4.0 ×107 cells each and 35 assigned to standard of care				**(prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Lanzoni et al;[253] preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell 100±20 ×106 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 inappropriate.	
Dilogo et al;[254] 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	

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;[255] 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	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or**

				allocation is probably inappropriate.	**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;[256] 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

Metroprolol

Mesenchymal stem-cell transplantation may reduce mortality.

Study; publication status	Patients and 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;[250] Clemente-Moragón et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 12 assigned to metoprolol 15 mg a day for 3 days and 8 assigned to SOC	Median age 60 ± 14.2, male 65%, hypertension 30%, diabetes 10%,	Corticosteroids 100%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Molnupiravir

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

Study; publication status	Patients and 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;[257] 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:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
AGILE trial;[258] Khoo et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 12 assigned to molnupiravir 600-1600 mg a day and 6 assigned to SOC	Median age 56 ± 58, male 27.8%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Fischer et al;[259] 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	

Mouthwash

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

Study; publication status	Patients and 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;[260] 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:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
GARGLES trial;[261] 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.	
KILLER trial;[262] Guenezan et al; peer reviewed; 2020	Patients with mild COVID-19. 12 assigned to mouthwash with 25 ml of 1% povidone iodine and 12 assigned to SOC	Mean age 45 ± 23, male 33%, hypertension 12.5%, diabetes 4%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	

				inappropriate.	
Elzein et al;[263] 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;[264] 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;[265] Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to mouthwash with ß-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;[266] 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	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	

	SOC			allocation is probably inappropriate.	
Eduardo et al;[267] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 34 assigned to mouthwash cetylpyridinium chloride, zinc, chlorhexidine, hydrogen peroxide and 9 assigned to SOC	Mean age 54.7, male 74.4%, hypertension 30.2%, diabetes 23.2%, COPD 11.6%, CHD 18.6%, CKD 11.6%, obesity 13.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Mycobacterium w

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ARMY-1 trial;[268] Sehgal et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to Mycobacterium w 0.3 ml SC once a day for 3 days and 20 assigned to SOC	Mean age 56 ± 15, male 69%, hypertension 31%, diabetes 33.3%, COPD 4.8%, asthma 4.8%	Corticosteroids 100%, hydroxychloroquine 26.2%, tocilizumab 12%, convalescent plasma 7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information **Hospitalization:** No information

N-acetylcysteine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
de Alencar et al;[269] peer-reviewed; 2020	Patients with severe COVID-19. 68 assigned to NAC 21 g once and 67 assigned to standard of care	Mean age 58.5 ± 22.5, male 59.2%, hypertension 46.6%, diabetes 37.7%, cancer 12.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Gaynitdinova et al;[270] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 24 assigned to NAC 1200-1500 mg once and 22 assigned to SOC	Mean age 57.9 ± 12.7	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Taher et al;[271] 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	

				inappropriate.	

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;[183] 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

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;[272] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 14 assigned to nasal hypertonic saline 250 cc twice daily, 14 assigned to nasal hypertonic saline plus surfactant and 17 assigned to standard of care	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%, diabetes 6.6%, chronic lung disease 15.5%, coronary heart disease 4.4%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Neem (*Azadirachta indica* A. Juss)
Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Nesari et al;[273] other; 2021	Patients exposed to COVID-19 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 ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** No information

Niclosamaide Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Abdulamir et al;[274] preprint; 2021	Patients with mild to critical COVID-19 infection. 75 assigned to niclosamaide 4 g once followed by 3 g a day for 7 days and 75 assigned to SOC	Mean age 49.3 ± 16, male 53.3%, hypertension 12.7%, diabetes 8%, asthma 0.7%, cancer 0.7%, obesity 0.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

***Nigella sativa* +/- Honey** **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
HNS-COVID-PK trial;[275] Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + *Nigella sativa* 1 g + 80 mg/kg three times a day for 13 days and 156 assigned to SOC	> 60 age 52 ±, male 56.8%, hypertension 31.6%, diabetes 36.7%	Corticosteroids 26.5%, azithromycin 73.8%, ivermectin 36.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Koshak et al;[276] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 91 assigned to *Nigella sativa* 500 mg twice a day for 10 days and 92 assigned to SOC	Mean age 36 ± 11, male 53%, hypertension 9%, diabetes 8%, asthma 4%, CHD 0.5%, obesity 25%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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;[277] Rocco et al; preprint; 2020	Patients with mild COVID-19. 194 assigned to nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	Age range 18 - 77, male 47%, comorbidities 13.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Fontanesi et al;[278] 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.	
Silva et al;[279] preprint; 2021	Patients with mild to moderate COVID-19 infection. 23 assigned to nitazoxanide 2-3 g a day for 14 days and 13 assigned to SOC	Male 72.2%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study. Concealment of allocation is probably inappropriate.	
Vanguard trial;[280] Rossignol et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 184 assigned to nitazoxanide 600 mg a day for 5 days and 195 assigned to SOC	Mean age 40.3 ± 15.4, male 43.5%, comorbidities 34%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

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;[281] preprint; 2021	Patients with severe COVID-19 infection. 14 assigned to iNO pulses of 30 min for 3 days and 11 assigned to SOC	Mean age 59.8 ± 10, male 72%, hypertension 44%, diabetes 56%, COPD 12%, CHD 24%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Winchester et al;[282] 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	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	

	SOC			study. Concealment of allocation is probably inappropriate.	**Hospitalization:** No information
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**
Non-RCT					
Eilidh et al;[283] 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;[284] 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;[285] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 224 received NSAID and 896 received alternative treatment schemes	Median age 54 ± 23, male 41.5%, chronic lung disease 3.9%, asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%	Corticosteroids 7.1%	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and matching were implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, and phase of the outbreak.	
Rinott et al;[286] 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;[287] preprint; 2020	Patients exposed to COVID-19 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;[288] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 466 received NSAID and 839 received alternative treatment schemes	Mean age 61 ± 16.3, male 53.8%, hypertension 56.2%, diabetes 30.1%, chronic lung disease 8.2%, asthma 8.8%, coronary heart disease 15.9%, chronic kidney disease 17.5%, immunosuppression 1%, cancer 6.4%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified).	
Esba et al;[289] 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).	
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;[237] 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

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;[290] Preprint; 2020	Patients with mild to moderate COVID-19. 15 assigned to omega-3 670 mg three times a day for 2 weeks and 15 assigned to SOC	Mean age 66.7 ± 2.5, male 60%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Doaei et al;[291] 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.	

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;[292] Patel et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 386 assigned to otilimab 90 mg once and 393 assigned to SOC	Mean age 59.6 ± 12, male 71.6%, hypertension 49.7%, diabetes 36.7%, CHD 11.9%	Corticosteroids 83%, remdesivir 34%, tocilizumab 1.2%, convalescent plasma 6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Ozone

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PROBIOZOVID trial;[293] Araimo et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 14 assigned to ozone 250 ml ozonized blood and 14 assigned to standard of care	Mean age 61.7 ± 13.2, male 50%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
SEOT trial;[294] 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.	

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;[295] Pandit et al; Peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to pegylated interferon alfa 1 µg/kg once and 19 assigned to SOC	Mean age 49.2 ± 13.5, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Bushan et al;[296] 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.	

Peg-interferon (IFN) lamda Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ILIAD trial;[297] Feld et al; preprint; 2020	Patients with mild to severe COVID-19. 30 assigned to peg-IFN lambda 180 µg subcutaneous injection once and 30 assigned to standard of care	Median age 46 ± 22, male 58%, comorbidities 15%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** Very low certainty ⊕○○○
COVID-Lambda trial;[298] 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.	

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;[299] peer-reviewed; 2020	Patients with severe to critical COVID-19. 26 assigned to pentoxifylline 400 mg three times a day while hospitalized and 12 assigned to standard of care	Mean age 57.5 ± 11.7, male 55.2%, hypertension 39.4%, diabetes 50%, obesity 55.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

PNB001 (CCK-A antagonist) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BCR-PNB-001 trial;[300] Lattaman et al; preprint; 2021	Patients with moderate COVID-19 infection. 20 assigned to PNB001 200 mg a day for 14 days and 20 assigned to SOC	Mean age 52, 65% male	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Polymerized type I collagen (PT1C) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Mendez-Flores et al;[301] preprint; 2021	Patients with mild to moderate COVID-19 infection. 44 assigned to PT1C 25 mg intramuscular for 3 days followed by 12.5 mg for another 4 days and 43 assigned to SOC	Mean age 48.5 ± 14.1, male 41.6%, hypertension 20.2%, diabetes 16.9%, COPD 2.3%, asthma 4.5%, CHD 0%, cancer 0%, obesity 28.1%	Corticosteroids 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯

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;[165] peer reviewed; 2021	Patients exposed to COVID-19 infection. 735 assigned to povidone iodine spray 3 times a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Probiotics Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and 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;[302] peer reviewed; 2021	Patients exposed to COVID-19 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:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** No information

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**
RCT					
Ghandehari et al;[303] preprint; 2020	Patients with severe COVID-19. 18 assigned to progesterone 100 mg twice a day for 5 days and 22 assigned to standard of care	Mean age 55.3 ± 16.4, male 100%, hypertension 48%, diabetes 25%, obesity 45%	Corticosteroids 60%, remdesivir 60%, hydroxychloroquine 2.5%, tocilizumab 12.5%, azithromycin 50%, convalescent plasma 5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Prolectin-M Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Prolectin-M trial;[304] 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**
RCT					
Bee-Covid trial;[305] Duarte Silveira et al; Preprint; 2020	Patients with moderate to critical COVID-19. 82 assigned to propolis 400-800 mg a day for 7 days and 42 assigned to SOC	Mean age 50 ± 12.8, male 69.4%, hypertension 45.2%, diabetes 21%, COPD 7.3%, asthma %, obesity 51.6%	Corticosteroids 80.6%, hydroxychloroquine 3.2%, azithromycin 95.2%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Proxalutamide **Proxalutamide may improve time to symptom resolution and 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					
[Cadegiani et al](#);[306] 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:** RR 0.22 (95%CI 0.16 to 0.31); RD -12.5% (95%CI -13.4% to -11%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.12 (95%CI 0.05 to 0.27); RD -15.2% (95%CI -16.4% to -12.6%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 2.62 (95%CI 1.82 to 3.75); RD 98.2% (95%CI -49.6% to 100%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR
[AB-DRUG-SARS-004 trial](#);[307] 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.	
[KP-DRUG-SARS-003 trial](#);[308] Cadegiani et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 317 assigned to proxalutamide 300 mg a day for 14 days and 328 assigned to SOC	Median age 50 ± 22.5, male 43.3%, hypertension 27.1%, diabetes 12.2%, COPD 2.5%, CKD 0%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
[AB-DRUG-SARS-005 trial](#);[309]	Patients with mild to moderate COVID-19	Mean age 44.2 ± 12.1, male 0%, hypertension	NR	High for mortality and mechanical ventilation;	

Cadegiani et al; peer reviewed; 2021	infection. 75 assigned to proxalutamide 200 mg a day for 7 days and 102 assigned to SOC	31.1%, diabetes 8.5%, COPD 0.6%, obesity 18.1%		High for symptom resolution, infection, and adverse events Notes: Randomization process presented as "Blocked" but described as a cluster randomization.	0.07 (95%CI 0.01 to 0.52); RD -6.9% (95%CI -7.3% to -3.6%); Low certainty ⊕⊕◯◯

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;[310] 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;[311] Preprint; 2020	Patients with moderate to severe COVID-19. 52 assigned to Quercetin 1000 mg and 395 assigned to SOC	Age > 50 65.7%, male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma 13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Di Pierro et al;[312] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to quercetin 400-600 mg a day for 14days and 21 assigned to SOC	Mean age 49.3 ± 19.5, male 47.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

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;[313] Amat-Santos et al; preprint; 2020	Patients exposed to COVID-19. 50 assigned to ramipril 2.5 mg a day progressively increased to 10 mg a day and 52 assigned to standard of care	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%, diabetes 20.65%, chronic lung disease 7.35%, coronary heart disease 22.45%, chronic kidney disease 34.15%, cerebrovascular disease 11.15%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** No information

Recombinant super-compound interferon Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Li et al;[314] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 46 assigned to recombinant super-compound interferon 12 million IU twice daily (nebulization) and 48 assigned to interferon alfa	Median age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, chronic lung disease 1.1%, coronary heart disease 7.4%, cerebrovascular disease 5.3%, liver disease 6.4%	Corticosteroids 9.6%, ATB 22.3%, intravenous immunoglobulin 3.2%, lopinavir-ritonavir 44.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Regdanvimab (monoclonal antibody) Regdabivimab may improve time to symptom resolution. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Eom et al;[315] Preprint; 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 ⨁◯◯◯ **Symptom resolution or improvement:** RR 0.94 (95%CI 0.82 to 1.08); RD 13.9% (95%CI 1.8% to 27.3%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯

REGEN-COV (casirivimab and imdevimab)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Weinreich et al;[316] preprint; 2020	Patients with recent onset mild disease with risk factors COVID-19 infection. 2091 assigned to REGEN-COV (casirivimab and imdevimab) 1.2 to 2.4 g single infusion and 2089 assigned to SOC	Median age 50 ± 21, male 48.7%, obesity 58%, comorbidities 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.94 (95%CI 0.87 to 1.02); RD -1% (95%CI -2.1% to 0.3%); Moderate certainty ⊕⊕⊕◯ **Mortality (seronegative):** RR 0.8 (95%CI 0.7 to 0.91); RD -3.2% (95%CI -4.8% to -1.4%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.96 (95%CI 0.89 to 1.03); RD -0.7% (95%CI -1.9% to -0.5%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation (seronegative):** RR 0.83 (95%CI 0.75 to 0.92); RD -2.9% (95%CI -4.3% to -1.4%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or**
RECOVERY - REGEN-COV trial;[317] Horby et al; preprint; 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%	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.	
O'Brien et al;[318] preprint; 2021	Patients with early asymptomatic COVID-19 infection. 100 assigned to REGEN-COV (Regeneron) 1.2 g	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	

	once and 104 assigned to SOC				**improvement:** RR 1.06 (95%CI 0.96 to 1.16); RD 3.6% (95%CI -2.4% to 9.7%); Moderate certainty ⊕⊕⊕◯
O'Brien et al;[319] peer reviewed; 2021	Patients with exposed to COVID-19 infection. 753 assigned to REGN-CoV2 (Regeneron) 1200mg once and 752 assigned to SOC	Median age 42.9, male 45.9%, diabetes 6.8%, CKD 1.9%, immunosuppressive therapy 1%, obesity 13.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Symptom resolution or improvement:** RR 1.12 (95%CI 1.01 to 1.25); RD 7.2% (95%CI 0.6% to 15.1%); Moderate certainty ⊕⊕⊕◯
OPTIMISE-C19 trial;[56] McCreary et al; preprint; 2021	Patients with mild COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2 (Regeneron) and 1013 assigned to bamlanivimab +/- etesevimab	Mean age 56 ± 16, male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD 6.5%, immunosuppresive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Symptomatic infection (prophylaxis studies):** RR 0.49 (95%CI 0.35 to 0.67); RD -8.9% (95%CI -11.3% to -5.7%); High certainty ⊕⊕⊕⊕ **Adverse events:** RR 0.63 (95%CI 0.48 to 0.81); RD -3.8% (95%CI -5.3% to -1.9%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.29 (95%CI 0.18 to 0.44); RD -5.3% (95%CI -6.1% to -4.1%); Moderate certainty ⊕⊕⊕◯

Remdesivir

Remdesivir may slightly reduce mortality, mechanical ventilation requirement and improve time to symptom resolution without significantly increasing the risk of 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					
ACTT-1 trial; Beigel et al;[320] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 541 assigned to remdesivir intravenously 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death and 522 assigned to standard of care	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.95 (95%CI 0.83 to 1.08); RD -0.8% (95%CI -2.7% to 1.3%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.71 (95%CI 0.43 to 1.18); RD -5% (95%CI -9.9% to 3.1%); Low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.8 (95%CI 0.48 to 1.33); RD -2% (95%CI -5.3% to 3.4%); Low
SIMPLE trial; Goldman et al;[321] peer-reviewed; 2020	Patients with severe COVID-19 infection. 200 assigned to remdesivir (5 days) 200 mg once followed 100 mg for 5 days and 197 assigned to remdesivir (10 days)	Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CAP-China remdesivir 2 trial;[322]	Patients with severe to critical COVID-19	Median age 65 ± 7.5, male 60.5%,	Corticosteroids 65.6%, lopinavir-ritonavir	Low for mortality and invasive mechanical	

Wang et al; peer-reviewed; 2020	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	hypertension 43%, diabetes 23.7%, coronary heart disease 7.2%	28.4%, IFN 32.2%, ATB 91.1%	ventilation; low for symptom resolution, infection, and adverse events	certainty ⨁⨁◯◯ **Hospitalization:** No information
SIMPLE 2 trial; Spinner et al;[323] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 384 assigned to remdesivir 200 mg on day 1 followed by 100 mg a day for 5 to 10 days and 200 assigned to standard of care	Median age 57 ± 9, male 61.3%, hypertension 42%, diabetes 40%, asthma 14%, coronary heart disease 56%	Corticosteroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	Some concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY;[152] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2743 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 2708 assigned to standard of care	age < 70 years 61%, male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	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.	
Mahajan et al;[324] peer reviewed; 2021	Patients with mild to severe COVID-19	Mean age 57.7 ± 13.1, male 65.5%,	NR	High for mortality and mechanical ventilation;	

	infection. 34 assigned to remdesivir 200 mg once followed by 100 mg once a day for 5 days and 36 assigned to SOC	hypertension 45.7%, diabetes 60%, asthma 1.4%, CHD 12.9%, CKD 4.3%		High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
rhG-CSF (in patients with lymphopenia) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Cheng et al;[325] peer-reviewed; 2020	Patients with moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100 assigned to standard of care	Mean age 45 ± 15, male 56%	Lopinavir-ritonavir 15.5%, IFN 9%, umifenovir 18%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ribavirin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al;[238] preprint; 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 g IV loading dose followed by orally 400-600 mg every 8 h for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**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

Ribavirin plus interferon beta-1b Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hung et al;[326] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 86 assigned to ribavirin plus interferon beta-1b 400 mg every 12 hours (ribavirin), and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]) on alternate days, for 14 days and 41 assigned to standard of care	Median age 52 ± 15, male 54%, hypertension 18.3%, diabetes 13.3%, coronary heart disease 7.9% cerebrovascular disease 1.5%, cancer 1.5%	Corticosteroids 6.2%, ATB 53.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ruxolitinib Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and 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;[327] 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:** 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

Sarilumab

Sarilumab may reduce mortality and mechanical ventilation requirements; however, the certainty of the evidence is low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
REMAP-CAP - tocilizumab trial;[328] Gordon et al; preprint; 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%, cancer %, obesity %	Corticosteroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.99 (95%CI 0.8 to 1.23); RD -0.2% (95%CI -3.2% to 3.7%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.93 (95%CI 0.68 to 1.26); RD -1.2% (95%CI -5.5% to 4.5%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 0.99 (95%CI 0.92 to 1.08); RD -0.6% (95%CI -4.8% to 4.8%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 1.02 (95%CI 0.89 to 1.17); RD 0.2% (95%CI -1.1% to 1.7%); Low certainty ⊕⊕◯◯
Lescure et al;[329] peer-reviewed; 2020	Patients with severe to critical COVID-19. 332 assigned to sarilumab 200-400 mg once and 84 assigned to SOC	Mean age 59 ± 18, male 62.7%, hypertension 42.5%, diabetes 26.4%, COPD 4.3%, asthma 4.1%, CHD 5.3%, CKD 4.3%, cancer 10.1%, obesity 20.7%	Corticosteroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Sarilumab-COVID19 Study trial;[330] Sivapalasingam, et al; preprint; 2021 (two studies reported)	Patients with severe to critical COVID-19 infection. 1148 assigned to sarilumab 200-400 mg once and 376 assigned to SOC	Critical patient population: Mean age 61 ± 20, male 68.4%, hypertension 52.1%, diabetes 18.7%, obesity 46.5%	Corticosteroids 34.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
CORIMUNO-SARI trial;[331] other;	Patients with severe COVID-19 infection.	Median age 62	Corticosteroids 4.9%, remdesivir 0%,	Low for mortality and mechanical ventilation;	

2021	68 assigned to sarilumab 400 mg once and 76 assigned to SOC		convalescent plasma 0%	low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	**Hospitalization:** No information
CORIMUNO-SARI ICU trial;[331] et al; other; 2021	Patients with critical COVID-19 infection. 48 assigned to sarilumab 400 mg once and 33 assigned to SOC	Median age 62	Corticosteroids 2.4%, remdesivir 0%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, 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.	
SARCOVID trial;[331] other; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to sarilumab 400 mg once and 10 assigned to SOC	Median age 62	Corticosteroids 83.3%, remdesivir 0%, 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.	
SARICOR trial;[331] other; 2021	Patients with moderate to severe COVID-19 infection. 76 assigned to sarilumab 200-400 mg once and 39 assigned to SOC	Median age 60	Corticosteroids 93%, remdesivir 12.2%, 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.	
SARTRE trial;[331] other; 2021	Patients with moderate to severe	Median age 58	Corticosteroids 100%, remdesivir 1%, ,	Low for mortality and mechanical ventilation;	

	COVID-19 infection. 70 assigned to sarilumab 200-400 mg once and 70 assigned to SOC		convalescent plasma 0%	low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
Secukinumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BISHOP trial;[332] Gomes Resende et al; preprint; 2021	Patients with severe COVID-19 infection. 25 assigned to secukinumab 300 mg once and 23 assigned to SOC	Mean age 54 ± 21.5, male 52%, hypertension 48%, diabetes 34%, CHD 8%, obesity 48%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Short-wave diathermy Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Tian et al;[333] peer reviewed; 2021	Patients with moderate COVID-19 infection. 27 assigned to short-wave diathermy and 13 assigned to SOC	Median age 65 ± 18, male 62.5%, hypertension 30%, diabetes %, COPD 45%, CHD 30%, CKD 7.5%, cerebrovascular disease 27.5%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Siltuximab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COV-AID-2 trial;[331] other; 2021	Patients with severe to critical COVID-19 infection. 77 assigned to siltuximab 11 mg/kg once and 72 assigned to SOC	Median age 64	Corticosteroids 59%, remdesivir 3.4%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

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;[334] preprint; 2021	Patients with moderate to severe COVID-19 infection. 66 assigned to sitagliptin 100 mg a day and 87 assigned to SOC	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD 6.4%, cancer 5.9%, obesity 18.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

Sofosbuvir +/- daclatasvir, ledipasvir, ravidasvir, or velpatasvir

Sofosbuvir alone or in combination with daclatasvir or ledipasvir may not reduce mortality or 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;[241] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.13 (95%CI 0.82 to 1.55); RD 2% (95%CI -2.9% to 8.8%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.04 (95%CI 0.29 to 3.7); RD 0.7% (95%CI -12.3% to 46.7%); Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.97 (95%CI 0.9 to 1.06); RD -1.8% (95%CI -6% to 3.6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:**
Sadeghi et al;[335] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 14 days and 33 assigned to standard of care	Median age 58 ± 13, male 20.21%, hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%, coronary heart disease 15.1%, cancer 4.5%, obesity 25.7%	Corticosteroids 30.2%, lopinavir-ritonavir 48.4%, antibiotics 89.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation is probably inappropriate.	
Yakoot et al;[336] preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %,	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection,	

	400/60 mg once a day for 10 days and 45 assigned to standard of care	asthma 1%, coronary heart disease 8%		and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Very low certainty ⊕◯◯◯
Roozbeh et al;[337] 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;[239] 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;[338] Mobarak et al; Preprint; 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 ± 54, male 54%, hypertension 34%, diabetes 27.6%, COPD 2.1%, asthma 4.8%, CHD 9.1%	Corticosteroids 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;[339] Preprint;	Patients with severe to critical COVID-19	Mean age 57.2 ±, male 49.1%, hypertension	NR	High for mortality and mechanical ventilation;	

2021	infection. 27 assigned to sofosbuvir 400 mg a day and 30 assigned to SOC	21%, diabetes 29.8%, COPD 7%, CHD 19.3%, CKD 1.7%, obesity 1.7%		High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Yadollahzadeh et al;[242] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100 mg twice a day for 7 days	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%, immunosuppression 3.6%, cancer 10.7%	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khalili et al;[340] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 42 assigned to sofosbuvir/ledipasvir 400/90 mg a day for 10 days and 40 assigned to SOC	Median age 62.2 ± 23.1, hypertension 45.1%, diabetes 45.1%, COPD 4.9%, CHD 31.7%, cancer 3.6%,	Corticosteroids 8.5%, hydroxychloroquine 10.9%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Elgohary et al;[341] preprint; 2021	Patients with moderate COVID-19 infection. 125 assigned to sofosbuvir/ledipasvir 400/90 mg once a day for 15 days and 125	Mean age 43 ±, male 0.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	assigned to SOC			study. Concealment of allocation is probably inappropriate.	
SOVECOD trial;[342] Sayad et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to sofosbuvir/velpatasvir 400/100 mg once a day for 10 days and 40 assigned to SOC	Mean age 54.1 ± 17.8, male 55%, hypertension 30%, diabetes 20%, COPD 10%, CHD 17.5%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
El-Bendari et al;[343] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 96 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 14 days and 78 assigned to SOC	Mean age 53 ± 15, male 54.6%, hypertension 21.3%, diabetes 37.3%, asthma 1.7%, CHD 10.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abbass et al;[344] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 80 assigned to sofosbuvir/daclatasvir 400/60 a day or sofosbuvir/ravidasvir 400/200mg 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%).	

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;[345] Gupta et al; preprint; 2021	Patients with recent onset mild to moderate COVID-19 infection, with risk factors for severity progression. 291 assigned to sotrovimab 500 mg once and 292 assigned to SOC	Median age 53 ±, male 46%, diabetes 23%, COPD 4%, asthma 16%, CKD 0.7%, obesity 63%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Stopped early for benefit.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.14 (95%CI 0.04 to 0.48); RD -6.3% (95%CI -7.1% to -3.8%); Moderate certainty ⊕⊕⊕◯

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;[334] preprint; 2021	Patients with moderate to severe COVID-19 infection. 50 assigned to spironolactone 100 mg a day and 87 assigned to SOC	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD 6.4%, cancer 5.9%, obesity 18.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

Statins Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
RESIST trial;[36] 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:** 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

Stem-cell nebulization Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
SENTAD-COVID trial;[346] Carmenate et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 69 assigned to stem-cell nebulization twice, 24 h apart, and 70 assigned to SOC	Mean age 45.1 ± 10.4, male 46.5%, hypertension 26.6%, diabetes 22.3%, COPD %, asthma 10.7%, CHD 9.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Steroids (corticosteroids)

Corticosteroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Corticosteroids may not significantly increase the risk of severe adverse events. Higher doses (i.e., dexamethasone 12 mg a day) may be 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;[347] Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone 40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	Mean age 69.5 ± 11.5, male 61.9%, hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%, cerebrovascular disease 12.7%	Hydroxychloroquine 96.8%, lopinavir-ritonavir 84.1%, azithromycin 92%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.90 (95%CI 0.80 to 1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.27 (95%CI 0.98 to 1.65); RD 16.4% (95%CI -1.2% to 39.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 0.89
Metcovid trial;[348] Prado Jeronimo et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 194 assigned to methylprednisolone 0.5 mg/kg twice a day for 5 days and 199 assigned to standard of care	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease 0.5%, asthma 2.5%, coronary heart disease 6.9%, alcohol use disorder 27%, liver disease 5.5%	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
RECOVERY - Dexamethasone trial;[349] 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	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	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	

	standard of care	2%, any comorbidities 56%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	(95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information
DEXA-COVID19 trial;[350] Villar et al; unpublished; 2020	Patients with severe to critical COVID-19. Seven assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day for 5 days and 12 assigned to standard of care	NR	NR	Low for mortality and invasive mechanical ventilation Notes: RoB judgment from published SR.	
CoDEX trial;[351] Tomazini et al; peer-reviewed; 2020	Patients with critical COVID-19. 151 assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day for 5 days and 148 assigned to standard of care	Mean age 61.4 ± 14.4, male 62.5%, hypertension 66.2%, diabetes 42.1%, coronary heart disease 7.7%, chronic kidney disease 5.3%, obesity 27%	hydroxychloroquine 21.4%, azithromycin 71.2%, ATB 87%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
REMAP-CAP trial;[352] 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;[351] Petersen et al; Unpublished; 2020	Patients with severe to critical COVID-19. 15 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;[353] 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;[351] 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 standard of care	NR	NR	Low for mortality and invasive mechanical ventilation Notes: Risk of bias judgment from published SR.	
Farahani et al;[354] 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;[355] 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;[356] 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;[357] 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.	
Rashad et al;[358] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 75 assigned to dexamethasone 4 mg/kg a day for 3 days followed by 8 mg	Mean age 62, male 56.9%, hypertension 47.7%, diabetes 28.4%, COPD 1.8%, asthma 2.7%, CHD 12.8%, CKD 8.2%, cancer 0.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	a day for 10 days and 74 assigned to TCZ			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.	
Ranjbar et al;[359] Preprint; 2020	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 to dexamethasone 6 mg a day for 10 days	Mean age 58.7 ± 17.4, male 56.9%, hypertension 45.3%, diabetes 32.5%, CHD 30.2%, CKD 2.3%,	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Unbalanced prognostic factors (age and gender).	**Mortality:** RR 0.75 (95%CI 0.50 to 1.13); RD -4% (95%CI -8% to 2.1%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.85 (95%CI 0.61 to 1.19); RD -1.5% (95%CI -4% to 1.9%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
COVID STEROID 2 trial;[360] 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	

Steroids (inhaled corticosteroids)

Inhaled corticosteroids probably improve symptom resolution and may decrease 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					
STOIC trial;[361] Ramakrishnan et al; peer reviewed ; 2020	Patients with mild to moderate COVID-19. 71 assigned to budesonide (inh) 800 µg twice a day and 69 assigned to SOC	Mean age 45 ± 56, male 42.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.16 (95%CI 1.08 to 1.24); RD 9.7% (95%CI 4.8% to 14.5%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Hospitalization:** RR 0.82 (95%CI 0.62 to 1.08); RD -1.3% (95%CI -2.8% to 0.6%); Low certainty ⊕⊕◯◯ **Adverse events:** No information
PRINCIPLE trial;[362] Yu et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 787 assigned to budesonide (inh) 800µg twice daily for 14 days and 1069 assigned to SOC	Mean age 64.2 ± 7.6, male 48%, hypertension 44.3%, diabetes 21.4%, COPD 12.6%, CHD 15.8%, cerebrovascular disease 5.6%	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study. Significant loss to follow-up.	
Song et al;[363] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 35 assigned to inhaled ciclesonide 320 µg twice per day for 14 days and 26 assigned to SOC	Median age 53 ± 26, male 47%, hypertension 27.8%, diabetes 14.7%, cerebrovascular disease 3.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study. Concealment of allocation probably inappropriate.	
ALV-020-001 trial;[364] Clemency et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 197 assigned to inhaled ciclesonide 640 µg a day for 30 days and 203 assigned to SOC	Mean age 43.3 ± 16.9, male 44.8%, hypertension 22.3%, diabetes 7.5%, asthma 6.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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;[365] Gonzalez Ochoa et al; preprint; 2020	Patients with mild (early within 3 days of onset) COVID-19. 124 assigned to sulodexide 500 RLU twice a day for 3 weeks and 119 assigned to standard of care	Median age 52 ± 10.6, male 47.4%, hypertension 34.2%, diabetes 22.2%, COPD 23%, coronary heart disease 21%,	Corticosteroids 62.5%, hydroxychloroquine 33.7%, ivermectin 43%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: Very low certainty ⨁◯◯◯

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;[366] Preprint; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to TD-0903 1-10 mg once a day for 7 days and 6 assigned to SOC	Mean age 57.1 ± 12.3, male 68%, hypertension 68%, diabetes 40%	Corticosteroids 92%, remdesivir 12%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Tenofovir + emtricitabine Uncertainty in potential benefits and harms. Further research is needed					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
AR0-CORONA trial;[367] Parientti et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 30 assigned to tenofovir + emtricitabine 245/200 mg twice a day on day one followed by 245/200 mg a day for 7 days and 30 assigned to SOC	Mean age 42 ± 15, male 43%, hypertension 5%, diabetes 3.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯

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;[368] 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.	**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

<table>
<tr><th colspan="6">Tocilizumab
Tocilizumab reduces mortality and mechanical ventilation requirements without increasing severe adverse events.</th></tr>
<tr><th>Study; publication status</th><th>Patients and interventions analyzed</th><th>Comorbidities</th><th>Additional interventions</th><th>Risk of bias and study limitations</th><th>Interventions effects vs standard of care and GRADE certainty of the evidence</th></tr>
<tr><td colspan="6">RCT</td></tr>
<tr><td>COVACTA trial; Rosas et al;[369] peer-reviewed; 2020</td><td>Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned to standard of care</td><td>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%</td><td>Corticosteroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%</td><td>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events</td><td rowspan="3">Mortality: RR 0.85 (95%CI 0.79 to 93); RD -2.4% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕

Invasive mechanical ventilation: RR 0.83 (95%CI 0.78 to 0.90); RD -2.9% (95%CI -3.8% to -1.7%); High certainty ⊕⊕⊕⊕

Symptom resolution or improvement: RR 1.1 (95%CI 1.02 to 1.2); RD 6.1% (95%CI 1.2% to 12.1%); Low certainty ⊕⊕◯◯

Symptomatic infection (prophylaxis studies): No information

Adverse events: RR 0.94 (95%CI 0.85 to 1.05); RD -0.6% (95%CI -1.5% to 0.5%); Moderate certainty ⊕⊕⊕◯</td></tr>
<tr><td>Wang et al;[370] preprint; 2020</td><td>Patients with moderate to severe COVID-19. 34 assigned to tocilizumab 400 mg once or twice and 31 assigned to standard of care</td><td>Median age 63 ± 16, male 50.8%, hypertension 30.8%, diabetes 15.4%</td><td>NR</td><td>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.</td></tr>
<tr><td>Zhao et al;[124] peer-reviewed; 2020</td><td>Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir</td><td>Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%</td><td>NR</td><td>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.</td></tr>
</table>

	plus tocilizumab				**Hospitalization:** No information
RCT-TCZ-COVID-19 trial;[371] Salvarani et al; peer-reviewed; 2020	Patients with severe COVID-19. 60 assigned to tocilizumab 8 mg/kg twice on day 1 and 66 assigned to standard of care	Median age 60 ± 19, male 61.1%, hypertension 44.4%, diabetes 15.1%, COPD 3.2%, obesity 32.2%	Hydroxychloroquine 91.3%, azithromycin 20.6%, antivirals 41.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BACC Bay Tocilizumab Trial trial;[372] 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;[373] Hermine et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 63 assigned to tocilizumab 8 mg/kg once followed by an optional 400 mg dose on day 3 and 67 assigned to standard of care	Median age 63.6 ± 16.2, male 67.7%, diabetes 33.6%, COPD 4.7%, asthma 6.3%, coronary heart disease 31.2%, chronic kidney disease 14%, cancer 7%,	Corticosteroids 43%, remdesivir 0.7%, hydroxychloroquine 6.2%, Lopinavir-ritonavir 3%, azithromycin 15.4%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
EMPACTA trial;[374] Salama et al; preprint; 2020	Patients with moderate to severe COVID-19. 249 assigned to tocilizumab 8 mg/kg	Mean age 55.9 ± 14.4, male 59.2%, hypertension 48.3%, diabetes 40.6%, COPD 4.5%, asthma 11.4%,	Corticosteroids 59.4%, remdesivir 54.6%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

	once and 128 assigned to standard of care	coronary heart disease 1.9%, cerebrovascular disease 3.4%, obesity 24.4%			
REMAP-CAP - tocilizumab trial;[328] 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%, cancer %, obesity %	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;[375] 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;[376] 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%, tocilizumab %, azithromycin 9%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have	

				introduced bias to symptoms and adverse events outcomes results.	
PreToVid trial;[377] Rutgers et al; preprint; 2021	Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice and 180 assigned to SOC	Median age 66.5 ± 16.5, male 67%, comorbidities 74.3%	Corticosteroids 88.4%, remdesivir 18.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Talaschian et al;[378] preprint; 2021	Patients with severe COVID-19 infection. 17 assigned to TCZ 8 mg/kg once or twice and 19 assigned to SOC	Mean age 61.7 ± 14.2, male 52.7%, hypertension 50%, diabetes 36.1%, COPD 8.3%, asthma %, CHD 44.4%, CKD 2.8%, cancer 0%	Corticosteroids 33.3%, hydroxychloroquine 63.9%, lopinavir-ritonavir 8.3%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Hamed et al;[379] peer reviewed; 2021	Patients with severe COVID-19 infection. 23 assigned to TCZ 400 mg once and 26 assigned to SOC	Mean age 48 ±, male 85.5%, hypertension 36.8%	Corticosteroids 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
ARCHITECTS trial;[331] other; 2021	Patients with severe to critical COVID-19 infection. 10 assigned	Median age 61 ±	Corticosteroids 95.2%, remdesivir 90.4%, convalescent plasma	Low for mortality and mechanical ventilation; low for symptom	

	to TCZ 8 mg/kg once or twice and 11 assigned to SOC		100%	resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
CORIMUNO-TOCI ICU trial;[331] other; 2021	Patients with severe to critical COVID-19 infection. 49 assigned to TCZ 8 mg/kg once or twice and 43 assigned to SOC	Median age 46	Corticosteroids 13%, remdesivir 0%, 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.	
COV-AID trial; et al;[331] other; 2021	Patients with severe to critical COVID-19 infection. 81 assigned to TCZ 8 mg/kg once and 72 assigned to SOC	Median age 63	Corticosteroids 52.6%, remdesivir 5.8%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVIDOSE-2 trial; et al;[331] other; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to TCZ 40-120 mg once and 8 assigned to SOC	Median age 65	Corticosteroids 30%, remdesivir 75%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVIDSTORM trial;[331] other; 2021	Patients with severe to critical COVID-19 infection. 26 assigned	Median age 66	Corticosteroids 77%, remdesivir 0%, convalescent plasma	Low for mortality and mechanical ventilation; low for symptom	

	to TCZ 8 mg/kg once and 13 assigned to SOC		0%	resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVITOZ-01 trial; et al;[331] 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;[331] 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;[331] other; 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 60	Corticosteroids 86%, remdesivir 19.2%, 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.	

ImmCoVA trial;[331] 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;[331] other; 2021	Patients with moderate to severe COVID-19 infection. 136 assigned to TCZ 400 to 600 mg once and 134 assigned to SOC	Median age 53	Corticosteroids 35%, remdesivir 0.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVINTOC trial; et al;[380] 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;[381] Hermine et al; preprint; 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.	
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;[382] 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.1 (95%CI 0.98 to 1.23); RD 6.1% (95%CI 1.2% to 13.9%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⊕⊕◯◯

					Hospitalization: No information

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;[383] 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 assigned to standard of care	Median age 58 ± 17, male 50%, hypertension 28.8%, diabetes 15.4%, chronic lung disease 5.8%, coronary heart disease 15.4%, cerebrovascular disease 7.7%	Corticosteroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%, umifenovir 61.5%, ribavirin 28.9%,	Low for mortality and invasive 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

Umifenovir Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al;[114] preprint; 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 NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
ELACOI trial;[235] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, IVIG 6.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Nojomi et al;[384] preprint; 2020	Patients with severe COVID-19. 50 assigned to umifenovir 100 mg two twice 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	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse	

	and 50 assigned to lopinavir-ritonavir 400 mg a day for 7 to 14 days	kidney disease 2%		events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Yethindra et al;[385] 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;[386] 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;[387] Darazam et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 51 assigned to umifenovir 600 mg a day for 10 days and 50 assigned to SOC	Mean age 61.2 ± 15.8, male 56.4%, hypertension 46.4%, diabetes 31.6%, COPD 10%, asthma 6.1%, CHD 11.2%, CKD 7.1%, cancer 1%	Corticosteroids 3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have	

				introduced bias to symptoms and adverse events outcomes results.	
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 and GRADE certainty of the evidence**
RCT					
Zhang et al;[388] 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:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom resolution or improvement:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕○○○
Kumari et al;[389] Peer reviewed; 2020	Patients with severe COVID-19. 75 assigned to Vit C 50 mg/kg a day and 75 assigned to SOC	Mean age 52.5 ± 11.5	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Jamali Moghadam Siahkali et al;[390] Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5 g a day for 5 days and 30	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,	

	assigned to SOC			and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVIDAtoZ - Vit C trial;[391] 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.	

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					
COVIDIOL trial; Entrenas Castillo et al;[392] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to vitamin D 0.532 once followed by 0.266 twice and 26 assigned to standard of care	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, coronary heart disease 3.9%, immunosuppression 9.2%, cancer %, obesity %	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information

SHADE trial;[393] 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.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Murai et al;[394] peer-reviewed; 2020	Patients with severe COVID-19. 117 assigned to vitamin D 200,000 IU once and 120 assigned to standard of care	Mean age 56.3 ± 14.6, male 56.3%, hypertension 52.5%, diabetes 35%, COPD %, asthma 6.3%, coronary heart disease 13.3%, chronic kidney disease 1%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Lakkireddy et al;[395] preprint; 2021	Patients with mild to moderate with low plasmatic vitamin D COVID-19 infection. 44 assigned to Vit 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;[396] peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 36 assigned to Vit D 5000 IU for 14 days and 33 assigned to Vit D 1000 IU for 14 days	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 Notes: Non-blinded study which might have	

				introduced bias to symptoms and adverse events outcomes results.	

XAV-19 (swine glyco-humanized polyclonal antibodies)
Uncertainty in potential benefits and harms. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
POLYCOR trial;[397] Gaborit et al; preprint; 2021	Patients with severe COVID-19 infection. 12 assigned to XAV-19 0.5 to 2 mg/kg on days 1 and 5 and 5 assigned to SOC	Mean age 71 ± 24, male 64.7%, hypertension 47.1%, diabetes 11.8%, COPD %, asthma 17.6%, CHD 29.4%, CKD 5.9%, cancer 11.8%, obesity 17.6%	Corticosteroids 100%, remdesivir 47.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

<table>
<tr><th colspan="6">Zinc
Uncertainty in potential benefits and harms. Further research is needed.</th></tr>
<tr><th>Study; publication status</th><th>Patients and interventions analyzed</th><th>Comorbidities</th><th>Additional interventions</th><th>Risk of bias and study limitations</th><th>Interventions effects vs standard of care and GRADE certainty of the evidence</th></tr>
<tr><td colspan="6">RCT</td></tr>
<tr><td>Hassan et al;[398] preprint; 2020</td><td>Patients with mild to critical COVID-19. 49 assigned to zinc 220 mg twice a day and 56 assigned to standard of care</td><td>Mean age 45.9 ± 17.5, male 58.2%, hypertension 10.4%, diabetes 11.2%, coronary heart disease 3%,</td><td>NR</td><td>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events

Notes: Concealment of allocation probably inappropriate.</td><td rowspan="3">Mortality: Very low certainty ⊕◯◯◯

Invasive mechanical ventilation: Very low certainty ⊕◯◯◯

Symptom resolution or improvement: Very low certainty ⊕◯◯◯

Symptomatic infection (prophylaxis studies): Very low certainty ⊕◯◯◯

Adverse events: No information

Hospitalization: Very low certainty ⊕◯◯◯</td></tr>
<tr><td>Abd-Elsalam et al;[399] peer-reviewed; 2020</td><td>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</td><td>Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%</td><td>Hydroxychloroquine 100%,</td><td>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events

Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</td></tr>
<tr><td>Abdelmaksoud et al;[400] Peer reviewed; 2020</td><td>Patients with mild to critical COVID-19. 49 assigned to Zinc 220 mg twice a day and 56 assigned to SOC</td><td>NR</td><td>NR</td><td>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events

Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</td></tr>
</table>

COVIDAtoZ -Zinc trial;[391] Thomas et al; ; 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;[401] 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;[165] peer reviewed; 2021	Patients exposed to COVID-19 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.	

α-lipoic acid Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zhong et al;[402] 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 **Hospitalization:** No information

Appendix 1. Summary of findings tables

Summary of findings Table 1.

Population: Patients with severe COVID-19 disease
Intervention: Corticosteroids
Comparator: Standard of care

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		Standard of care	Corticosteroids		
Mortality 28 days	Relative risk: 0.9 (CI 95% 0.8 - 1.02) Based on data from 8000 patients in 12 studies	**160** per 1000	**144** per 1000	**Moderate** Due to serious imprecision[1]	Corticosteroids probably decreases mortality
		Difference: **16 fewer per 1000** (CI 95% 32 fewer - 3 more)			
Mechanical ventilation 28 days	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 5942 patients in 6 studies Follow-up 28	**172** per 1000	**150** per 1000	**Moderate** Due to serious imprecision[2]	Corticosteroids probably decreases mechanical ventilation
		Difference: **22 fewer per 1000** (CI 95% 48 fewer - 9 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.27 (CI 95% 0.98 - 1.65) Based on data from 646 patients in 5 studies	**606** per 1000	**770** per 1000	**Moderate** Due to serious risk of bias[3]	Corticosteroids probably increases symptom resolution or improvement
		Difference: **164 more per 1000** (CI 95% 12 fewer - 394 more)			
Severe adverse events 28 days	Relative risk: 0.89 (CI 95% 0.68 - 1.17) Based on data from 833 patients in 6 studies	**102** per 1000	**91** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Corticosteroids may have little or no difference on severe adverse events
		Difference: **11 fewer per 1000** (CI 95% 33 fewer - 17 more)			
Mortality (high vs standard dose) 28 days	Relative risk: 0.75 (CI 95% 0.5 - 1.13)	**160** per 1000	**120** per 1000	**Low** Due to very serious imprecision[5]	High dose of corticosteroids (i.e., dexamethasone 12 mg a

	Based on data from 1068 patients in 2 studies	Difference: **40 fewer per 1000** (CI 95% 80 fewer - 21 more)			day) may decrease mortality in comparison to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day)
Severe adverse events (high vs. standard dose) 28 days	Relative risk: 0.85 (CI 95% 0.61 - 1.19) Based on data from 833 patients in 6 studies	**102** per 1000	**87** per 1000	**Low** Due to very serious imprecision[6]	High dose of corticosteroids (i.e., dexamethasone 12 mg a day) may not increase severe adverse events in comparison to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day)
		Difference: **15 fewer per 1000** (CI 95% 40 fewer - 19 more)			

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: Very serious.** 95%CI includes mortality increase;
6. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals.

Summary of findings Table 2.

Population: Patients with COVID-19 infection
Intervention: Remdesivir
Comparator: Standard of care

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	Remdesivir		
Mortality 28 days	Relative risk: 0.94 (CI 95% 0.82 - 1.08) Based on data from 7330 patients in 4 studies Follow-up median 28 days	**160** per 1000	**150** per 1000	**Low** Due to serious imprecision, Due to serious risk of bias[1]	Remdesivir may decrease mortality slightly
		Difference: **10 fewer per 1000** (CI 95% 29 fewer - 13 more)			
Mechanical ventilation 28 days	Relative risk: 0.65 (CI 95% 0.39 - 1.11) Based on data from 6551 patients in 4 studies Follow-up median 28 days	**173** per 1000	**112** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Remdesivir may decrease mechanical ventilation requirements
		Difference: **61 fewer per 1000** (CI 95% 106 fewer - 19 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.17 (CI 95% 1.03 - 1.33) Based on data from 1873 patients in 3 studies Follow-up 28 days	**606** per 1000	**709** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Remdesivir may improve symptom resolution or improvement
		Difference: **103 more per 1000** (CI 95% 18 more - 200 more)			
Severe adverse events	Relative risk: 0.8 (CI 95% 0.48 - 1.33) Based on data from 1869 patients in 3 studies	**102** per 1000	**82** 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
		Difference: **20 fewer per 1000** (CI 95% 53 fewer - 34 more)			

1. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **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: Serious.** 95% included significant mechanical ventilation requirement reduction and absence of 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; **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.

Summary of findings Table 3.

Population: Patients with COVID-19 infection or exposed to COVID-19
Intervention: Hydroxychloroquine (HCQ)
Comparator: Standard of care

Outcome Time frame	Study results and measurements	Absolute effect estimates SOC	Absolute effect estimates HCQ	Certainty of the evidence (quality of evidence)	Plain language summary
Mortality 15 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 9104 patients in 13 studies Follow-up median 15 days	**160** per 1000	**171** per 1000	**Moderate** Due to serious risk of bias[1]	HCQ probably increases mortality
		Difference: **11 more per 1000** (CI 95% 3 fewer - 27 more)			
Mechanical ventilation 15 days	Relative risk: 1.07 (CI 95% 0.93 - 1.24) Based on data from 7297 patients in 9 studies Follow-up median 15 days	**173** per 1000	**185** per 1000	**Moderate** Due to serious risk of bias[2]	HCQ probably has little or no difference on mechanical ventilation
		Difference: **12 more per 1000** (CI 95% 12 fewer - 42 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.02 (CI 95% 0.94 - 1.1) Based on data from 6539 patients in 9 studies Follow-up 28 days	**606** per 1000	**618** per 1000	**Moderate** Due to serious inconsistency[3]	HCQ probably has little or no difference on symptom resolution or improvement
		Difference: **12 more per 1000** (CI 95% 36 fewer - 61 more)			
COVID-19 infection (in exposed individuals) (Low risk of bias studies)	Relative risk: 0.85 (CI 95% 0.72 - 1.01) Based on data from 8320 patients in 9 studies	**174** per 1000	**148** per 1000	**Low** Due to serious imprecision, Due to serious risk of bias[4]	HCQ may reduce covid-19 infections (in exposed individuals)
		Difference: **26 fewer per 1000** (CI 95% 49 fewer - 2 more)			
Hospitalizations (in patients with non-severe disease)	Relative risk: 0.91 (CI 95% 0.56 - 1.47) Based on data from 2789 patients in 7 studies	**74** per 1000	**67** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether hcq increases or decreases hospitalizations
		Difference: **7 fewer per 1000** (CI 95% 33 fewer - 35 more)			
Severe adverse events	Relative risk: 0.94 (CI 95% 0.66 - 1.34) Based on data from 8449 patients in 17 studies	**102** per 1000	**96** 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
		Difference: **6 fewer per 1000** (CI 95% 35 fewer - 35 more)			

1. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
2. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
3. **Risk of bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious.** I2 82%; **Imprecision: no serious.** Secondary to inconsistency;
4. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** 95%CI includes no infection reduction;

5. **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: very serious.** 95%CI includes significant benefits and harms;
6. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients.

Summary of findings Table 4.

Population: Patients with COVID-19 infection
Intervention: Lopinavir-ritonavir (LPV)
Comparator: Standard of care

<table>
<tr><th rowspan="2">Outcome
Time frame</th><th rowspan="2">Study results and measurements</th><th colspan="2">Absolute effect estimates</th><th rowspan="2">Certainty of the evidence
(quality of evidence)</th><th rowspan="2">Plain text summary</th></tr>
<tr><th>SOC</th><th>LPV</th></tr>
<tr><td rowspan="2">Mortality
28 days</td><td rowspan="2">Relative risk: 1.01
(CI 95% 0.92 - 1.11)
Based on data from 8053 patients in 4 studies
Follow-up median 28 days</td><td>160
per 1000</td><td>162
per 1000</td><td rowspan="2">Moderate
Due to serious imprecision[1]</td><td rowspan="2">LPV probably has little or no difference on mortality</td></tr>
<tr><td colspan="2">Difference: 2 more per 1000
(CI 95% 13 fewer - 18 more)</td></tr>
<tr><td rowspan="2">Mechanical ventilation
28 days</td><td rowspan="2">Relative risk: 1.07
(CI 95% 0.98 - 1.17)
Based on data from 7622 patients in 4 studies
Follow-up median 28 days</td><td>173
per 1000</td><td>185
per 1000</td><td rowspan="2">High</td><td rowspan="2">LPV does not reduce mechanical ventilation</td></tr>
<tr><td colspan="2">Difference: 12 more per 1000
(CI 95% 3 fewer - 29 more)</td></tr>
<tr><td rowspan="2">Symptom resolution or improvement
28 days</td><td rowspan="2">Relative risk: 1.03
(CI 95% 0.92 - 1.15)
Based on data from 5239 patients in 2 studies
Follow-up 28 days</td><td>606
per 1000</td><td>624
per 1000</td><td rowspan="2">Moderate
Due to serious risk of bias[2]</td><td rowspan="2">LPV probably has little or no difference on symptom resolution or improvement</td></tr>
<tr><td colspan="2">Difference: 18 more per 1000
(CI 95% 48 fewer - 91 more)</td></tr>
<tr><td rowspan="2">Symptomatic infection (exposed individuals)</td><td rowspan="2">Relative risk: 1.4
(CI 95% 0.78 - 2.54)
Based on data from 318 patients in 1 study</td><td>174
per 1000</td><td>244
per 1000</td><td rowspan="2">Very low
Due to serious risk of bias, Due to very serious imprecision[3]</td><td rowspan="2">We are uncertain whether LPV increases or decreases symptomatic infection in exposed individuals</td></tr>
<tr><td colspan="2">Difference: 70 more per 1000
(CI 95% 38 fewer - 268 more)</td></tr>
<tr><td rowspan="2">Severe adverse events</td><td rowspan="2">Relative risk: 0.6
(CI 95% 0.37 - 0.98)
Based on data from 199 patients in 1 study</td><td>102
per 1000</td><td>61
per 1000</td><td rowspan="2">Low
Due to serious risk of bias, Due to serious imprecision[4]</td><td rowspan="2">LPV may have little or no difference on severe adverse events</td></tr>
<tr><td colspan="2">Difference: 41 fewer per 1000
(CI 95% 64 fewer - 2 fewer)</td></tr>
</table>

Hospitalization	Relative risk: 1.24 (CI 95% 0.6 - 2.56) Based on data from 471 patients in 1 study	**74** per 1000	**92** per 1000	**Very low** Due to very serious imprecision[5]	We are uncertain whether LPV increases or decreases hospitalization
		Difference: **18 more per 1000** (CI 95% 30 fewer - 115 more)			

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.

Population: Patients with COVID-19 infection
Intervention: Convalescent plasma
Comparator: Standard of care

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates** SOC	CP	**Certainty of the evidence** (quality of evidence)	**Plain language summary**
Mortality (Low RoB studies)[1] 28 days	Relative risk: 1.0 (CI 95% 0.94 - 1.06) Based on data from 15732 patients in 9 studies Follow-up median 28 days	**160** per 1000	**160** per 1000	**High** [2]	Convalescent plasma has little or no difference on mortality
		Difference: **0 fewer per 1000** (CI 95% 10 fewer - 10 more)			
Mechanical ventilation (Low RoB studies) 28 days	Relative risk: 1.05 (CI 95% 0.94 - 1.17) Based on data from 10297 patients in 7 studies Follow-up median 28 days	**173** per 1000	**182** per 1000	**High**	Convalescent plasma has little or no difference on mechanical ventilation
		Difference: **9 more per 1000** (CI 95% 10 fewer - 29 more)			
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.94 - 1.05) Based on data from 13321 patients in 9 studies Follow-up 28 days	**606** per 1000	**600** per 1000	**Moderate** Due to serious inconsistency[3]	Cp probably has little or no difference on symptom resolution or improvement
		Difference: **6 fewer per 1000** (CI 95% 36 fewer - 30 more)			
Hospitalizations	Relative risk: 0.9 (CI 95% 0.64 - 1.26) Based on data from 511 patients in 1 study	**74** per 1000	**67** per 1000	**Low** Due to very serious imprecision[4]	CP may not significantly reduce hospitalizations
		Difference: **7 fewer per 1000** (CI 95% 27 fewer - 19 more)			
Severe adverse events (Low RoB studies)	Relative risk: 1.38 (CI 95% 1.07 - 1.78) Based on data from 3234 patients in 3 studies	**102** per 1000	**141** per 1000	**Moderate** Due to serious imprecision[5]	Convalescent plasma probably increases severe adverse events
		Difference: **39 more per 1000** (CI 95% 7 more - 80 more)			

1. Low risk of bias studies;
2. **Inconsistency: no serious.** Point estimates vary widely;
3. **Inconsistency: serious.** Point estimates vary widely;
4. **Imprecision: very serious.** Wide confidence intervals;
5. **Imprecision: serious.** Wide confidence intervals.

Summary of findings Table 6.

Population: Patients with COVID-19 infection
Intervention: Tocilizumab (TCZ)
Comparator: Standard of care

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates** SOC	TCZ	**Certainty of the evidence** (quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 0.85 (CI 95% 0.79 - 0.93) Based on data from 8455 patients in 20 studies Follow-up median 28 days	**160** per 1000	**136** per 1000	**High**	TCZ decreases mortality
		Difference: **24 fewer per 1000** (CI 95% 34 fewer - 11 fewer)			
Mechanical ventilation 28 days	Relative risk: 0.83 (CI 95% 0.78 - 0.9) Based on data from 7072 patients in 20 studies Follow-up median 28 days	**173** per 1000	**144** per 1000	**High** [1]	TCZ decreases mechanical ventilation
		Difference: **29 fewer per 1000** (CI 95% 38 fewer - 17 fewer)			
Symptom resolution or improvement 28 days	Relative risk: 1.1 (CI 95% 1.02 - 1.2) Based on data from 5456 patients in 6 studies Follow-up 28 days	**606** per 1000	**667** per 1000	**Low** Due to serious imprecision, Due to serious risk of bias[2]	TCZ may increase symptom resolution or improvement
		Difference: **61 more per 1000** (CI 95% 12 more - 121 more)			
Severe adverse events	Relative risk: 0.94 (CI 95% 0.85 - 1.05) Based on data from 4254 patients in 12 studies	**102** per 1000	**96** per 1000	**Moderate** Due to serious risk of bias[3]	Tcz probably has little or no difference on severe adverse events
		Difference: **6 fewer per 1000** (CI 95% 15 fewer - 5 more)			

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.

Population: Patients with COVID-19 infection
Intervention: Anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 m/kg twice a day)
Comparator: Anticoagulants in prophylactic dose (i.e., enoxaparin 40 mg a day)

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates** SOC	ACO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 0.97 (CI 95% 0.79 - 1.19) Based on data from 5152 patients in 7 studies	**160** per 1000	**155** per 1000	**Moderate** Due to serious imprecision[1]	Anticoagulantes in intermediate or full dose probably has little or no difference on mortality in comparison with prophylactic dose
		Difference: **5 fewer per 1000** (CI 95% 34 fewer - 30 more)			
Venous thromboembolic events (intermediate dose)	Relative risk: 1.02 (CI 95% 0.53 - 1.96) Based on data from 737 patients in 2 studies	**70** per 1000	**71** per 1000	**Low** Due to very serious imprecision[2]	Anticoagulantes in intermediate dose may slightly reduce venous thromboembolic events
		Difference: **1 more per 1000** (CI 95% 33 fewer - 67 more)			
Venous thromboembolic events (full dose)	Relative risk: 0.59 (CI 95% 0.44 - 0.79) Based on data from 4419 patients in 4 studies	**70** per 1000	**41** per 1000	**Moderate** Due to serious imprecision[3]	Anticoagulantes in intermediate or full dose probably decreases venous thromboembolic events (full dose)
		Difference: **29 fewer per 1000** (CI 95% 39 fewer - 15 fewer)			
Major bleeding	Relative risk: 1.72 (CI 95% 1.14 - 2.61) Based on data from 5153 patients in 6 studies	**19** per 1000	**33** per 1000	**Moderate** Due to serious imprecision[4]	Anticoagulantes in intermediate or full dose probably increases major bleeding
		Difference: **14 more per 1000** (CI 95% 3 more - 31 more)			

1. **Imprecision: Serious.** 95%CI includes small benefits and harms;
2. **Imprecision: Very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: Serious.** OIS not met;
4. **Imprecision: Serious.** 95%CI includes harms and absence of harms.

Summary of findings Table 8.

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.

Population: Patients with COVID-19 infection
Intervention: Interferon beta-1a (IFN-B-1a)
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	IFN		
Mortality 28 days	Relative risk: 1.04 (CI 95% 0.88 - 1.23) Based on data from 4242 patients in 3 studies Follow-up median 28 days	**160** per 1000	**166** per 1000	**Moderate** Due to serious imprecision[1]	IFN-B-1a probably has little or no difference on mortality
		Difference: **6 more per 1000** (CI 95% 19 fewer - 37 more)			
Mechanical ventilation 28 days	Relative risk: 0.98 (CI 95% 0.83 - 1.16) Based on data from 3981 patients in 3 studies Follow-up 28 days	**173** per 1000	**170** per 1000	**Moderate** Due to serious imprecision[2]	IFN-B-1a probably has little or no difference on mechanical ventilation
		Difference: **3 fewer per 1000** (CI 95% 29 fewer - 28 more)			
Symptom resolution or improvement 28 days	Hazard Ratio: 1.1 (CI 95% 0.64 - 1.87) Based on data from 121 patients in 2 studies Follow-up 28 days	**606** per 1000	**641** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether IFN-B-1a increases or decreases symptom resolution or improvement
		Difference: **35 more per 1000** (CI 95% 157 fewer - 219 more)			
Symptom resolution or improvement (inhaled)[4] 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[5]	IFN-B-1a (inhaled) may increase symptom resolution or improvement
		Difference: **264 more per 1000** (CI 95% 11 more - 381 more)			

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. **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, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very serious.** 95%CI includes significant benefits and absence of benefit ;
4. Nebulizations;
5. **Imprecision: Very serious.** 95%CI includes significant benefits and absence of benefits.

Summary of findings Table 10.

Population: Patients with COVID-19 infection
Intervention: Bamlanivimab +/- etesevimab
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	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
		Difference: **51 fewer per 1000** (CI 95% 133 fewer - 288 more)			
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
		Difference: **12 more per 1000** (CI 95% 6 fewer - 36 more)			
Symptomatic infection[5]	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
		Difference: **77 fewer per 1000** (CI 95% 106 fewer - 33 fewer)			
Severe adverse events	Hazard Ratio: 1.16 (CI 95% 0.76 - 1.78) Based on data from 3340 patients in 5 studies	**102** per 1000	**117** per 1000	**Low** Due to very serious imprecision[6]	Bamlanivimab may increase severe adverse events
		Difference: **15 more per 1000** (CI 95% 23 fewer - 72 more)			
Hospitalization[7]	Hazard Ratio: 0.29 (CI 95% 0.17 - 0.51) Based on data from 1487 patients in 2 studies	**74** per 1000	**22** per 1000	**Moderate** Due to serious imprecision[8]	We are uncertain whether bamlanivimab increases or decreases hospitalization
		Difference: **52 fewer per 1000** (CI 95% 61 fewer - 36 fewer)			

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. Hospitalizations in persons with mild to moderate SARS-CoV2;
8. **Imprecision: Serious.** Low number of patients.

Summary of findings Table 11.

Population: Patients with COVID-19 infection
Intervention: Favipiravir
Comparator: Standard of care

Outcome Time frame	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain language summary
		SOC	Favipiravir		
Mechanical ventilation 28 days	Relative risk: 1.16 (CI 95% 0.25 - 5.35) Based on data from 525 patients in 3 studies Follow-up median 28 days	**173** per 1000 Difference: **28 more per 1000** (CI 95% 130 fewer - 753 more)	**201** per 1000	**Low** Due to very serious imprecision[1]	Favipravir may have little or no difference on mechanical ventilation
Mortality 28 days	Relative risk: 1.16 (CI 95% 0.7 - 1.94) Based on data from 672 patients in 4 studies Follow-up median 28 days	**160** per 1000 Difference: **26 more per 1000** (CI 95% 48 fewer - 150 more)	**186** per 1000	**Low** Due to very serious imprecision[2]	Favipravir may have little or no difference on mortality
Severe adverse events[3] 30 days	Relative risk: 0.64 (CI 95% 0.29 - 1.41) Based on data from 519 patients in 3 studies Follow-up 28 days	**606** per 1000 Difference: **218 fewer per 1000** (CI 95% 430 fewer - 248 more)	**388** per 1000	**Very low** Due to very serious imprecision, Due to serious risk of bias[4]	We are uncertain whether favipravir increases or decreases severe adverse events
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.9 - 1.09) Based on data from 373 patients in 1 study Follow-up 28 days	**606** per 1000 Difference: **6 fewer per 1000** (CI 95% 61 fewer - 55 more)	**600** per 1000	**Moderate** Due to serious imprecision[5]	Favipravir probably has little or no difference on symptom resolution or improvement
Hospitalization (in patients with non-severe disease)	Relative risk: 0.75 (CI 95% 0.13 - 4.36) Based on data from 168 patients in 1 study Follow-up 28 days	**606** per 1000 Difference: **151 fewer per 1000** (CI 95% 527 fewer - 2036 more)	**455** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[6]	We are uncertain whether favipravir increases or decreases 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 significant mortality reduction and increase;
3. Nebulizations;
4. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;
5. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
6. **Risk of bias: serious.** 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.

Summary of findings Table 12.

Population: Patients with COVID-19 infection
Intervention: Ivermectin
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	Ivermectin		
Mortality (Low risk of bias studies)[1]	Relative risk: 0.96 (CI 95% 0.58 - 1.59) Based on data from 1412 patients in 6 studies	**160** per 1000	**154** per 1000	**Low** Due to very serious imprecision[2]	Ivermectin may have little or no difference in mortality
		Difference: **6 fewer per 1000** (CI 95% 67 fewer - 94 more)			
Mechanical ventilation	Relative risk: 1.05 (CI 95% 0.64 - 1.72) Based on data from 1046 patients in 6 studies	**173** per 1000	**182** per 1000	**Low** Due to very serious imprecision[3]	Ivermectin may have little or no difference on mechanical ventilation
		Difference: **9 more per 1000** (CI 95% 62 fewer - 125 more)			
Symptom resolution or improvement (Low risk of bias studies)	Relative risk: 1.02 (CI 95% 0.96 - 1.1) Based on data from 635 patients in 3 studies	**606** per 1000	**618** per 1000	**Moderate** Due to serious imprecision[4]	Ivermectin probably has little or no difference on symptom resolution or improvement
		Difference: **12 more per 1000** (CI 95% 24 fewer - 61 more)			
Symptomatic infection[5]	Relative risk: 0.22 (CI 95% 0.09 - 0.53) Based on data from 1974 patients in 4 studies	**174** per 1000	**38** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision[6]	We are uncertain whether ivermectin increases or decreases symptomatic infection
		Difference: **136 fewer per 1000** (CI 95% 158 fewer - 82 fewer)			
Severe adverse events	Relative risk: 1.04 (CI 95% 0.32 - 3.38) Based on data from 824 patients in 4 studies Follow-up 28 days	**102** per 1000	**106** per 1000	**Very low** Due to very serious imprecision, Due to very serious risk of bias[7]	We are uncertain whether ivermectin increases or decreases severe adverse events
		Difference: **4 more per 1000** (CI 95% 69 fewer - 243 more)			
	Relative risk: 0.62 (CI 95% 0.36 - 1.07)	**102** per 1000	**63** per 1000	**Low**	Ivermectin may decrease

Hospitalization (in non-severe patients)	Based on data from 1088 patients in 4 studies Follow-up 28 days	Difference: **39 fewer per 1000** (CI 95% 65 fewer - 7 more)	Due to very serious imprecision[8]	hospitalizations in non-severe patients

1. Base on low risk of bias studies;
2. **Imprecision: Very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: Very serious.** Wide confidence intervals; **Publication bias: Serious;**
4. **Imprecision: Serious.** Wide confidence intervals;
5. Symptomatic infection in persons at risk or exposed to SARS-CoV2;
6. **Risk of bias: Very 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: Serious.** Few events, optimal information size not met (n=86);
7. **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;
8. **Imprecision: Serious.** 95%CI includes significant benefits and absence of benefits; **Publication bias: Serious.**

Summary of findings Table 13.

Population: Patients with COVID-19 infection
Intervention: Baricitinib
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	**Baricitinib**		
Mortality	Relative risk: 0.63 (CI 95% 0.48 - 0.81) Based on data from 2558 patients in 2 studies	160 per 1000	101 per 1000	Moderate Due to serious risk of bias[1]	Baricitinib probably decreases mortality
		Difference: 59 fewer per 1000 (CI 95% 83 fewer - 30 fewer)			
Invasive mechanical ventilation	Relative risk: 0.66 (CI 95% 0.46 - 0.93) Based on data from 922 patients in 1 study Follow-up 30 days	173 per 1000	114 per 1000	Low Due to serious risk of bias, Due to serious imprecision[2]	Baricitinib may decrease invasive mechanical ventilation
		Difference: 59 fewer per 1000 (CI 95% 93 fewer - 12 fewer)			
Symptom resolution or improvement	Relative risk: 1.25 (CI 95% 1.11 - 1.41) Based on data from 1797 patients in 2 studies Follow-up 30 days	606 per 1000	758 per 1000	Moderate Due to serious risk of bias[3]	Baricitinib probably improves symptom resolution or improvement
		Difference: 152 more per 1000 (CI 95% 67 more - 248 more)			
Severe adverse events	Relative risk: 0.77 (CI 95% 0.63 - 0.95) Based on data from 2558 patients in 2 studies Follow-up 30 days	102 per 1000	79 per 1000	Low Due to serious risk of bias, Due to serious imprecision[4]	Baricitinib may have little or no difference on severe adverse events
		Difference: 23 fewer per 1000 (CI 95% 38 fewer - 5 fewer)			

1. **Risk of bias: Serious. Incomplete data and/or large loss to follow-up;**
2. **Risk of bias: Serious. Incomplete data and/or large loss to follow-up; Imprecision: Serious. Low number of patients;**
3. **Risk of bias: Serious. Incomplete data and/or large loss to follow-up;**
4. **Risk of bias: Serious. Incomplete data and/or large loss to follow-up; Imprecision: Serious. Low number of events.**

Summary of findings Table 14.

Population: Patients with COVID-19 infection
Intervention: Azithromycin
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	Azithromycin		
Mortality	Relative risk: 1.01 (CI 95% 0.92 - 1.1) Based on data from 8272 patients in 3 studies	**160** per 1000	**162** per 1000	**Moderate** Due to serious imprecision[1]	Azithromycin probably has little or no difference on mortality
		Difference: **2 more per 1000** (CI 95% 13 fewer - 16 more)			
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.78 - 1.13) Based on data from 8544 patients in 3 studies	**173** per 1000	**163** per 1000	**Moderate** Due to serious imprecision[2]	Azithromycin probably has little or no difference on invasive mechanical ventilation
		Difference: **10 fewer per 1000** (CI 95% 38 fewer - 22 more)			
Symptom resolution or improvement[3]	Relative risk: 1.02 (CI 95% 0.99 - 1.04) Based on data from 9287 patients in 4 studies	**606** per 1000	**618** per 1000	**High**	Azithromycin has little or no difference on symptom resolution or improvement
		Difference: **12 more per 1000** (CI 95% 6 fewer - 24 more)			
Severe adverse events	Relative risk: 1.23 (CI 95% 0.51 - 2.96) Based on data from 439 patients 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 azithromycin increases or decreases severe adverse events
		Difference: **23 more per 1000** (CI 95% 50 fewer - 200 more)			
Hospitalizations	Relative risk: 0.98 (CI 95% 0.52 - 1.86) Based on data from 493 patients in 2 studies Follow-up 21 days	**102** per 1000	**100** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Azithromycin may have little or no difference on hospitalizations
		Difference: **2 fewer per 1000** (CI 95% 49 fewer - 88 more)			

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.

Population: Patients with COVID-19 infection
Intervention: Colchicine
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	Colchicine		
Mortality	Relative risk: 1.0 (CI 95% 0.93 - 1.08) Based on data from 16005 patients in 4 studies	**160** per 1000	**160** per 1000	**Moderate** Due to serious imprecision[1]	Colchicine probably has little or no difference on mortality
		Difference: **0 fewer per 1000** (CI 95% 11 fewer - 13 more)			
Invasive mechanical ventilation	Relative risk: 1.02 (CI 95% 0.92 - 1.13) Based on data from 15404 patients in 3 studies Follow-up 30 days	**173** per 1000	**176** per 1000	**Moderate** Due to serious imprecision[2]	Colchicine probably has little or no difference on invasive mechanical ventilation
		Difference: **3 more per 1000** (CI 95% 14 fewer - 22 more)			
Symptom resolution or improvement	Relative risk: 0.99 (CI 95% 0.96 - 1.01) Based on data from 11340 patients in 1 study Follow-up 30 days	**173** per 1000	**171** per 1000	**High**	Colchicine has little or no difference on symptom resolution or improvement
		Difference: **2 fewer per 1000** (CI 95% 7 fewer - 2 more)			
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 1.0) Based on data from 4488 patients in 1 study Follow-up 30 days	**102** per 1000	**80** per 1000	**High**	Colchicine has little or no difference on severe adverse events
		Difference: **22 fewer per 1000** (CI 95% 40 fewer - 0 fewer)			
Pulmonary embolism	Relative risk: 5.55 (CI 95% 1.23 - 25.0) Based on data from 4399 patients in 1 study Follow-up 30 days	**0.9** per 1000	**5.0** per 1000	**Low** Due to very serious imprecision[3]	Colchicine may have little or no difference on pulmonary embolism
		Difference: **4.1 more per 1000** (CI 95% 0.21 more - 21.6 more)			
	Relative risk: 0.8 (CI 95% 0.62 - 1.03)	**74** per 1000	**59** per 1000	**Low**	Colchicine may decrease

Hospitalization (in patients with non-severe disease)	Based on data from 4488 patients in 1 study Follow-up 30 days	Difference: **15 fewer per 1000** (CI 95% 28 fewer - 2 more)	Due to very serious imprecision[4]	hospitalization in patients with non-severe disease

1. **Imprecision: Serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: Serious.** 95%CI includes benefits and harms;
3. **Imprecision: Very serious.** 95%CI includes significant benefits and absence of benefits , Low number of patients, Wide confidence intervals;
4. **Imprecision: Very serious.** Low number of patients, Wide confidence intervals.

Summary of findings Table 16.

Population: Patients with COVID-19 infection
Intervention: Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir
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	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir		
Mortality	Relative risk: 1.13 (CI 95% 0.82 - 1.55) Based on data from 1163 patients in 2 studies	**160** per 1000	**181** per 1000	**Low** Due to very serious imprecision[1]	Sofosbuvir alone or in combination may have little or no difference on mortality
		Difference: **21 more per 1000** (CI 95% 29 fewer - 88 more)			
Invasive mechanical ventilation	Relative risk: 1.04 (CI 95% 0.29 - 3.7) Based on data from 1083 patients in 1 study Follow-up 30 days	**173** per 1000	**180** per 1000	**Very low** Due to very serious imprecision[2]	We are uncertain whether sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir increases or decreases invasive mechanical ventilation
		Difference: **7 more per 1000** (CI 95% 123 fewer - 467 more)			
Symptom resolution or improvement	Relative risk: 0.97 (CI 95% 0.9 - 1.06) Based on data from 1343 patients in 5 studies Follow-up 7 days	**606** per 1000	**588** per 1000	**Moderate** Due to serious imprecision[3]	Sofosbuvir alone or in combination probably has little or no difference on symptom resolution or improvement
		Difference: **18 fewer per 1000** (CI 95% 61 fewer - 36 more)			

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

Summary of findings Table 17.

Patients with COVID-19 infection
Intervention: REGEN-COV (casirivimab and imdevimab)
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	REGEN-COV (casirivimab and imdevimab)		
Mortality	Relative risk: 0.94 (CI 95% 0.87 - 1.02) Based on data from 13965 patients in 2 studies	**160** per 1000	**150** per 1000	**Moderate** Due to very serious imprecision[1]	Regen-cov (casirivimab and imdevimab) probably has little or no difference on mortality
		Difference: **10 fewer per 1000** (CI 95% 21 fewer - 3 more)			
Mortality (seronegative)	Relative risk: 0.8 (CI 95% 0.7 - 0.91) Based on data from 3153 patients in 1 study	**160** per 1000	**128** per 1000	**Moderate** Due to serious indirectness[2]	Regen-cov (casirivimab and imdevimab) probably decreases mortality in seronegative patients
		Difference: **32 fewer per 1000** (CI 95% 48 fewer - 14 fewer)			
Invasive mechanical ventilation	Relative risk: 0.96 (CI 95% 0.89 - 1.03) Based on data from 13387 patients in 2 studies Follow-up 30 days	**173** per 1000	**166** per 1000	**Moderate** Due to very serious imprecision[3]	Regen-cov (casirivimab and imdevimab) probably has little or no difference on invasive mechanical ventilation
		Difference: **7 fewer per 1000** (CI 95% 19 fewer - 5 more)			
Invasive mechanical ventilation (seronegative)	Relative risk: 0.88 (CI 95% 0.73 - 1.06) Based on data from 3083 patients in 1 study Follow-up 30 days	**173** per 1000	**152** per 1000	**Low** Due to serious indirectness, Due to serious imprecision[4]	Regen-cov (casirivimab and imdevimab) may decrease invasive mechanical ventilation in seronegative patients
		Difference: **21 fewer per 1000** (CI 95% 47 fewer - 10 more)			
	Relative risk: 1.06 (CI 95% 0.96 - 1.16)	**606** per 1000	**642** per 1000	**Moderate** Due to serious imprecision[5]	Regen-cov (casirivimab and

Symptom resolution or improvement	Based on data from 13549 patients in 2 studies Follow-up 30 days	Difference: **36 more per 1000** (CI 95% 24 fewer - 97 more)			imdevimab) probably has little or no difference on symptom resolution or improvement
Symptom resolution or improvement (seronegative)	Relative risk: 1.12 (CI 95% 1.01 - 1.25) Based on data from 5757 patients in 2 studies Follow-up 30 days	**606** per 1000 Difference: **73 more per 1000** (CI 95% 6 more - 152 more)	**679** 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: 0.29 (CI 95% 0.18 - 0.44) Based on data from 4384 patients in 2 studies Follow-up 30 days	**74** per 1000 Difference: **53 fewer per 1000** (CI 95% 61 fewer - 41 fewer)	**21** per 1000	**Moderate** Due to serious imprecision[7]	Regen-cov (casirivimab and imdevimab) probably improves hospitalization in patients with recent onset non-severe disease
Symptomatic infection (in exposed individuals)	Relative risk: 0.69 (CI 95% 0.47 - 1.0) Based on data from 204 patients in 1 study Follow-up 30 days	**74** per 1000 Difference: **23 fewer per 1000** (CI 95% 39 fewer - 0 fewer)	**51** per 1000	**Low** Due to serious imprecision, Due to very serious imprecision[8]	Regen-cov (casirivimab and imdevimab) may decrease symptomatic infection in exposed individuals
Severe adverse events	Relative risk: 0.63 (CI 95% 0.48 - 0.81) Based on data from 5735 patients in 2 studies Follow-up 30 days	**102** per 1000 Difference: **38 fewer per 1000** (CI 95% 53 fewer - 19 fewer)	**64** per 1000	**Moderate** Due to serious imprecision[9]	Regen-cov (casirivimab and imdevimab) probably has little or no difference on severe adverse events

1. **Risk of bias: No serious.** Incomplete data and/or large loss to follow-up; **Imprecision: Very serious.** Wide confidence intervals;
2. **Risk of bias: No serious.** Incomplete data and/or large loss to follow-up; **Indirectness: Serious.** Subgroup analysis; **Imprecision: Very serious;**
3. **Risk of bias: No serious.** Incomplete data and/or large loss to follow-up; **Imprecision: Very serious.** Wide confidence intervals;
4. **Risk of bias: No serious.** Incomplete data and/or large loss to follow-up; **Indirectness: Serious.** Subgroup analysis; **Imprecision: Serious.** Low number of events, Wide confidence intervals;
5. **Imprecision: Serious.** Wide confidence intervals;
6. **Indirectness: Serious.** Subgroup analysis;
7. **Risk of bias: No serious.** Incomplete data and/or large loss to follow-up; **Imprecision: Serious.** Low number of events;
8. **Risk of bias: No serious.** Incomplete data and/or large loss to follow-up; **Imprecision: Very serious.** Low number of events, Wide confidence intervals;
9. **Imprecision: Serious.** Low number of events.

Summary of findings Table 18.

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

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates** SOC	Inhaled coticosteroids	**Certainty of the evidence** (quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.85 (CI 95% 0.64 - 1.12) Based on data from 1856 patients in 1 study	**160** per 1000	**136** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[1]	We are uncertain whether inhaled corticosteroids increases or decreases mortality
		Difference: **24 fewer per 1000** (CI 95% 58 fewer - 19 more)			
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.44 - 1.98) Based on data from 1560 patients in 1 study	**173** per 1000	**163** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether inhaled corticosteroids increases or decreases invasive mechanical ventilation
		Difference: **10 fewer per 1000** (CI 95% 97 fewer - 170 more)			
Symptom resolution or improvement[3]	Relative risk: 1.16 (CI 95% 1.08 - 1.24) Based on data from 2187 patients in 4 studies	**606** per 1000	**703** per 1000	**Moderate** Due to serious risk of bias[4]	Inhaled corticosteroids probably increases symptom resolution or improvement
		Difference: **97 more per 1000** (CI 95% 48 more - 145 more)			
Hospitalizations	Relative risk: 0.82 (CI 95% 0.62 - 1.08) Based on data from 2256 patients in 2 studies	**74** per 1000	**61** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Inhaled corticosteroids may decrease hospitalizations
		Difference: **13 fewer per 1000** (CI 95% 28 fewer - 6 more)			

1. **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;
2. **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;
3. Symptomatic infection in persons at risk or exposed to SARS-CoV2;
4. **Risk of bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
5. **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; wide confidence intervals.

Summary of findings Table 19.

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

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates** SOC	Fluvoxamine	**Certainty of the evidence** (quality of evidence)	**Plain language summary**
Hospitalizations	Relative risk: 0.78 (CI 95% 0.59 - 1.04) Based on data from 1856 patients in 1 study	**74** per 1000	**58** per 1000	**Moderate** Due to serious imprecision[1]	Fluvoxamine probably reduces hospitalizations
		Difference: **16 fewer per 1000** (CI 95% 30 fewer - 3 more)			
Mortality	Relative risk: 0.7 (CI 95% 0.38 - 1.3) Based on data from 1472 patients in 1 study	**160** per 1000	**112** 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
		Difference: **48 fewer per 1000** (CI 95% 99 fewer - 48 more)			
Severe adverse events[3]	Relative risk: 0.74 (CI 95% 0.49 - 1.13) Based on data from 1472 patients in 1 study	**102** per 1000	**75** per 1000	**Low** Due to serious risk of bias, Due to very serious imprecision[4]	Fluvoxamine may not increase severe adverse events
		Difference: **27 fewer per 1000** (CI 95% 52 fewer - 13 more)			

1. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. Symptomatic infection in persons at risk or exposed to SARS-CoV2;
4. **Risk of bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Wide confidence intervals.

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