

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

Summary of Evidence • Rapid Review, 14 December 2021

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

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Disclaimer

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

Contents

[Executive summary](#)

[Background](#)

[Summary of evidence](#)

[Key findings](#)

[Changes since previous edition](#)

[Concluding remarks](#)

[Hallazgos clave](#)

[Cambios respecto a la anterior versión](#)

[Conclusiones](#)

[Systematic review of therapeutic options for treatment of COVID-19](#)

[Background](#)

[Methods](#)

[Search strategy](#)

[Study selection](#)

[Inclusion criteria](#)

[Living evidence synthesis](#)

[Results](#)

[Studies identified and included](#)

[Risk of bias](#)

[Main findings](#)

[Full description of included studies](#)

[Appendix 1. Summary of findings tables](#)

[References](#)

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 163 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=483)

Intervention	Overall number of studies including the intervention, n=483	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		51	13	9	10	9	17	7
Ivermectin		33	6 (*)	6	3 (*)	4	5	5
Convalescent plasma		27	10(*)	8(*)	10		3(*)	2
Tocilizumab		26	20	21	8		15	
Favipiravir	NEW	19	7	6	3(*)		5	3
Corticosteroids	NEW	18	17(@)	7	6		6	
Lopinavir-Ritonavir		17	4	4	2	1	2	1
Anticoagulants	NEW	13	11(@@)				5 (*)	
Sofosbuvir +/- Daclatasvir or others	NEW	13	2(*)	2(*)	2(*)			
ACEIs or ARBs	NEW	10	6(*)	9	3			1
Azithromycin		10	4	3	4		1	2
Mouthwash	NEW	10	2	1	2			
REGEN-COV (casirivimab and imdevimab)	NEW	9	2(##)	2(##)	3(##)	3	3	3
Sarilumab		9	9	7	3		5	
Bamlanivimab +/- etesevimab		8	3		3	1	5	2
Remdesivir	NEW	8	7 (#)	6	4		3	
Colchicine		7	4(**)	3(**)	1(**)		3	2
Umifenovir		7	1	2			1	
Zinc		7	2	1	2		1	
Interferon beta-1a		6	5	4	2		2	
Vitamin D		6	2	1			1	
Corticosteroids (inhaled)		5	1	1	5			3
IVIg		5	9	9				
Melatonin		5	2		3			
Mesenchymal cell transplantation		5	4	1	2		2	
Vitamin C		5	5	4	2			
Bromhexine Hydrochloride		4	2	1	2	1	1	
Anakinra	NEW	4	4	2	4		3	
Nilazoxanide		4	1	1	1		2	2
Proxalutamide		4	3	3	2			2
Aspirin		3	2	2	1			
Baricitinib		3	3	1	3		3	
N-acetylcysteine		3	2	2			1	
Nasal hypertonic saline	NEW	3			1			
Quercetin	NEW	3	3		2			1
Molnupiravir		3					3	
Canakinumab		2	2	1	1		1	
Cofactors	NEW	2			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						
Levamisole	NEW	2	1		1			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		2	2		2			
Pentoxifylline		2	2	2	1			
Probiotics		2	1	1		1		
Regdanvimab		2			2		2	1
Resveratrol		2	2	2			2	2
Ruxolitinib		2	2	2	2		2	
Tenofovir + emtricitabine		2	1				1	2
Thalidomide		2	1	1			1	
99mTc-MDP		1						
Adalimumab		1	1	1				
Ammonium chloride		1	1	1				
AMP5A (inhaled)	NEW	1	1				1	
Aprepitant		1						
Artemisinin		1			1		1	
Auxora		1	1	1				
Aviptadil		1	1		1		1	
Azelastine (inhaled)		1			1		1	
Azvidine		1						

Intervention	Overall number of studies including the intervention, n=483	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)
Baloxavir		1			1		
BCG		1	1				
Beta-glucans	NEW	1				1	
Bioven		1	1				1
Calcitriol		1	1				1
Camostat mesilate		1	1	1	1		1
Cannabidiol		1	1	1	1		1
CERC-002		1	1				1
Chloroquine nasal drops		1					
Clarithromycin		1					
CIGB-325		1			1		1
Colchicine + rosuvastatin		1	1	1			1
Corticosteroids (nasal)	NEW	1					
Darunavir-Cobicistat		1					
Dapagliflozin		1	1	1			1
Dimethyl sulfoxide (DSMO)		1				1	
Electrolyzed saline		1	1		1		1
Emtricitabine/tenofovir		1	1	1			1
Enisamilum		1			1		
Famotidine		1	1				
Febuxostat		1					1
Finasteride		1	1				
Fostamatinib		1	1		1		1
Helium (inhaled)		1					
Hemadsorption	NEW	1	1	1			
Hesperidin		1	1	1	1		1
Hyperbaric oxygen		1	1	1	1		
Hyperimmune anti-COVID-19 IVIG		1	1		1		1
Icatibant/ IC1e/K		1	1				
Icosapent ethyl		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		1	1				1
Lactococcus Lactis (intranasal)		1			1		1
Lactoferrin	NEW	1			1		
Lenzilumab		1	1	1			1
Levilimab		1	1	1	1		1
Lincomycin		1					
Low-dose radiation therapy		1	1				
Mavrilimumab		1	1	1	1		1
Metisoprinol		1					
Methylene blue		1	1				
Metoprolol		1	1				
Mupadolimab		1					1
Mycobacterium w		1	1				
Nafamostat mesylate		1	1				1
Namilumab		1	1		1		1
Nano-curcumin		1					1
Neem (Azadirachta Indica A. Juss)		1				1	
Niclosamide		1	1	1			1
Novaferon		1					
NSAIDS		1	1		1		1
Nutritional support		1	1	1			
Opaganib		1	1	1	1		1
Otilimab		1	1				1

Intervention	Overall number of studies including the intervention, n=483	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)
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
Progesterone	1	1	1			1	
Prolectin-M	1	1	1			1	
Propolis	1	1	1	1			
Prostacyclin	1	1					1
Pyridostigmine	1	1	1	1			1
Ramipril	1	1			1		
RD-X19 (light therapy)	1			1			
Recombinant Super-Compound IFN	1	1		1			
Ribavirin	1						
Ribavirin + Interferon beta-1b	1						
rhG-CSF	1	1		1			1
rhG-CSF (inhaled)	1	1	1	1			1
Secukinumab	1	1	1				1
Short-wave diathermy	1	1		1			1
Siltuximab	1	1	1				
Sitagliptin	1	1	1				
Sotrovimab	1	1	1	1		1	1
Spirolactone	1	1	1				
Statins	1	1	1				
Stem-cell nebulization	1	1		1			1
Sulodexide	1	1	1				1
TD-0903 (inhaled JAK-inhibitor)	1	1					1
Tissue-plasminogen activator (tPA)	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						

(*) 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-statistically 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 not be more effective than standard dose schemes (i.e dexamethasone 6 mg a day); (@@) Excluding high risk of bias studies.

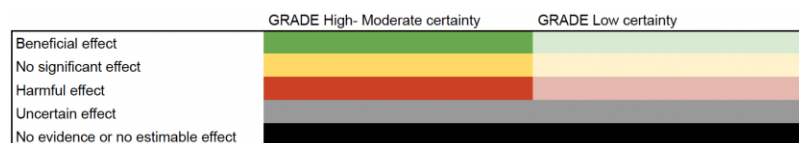


Table 2. List of non-RCTs of interventions for COVID-19 with primary outcome measures and certainty (n=7)

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				

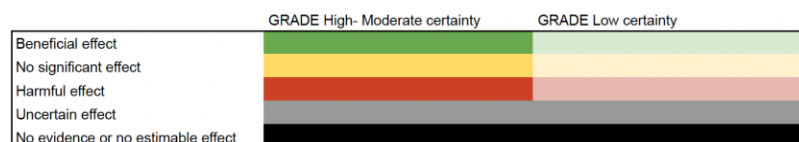


Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=163), as at 13 December 2021

	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	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.
4	Ammonium chloride	Uncertainty in potential benefits and harms. Further research is needed.
5	AMP5A (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
6	Anakinra	It is uncertain if anakinra affects mortality, mechanical ventilation requirements, symptom resolution or increases severe adverse events. Further research is needed.
7	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) may 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. In mild ambulatory patients, anticoagulants in prophylactic dose, may not importantly improve time to symptom resolution.
8	Aprepitant	Uncertainty in potential benefits and harms. Further research is needed.
9	Artemisinin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
10	Aspirin	Aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement.
11	Auxora	Uncertainty in potential benefits and harms. Further research is needed.
12	Aviptadil	Uncertainty in potential benefits and harms. Further research is needed.
13	Azelastine	Uncertainty in potential benefits and harms. Further research is needed.
14	Azithromycin	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
15	Azvudine	Uncertainty in potential benefits and harms. Further research is needed.
16	Baricitinib	Baricitinib probably reduces mortality and time to symptom resolution without increasing severe adverse events. Certainty of the evidence was moderate because of risk of bias.
17	Baloxavir	Uncertainty in potential benefits and harms. Further research is needed.
18	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.
19	BCG	Uncertainty in potential benefits and harms. Further research is needed.
20	Beta-glucans	Uncertainty in potential benefits and harms. Further research is needed.
21	Bioven	Uncertainty in potential benefits and harms. Further research is needed.
22	Bromhexine hydrochloride	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
23	Calcitriol	Uncertainty in potential benefits and harms. Further research is needed.
24	Camostat mesilate	Uncertainty in potential benefits and harms. Further research is needed.
25	Canakinumab	Uncertainty in potential benefits and harms. Further research is needed.
26	Cannabidiol	Uncertainty in potential benefits and harms. Further research is needed.
27	CERC-002	Uncertainty in potential benefits and harms. Further research is needed.
28	Chloroquine nasal drops	Uncertainty in potential benefits and harms. Further research is needed.
29	CIGB-325	Uncertainty in potential benefits and harms. Further research is needed.
30	Clarithromycin	Uncertainty in potential benefits and harms. Further research is needed.
31	Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)	Uncertainty in potential benefits and harms. Further research is needed.
32	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.
33	Colchicine + rosuvastatin	Uncertainty in potential benefits and harms. Further research is needed.
34	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

	Intervention	Summary of findings
		patients convalescent plasma may not reduce hospitalizations. Convalescent plasma probably increases severe adverse events.
35	Dapagliflozin	Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.
36	Darunavir-cobicistat	Uncertainty in potential benefits and harms. Further research is needed.
37	Dimethyl sulfoxide (DSMO)	Uncertainty in potential benefits and harms. Further research is needed.
38	Doxycycline	Doxycycline does not increase symptom resolution or improvement and may not reduce hospitalizations.
39	Dutasteride	Uncertainty in potential benefits and harms. Further research is needed.
40	Electrolyzed saline	Uncertainty in potential benefits and harms. Further research is needed.
41	Emtricitabine/tenofovir	Uncertainty in potential benefits and harms. Further research is needed.
42	Enisamium	Uncertainty in potential benefits and harms. Further research is needed.
43	Famotidine	Uncertainty in potential benefits and harms. Further research is needed.
44	Favipiravir	Favipiravir may increase mortality and mechanical ventilation requirements, and it probably does not improve time to symptom resolution. Further research is needed.
45	Febuxostat	Uncertainty in potential benefits and harms. Further research is needed.
46	Finasteride	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
47	Fluvoxamine	Fluvoxamine probably reduces hospitalizations and may not increase severe adverse events. Certainty of the evidence was low to moderate. Further research is needed.
48	Fostamatinib	Uncertainty in potential benefits and harms. Further research is needed.
49	Helium (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
50	Hemadsorption	Uncertainty in potential benefits and harms. Further research is needed.
51	Hesperidin	Hesperidin may not improve symptom resolution, however the certainty of the evidence was low. Further research is needed.
52	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.
53	Hyperbaric oxygen	Uncertainty in potential benefits and harms. Further research is needed.
54	Hyperimmune anti-COVID-19 Intravenous Immunoglobulin (C-IVIG)	Uncertainty in potential benefits and harms. Further research is needed.
55	Icatibant/iC1e/K	Uncertainty in potential benefits and harms. Further research is needed.
56	Icosapent ethyl	Uncertainty in potential benefits and harms. Further research is needed.
57	IFX-1	Uncertainty in potential benefits and harms. Further research is needed.
58	Imatinib	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
59	Indomethacin	Uncertainty in potential benefits and harms. Further research is needed.
60	Infliximab	Uncertainty in potential benefits and harms. Further research is needed.
61	INM005 (polyclonal fragments of equine antibodies)	Uncertainty in potential benefits and harms. Further research is needed.
62	Interferon alpha-2b and interferon gamma	Uncertainty in potential benefits and harms. Further research is needed.
63	Interferon beta-1a	IFN beta-1a probably does not reduce mortality nor invasive mechanical ventilation requirements. Further research is needed.
64	Interferon beta-1a (inhaled)	Inhaled interferon beta-1a may improve time to symptom resolution. Further research is needed.
65	Interferon beta-1b	Uncertainty in potential benefits and harms. Further research is needed.
66	Interferon gamma	Uncertainty in potential benefits and harms. Further research is needed.
67	Interferon kappa and TFF2	Uncertainty in potential benefits and harms. Further research is needed.
68	Iota-carrageenan	Uncertainty in potential benefits and harms. Further research is needed.
69	Itolizumab	Uncertainty in potential benefits and harms. Further research is needed.
70	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

	Intervention	Summary of findings
		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.
71	Ivermectin (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
72	Intravenous immunoglobulin	Uncertainty in potential benefits and harms. Further research is needed.
73	KB109	Uncertainty in potential benefits and harms. Further research is needed.
74	L-arginine	Uncertainty in potential benefits and harms. Further research is needed.
75	<i>Lactococcus lactis</i> (intranasal)	Uncertainty in potential benefits and harms. Further research is needed.
76	Lactoferrin	Uncertainty in potential benefits and harms. Further research is needed.
77	Leflunomide	Uncertainty in potential benefits and harms. Further research is needed.
78	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.
79	Levamisole	Uncertainty in potential benefits and harms. Further research is needed.
80	Levilimab	Levilimab may improve time to symptom resolution, however the certainty of the evidence was low. Further research is needed.
81	Lincomycin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
82	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.
83	Low-dose radiation therapy	Uncertainty in potential benefits and harms. Further research is needed.
84	Mavrilimumab	Uncertainty in potential benefits and harms. Further research is needed.
85	Melatonin	Uncertainty in potential benefits and harms. Further research is needed.
86	Mesenchymal stem-cell transplantation	Mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence is low. Further research is needed.
87	Methylene blue	Uncertainty in potential benefits and harms. Further research is needed.
88	Metisoprinol	Uncertainty in potential benefits and harms. Further research is needed.
89	Metoprolol	Uncertainty in potential benefits and harms. Further research is needed.
90	Molnupiravir	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
91	Mouthwash	Uncertainty in potential benefits and harms. Further research is needed.
92	Mupadolimab	Uncertainty in potential benefits and harms. Further research is needed.
93	Mycobacterium w	Uncertainty in potential benefits and harms. Further research is needed.
94	N-acetylcysteine	Uncertainty in potential benefits and harms. Further research is needed.
95	Nafamostat mesylate	Uncertainty in potential benefits and harms. Further research is needed.
96	Namilumab	Uncertainty in potential benefits and harms. Further research is needed.
97	Nano-curcumin	Uncertainty in potential benefits and harms. Further research is needed.
98	Nasal hypertonic saline	Uncertainty in potential benefits and harms. Further research is needed.
99	Neem (<i>Azadirachta indica</i> A. Juss)	Uncertainty in potential benefits and harms. Further research is needed.
100	Niclosamide	Uncertainty in potential benefits and harms. Further research is needed.
101	<i>Nigella sativa</i> +/- honey	Uncertainty in potential benefits and harms. Further research is needed.
102	Nitazoxanide	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
103	Nitric oxide	Uncertainty in potential benefits and harms. Further research is needed.
104	Novaferon	Uncertainty in potential benefits and harms. Further research is needed.
105	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.
106	Nutritional support	Uncertainty in potential benefits and harms. Further research is needed.
107	Omega-3 fatty acids	Uncertainty in potential benefits and harms. Further research is needed
108	Opaganib	Uncertainty in potential benefits and harms. Further research is needed
109	Otilimab	Uncertainty in potential benefits and harms. Further research is needed
110	Ozone	Uncertainty in potential benefits and harms. Further research is needed.
111	Peg-interferon alfa	Uncertainty in potential benefits and harms. Further research is needed.
112	Peg-interferon lamda	Uncertainty in potential benefits and harms. Further research is needed.
113	Pentoxifylline	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
114	PNB001 (CCK-A antagonist)	Uncertainty in potential benefits and harms. Further research is needed.
115	Polymerized type I collagen (PT1C)	Uncertainty in potential benefits and harms. Further research is needed.
116	Povidone iodine (nasal spray)	Uncertainty in potential benefits and harms. Further research is needed.
117	Probiotics	Uncertainty in potential benefits and harms. Further research is needed.
118	Progesterone	Uncertainty in potential benefits and harms. Further research is needed
119	Prolectin-M	Uncertainty in potential benefits and harms. Further research is needed
120	Propolis	Uncertainty in potential benefits and harms. Further research is needed
121	Prostacyclin	Uncertainty in potential benefits and harms. Further research is needed
122	Proxalutamide	Uncertainty in potential benefits and harms. Further research is needed
123	Pyridostigmine	Uncertainty in potential benefits and harms. Further research is needed
124	Quercetin	Uncertainty in potential benefits and harms. Further research is needed
125	Ramipril	Uncertainty in potential benefits and harms. Further research is needed.
126	RD-X19 (light therapy)	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
127	Recombinant super-compound interferon	Uncertainty in potential benefits and harms. Further research is needed.
128	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.
129	Regdanvimab	Regdanvimab may improve time to symptom resolution in mild to moderate patients. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.
130	Remdesivir	Remdesivir may not reduce mortality but it may 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.
131	Resveratrol	Uncertainty in potential benefits and harms. Further research is needed.
132	rhG-CSF (in patients with lymphopenia)	Uncertainty in potential benefits and harms. Further research is needed.
133	rhG-CSF (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
134	Ribavirin	Uncertainty in potential benefits and harms. Further research is needed.
135	Ribavirin + interferon beta-1b	Uncertainty in potential benefits and harms. Further research is needed.
136	Ruxolitinib	Ruxolitinib may not improve time to symptom resolution, however the certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
137	Sarilumab	Sarilumab may not reduce mortality and probably does not improve time to symptom resolution, but may decrease mechanical ventilation requirements without increasing severe adverse events. However, the certainty is low because of imprecision and inconsistency.
138	Secukinumab	Uncertainty in potential benefits and harms. Further research is needed.
139	Short-wave diathermy	Uncertainty in potential benefits and harms. Further research is needed.
140	Siltuximab	Uncertainty in potential benefits and harms. Further research is needed.
141	Sitagliptin	Uncertainty in potential benefits and harms. Further research is needed.
142	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.
143	Sotrovimab	Sotrovimab probably reduces hospitalizations in patients with recent onset mild COVID-19.
144	Spironolactone	Uncertainty in potential benefits and harms. Further research is needed.
145	Statins	Uncertainty in potential benefits and harms. Further research is needed.
146	Stem-cell nebulization	Uncertainty in potential benefits and harms. Further research is needed.
147	Steroids (corticosteroids)	Corticosteroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Corticosteroids may not significantly increase the risk of severe adverse events. Higher-dose schemes (i.e., dexamethasone 12 mg a day) may not be more effective than standard dose schemes (i.e., dexamethasone 6mg a day).

	Intervention	Summary of findings
148	Steroids (corticosteroids, inhaled)	Inhaled corticosteroids probably improve time to symptom resolution. Its effects on other important outcomes are uncertain. Further research is needed.
149	Steroids (corticosteroids, nasal)	Uncertainty in potential benefits and harms. Further research is needed.
150	Sulodexide	Uncertainty in potential benefits and harms. Further research is needed.
151	TD-0903 (inhaled JAK-inhibitor)	Uncertainty in potential benefits and harms. Further research is needed.
152	Tenofovir + emtricitabine	Uncertainty in potential benefits and harms. Further research is needed.
153	Thalidomide	Uncertainty in potential benefits and harms. Further research is needed.
154	Tissue-plasminogen activator (tPA)	Uncertainty in potential benefits and harms. Further research is needed.
155	Tocilizumab	Tocilizumab reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
156	Tofacitinib	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low, further research is needed.
157	Triazavirin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
158	Umifenovir	Uncertainty in potential benefits and harms. Further research is needed.
159	Vitamin C	Uncertainty in potential benefits and harms. Further research is needed.
160	Vitamin D	Uncertainty in potential benefits and harms. Further research is needed.
161	XAV-19 (swine glyco-humanized polyclonal antibodies)	Uncertainty in potential benefits and harms. Further research is needed.
162	Zinc	Uncertainty in potential benefits and harms. Further research is needed.
163	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 163 therapeutic options.
- **Corticosteroids:** The body of evidence on corticosteroids, which includes 18 RCTs, shows that low- or moderate-dose treatment schemes (RECOVERY trial dose was 6 mg of oral or intravenous preparation once daily for 10 days) are probably effective in reducing mortality in patients with severe COVID-19 infection. These results remained robust after including studies in which patients with acute respiratory distress syndrome (ARDS) secondary to alternative etiologies (not COVID-19 related) were randomized to corticosteroids or placebo/no corticosteroids. Higher-dose schemes (i.e., dexamethasone 12 mg a day) may not be more effective than standard dose schemes (i.e., dexamethasone 6mg a day).

- **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 not have an important effect on mortality but it may reduce 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 27 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 and probably does not improve time to symptom resolution 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 three 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 seven RCTs assessing colchicine, including the COLCORONA study that recruited 4,488 patients with recent COVID-19 diagnosis and risk factors for severity and the RECOVERY trial that recruited 11,340 hospitalized patients, show that colchicine probably does not reduce mortality, mechanical ventilation requirements 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 due to a small number of events.
- **Ivermectin:** Although 33 RCTs assessed ivermectin in patients with COVID-19, only 14 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:** Nineteen RCTs assessed favipiravir vs SOC or other interventions. Their results suggest that favipiravir may increase mortality and 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 three RCTs show that, in patients with moderate to critical disease, baricitinib probably reduces mortality and time to symptom resolution without increasing severe adverse events. The certainty of the evidence was moderate because of risk of bias.
- **REGEN-COV (casirivimab and imdevimab):** The results of seven RCTs suggest that, in patients with severe to critical disease, overall REGEN-COV may reduce mortality, mechanical ventilation or increase symptom resolution or improvement. However, the certainty of the evidence was low. A subgroup analysis suggests a differential effect on seronegative patients in which REGEN-COV probably reduces mortality and mechanical ventilation requirements, and increases symptom resolution or improvement. In patients with 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, sotrovimab probably reduces hospitalizations and improves time to symptom resolution without increasing severe adverse events. The certainty of the evidence was moderate because of imprecision.
- **Regdanvimab:** The results of two 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. Its 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 very low because of very serious risk of bias, imprecision, and indirectness. Further research is needed to confirm or discard these findings.

- **Dapagliflozin:** The results of one RCT suggest that, in patients with cardiometabolic risk factors hospitalized with moderate COVID-19, dapagliflozin may reduce mortality, but probably does not increase symptom resolution. However, the certainty of the evidence was low because of imprecision. Further research is needed to confirm or discard these findings.
- **Mesenchymal stem-cell transplantation:** The results of five 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 five RCTs show that inhaled corticosteroids probably improve time to symptom resolution. However, 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, excluding three studies classified as with high risk of bias, the results of eight 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 low certainty (imprecision and inconsistency). Results of three RCTs inform that aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement. In mild ambulatory patients two RCT suggest that rivaroxaban in prophylactic dose may not importantly improve time to symptom resolution.

- **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

- **Cofactors:** New evidence included without significant changes.
- **Nasal steroids:** New evidence included without significant changes.
- **Nasal hypertonic saline:** New evidence included without significant changes.
- **Hemadsorption:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Lactoferrin:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **ACEI/ARB:** New evidence included without significant changes.
- **REGEN-COV (casirivimab and imdevimab):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Favipiravir:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Convalescent plasma:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Corticosteroids:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

- **Remdesivir:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **AMP5A (inhaled):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Levamisole:** New evidence included without significant changes.
- **Prostacycline:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Mouthwash:** New evidence included without significant changes.
- **Anticoagulants:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Beta-glucans:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Quercetin:** 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 de Registros Internacionales de Ensayos Clínicos (ICTRP) de la Organización Mundial de la Salud (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 163 opciones terapéuticas potenciales.

- **Corticosteroides:** El conjunto de evidencia sobre los corticosteroides incluye 18 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 reduce la mortalidad en pacientes con infección grave por SARS-CoV-2. Los resultados se mantuvieron uniformes tras agregar al análisis estudios en los que pacientes con síndrome de dificultad respiratoria aguda (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 no resultar más efectivos que los esquemas habituales (por ejemplo dexametasona 6mg por día).

- **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 no tener un efecto importante sobre la mortalidad, pero podría reducir 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.

- **Hidroxiclороquina, interferón beta 1-a y lopinavir-ritonavir:** El conjunto de evidencia sobre la hidroxiclороquina, el interferón beta 1-a y el lopinavir-ritonavir, incluidos los resultados preliminares de los estudios RECOVERY y Solidaridad, no muestra beneficios en la reducción de la mortalidad, la necesidad de ventilación mecánica invasiva o el plazo necesario para la mejoría clínica. Incluso la evidencia sobre hidroxiclороquina sugiere que su utilización probablemente genere un incremento en la mortalidad. Nueve estudios que evaluaron la hidroxiclороquina 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 27 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 los efectos adversos graves en pacientes con enfermedad grave o crítica.
- **Sarilumab:** Los resultados de nueve ECCA muestran que sarilumab podría no reducir la mortalidad y probablemente no mejore el tiempo a la resolución de los síntomas, aunque sí podría reducir la necesidad de ventilación invasiva sin un incremento importante en los 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 tres ECCA que evaluaron anakinra en pacientes hospitalizados con enfermedad no grave muestran resultados incongruentes en la mortalidad y la resolución de los 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 con un posible aumento de los eventos adversos graves. La certeza en la evidencia es baja y se necesita más información.
- **Colchicina:** Los resultados de siete 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 33 ECCA evaluaron ivermectina en pacientes con COVID-19, solo 14 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:** Diecisiete ECCA evaluaron favipiravir en comparación con la prestación de cuidados estándares u otras intervenciones. Sus resultados sugieren que favipiravir podría aumentar la mortalidad y 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 tres 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 sin aumentar los eventos adversos severos. La certeza en la evidencia es moderada por riesgo de sesgo.

- **REGEN-COV (casirivimab e imdevimab):** Los resultados de siete ECCA muestran que, en pacientes con enfermedad grave o crítica, REGEN-COV podría reducir la mortalidad, la necesidad de ventilación invasiva y mejorar la velocidad de resolución de los síntomas de forma significativa. Sin embargo la certeza resultó baja. 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 con moderada certeza. 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, 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 notificó 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 grave notificó 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 dos 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 y la necesidad de ventilación mecánica, así como mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es muy baja por riesgo de sesgo muy grave, 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 cinco 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 cinco ECCA muestran que los corticosteroides inhalados probablemente mejoran el tiempo de resolución de los síntomas. Sin embargo, 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 mecánica 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.

- **Anticoagulantes:** 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 tromboprolifáticas. En relación con el esquema tromboprolifático, excluyendo tres estudios clasificados con riesgo alto de sesgo, los resultados de ocho estudios aleatorizados y controlados que compararon los anticoagulantes en 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 baja (imprecisión e inconsistencia). Los resultados de tres estudios aleatorizados informan que la indicación de aspirina probablemente tampoco se asocia a una reducción en la mortalidad y la necesidad de ventilación mecánica ni a la mejoría en la velocidad de resolución de los síntomas. Los resultados de dos ECA sugieren que, en pacientes ambulatorios con enfermedad

leve, rivaroxaban en dosis profilácticas podría no mejorar el tiempo de resolución de los síntomas de forma considerable.

- **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

- **Cofactores:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Esteroides intranasales:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Solución hipertónica intranasal:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Hemadsorción:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Lactoferrina:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **IECA/ARAI:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **REGEN-COV (casirivimab e imdevimab):** La evidencia nueva incluida modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Favipiravir:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Plasma de convalescientes:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

- **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Corticosteroides:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Remdesivir:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **AMP5A (inhalaado):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Levamisol:** La evidencia nueva incluida no modifica la interpretación de los resultados o la certeza de la evidencia.
- **Prostaciclina:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Enjuague bucal:** La evidencia nueva incluida no modifica la interpretación de los resultados o la certeza de la evidencia.
- **Anticoagulantes:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Beta-glucanos:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Quercetina:** La evidencia nueva incluida no modifica la interpretación de los resultados o la certeza de la evidencia.

Conclusiones

- La Organización Panamericana de la Salud (OPS) hace seguimiento en todo momento de la evidencia en relación con cualquier posible intervención terapéutica. A medida que se disponga de evidencia nueva, la OPS la incorporará con rapidez y actualizará sus recomendaciones, especialmente si dicha evidencia se refiere a grupos en situación de vulnerabilidad como los niños y niñas, las mujeres embarazadas, 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§ion=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 December 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.

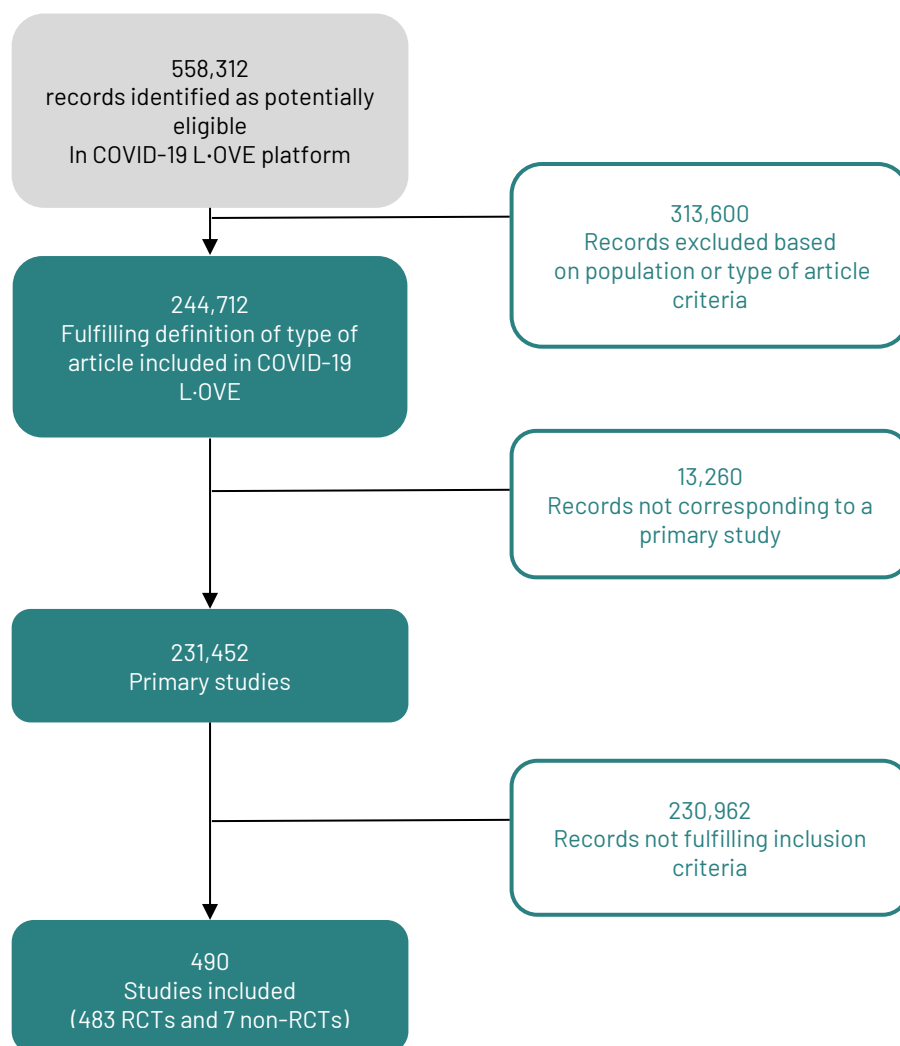
A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect (Table 4).⁸ For non-RCTs, potential residual confounding was assumed in all cases and certainty of the evidence was downgraded twice 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 490 studies were selected for inclusion, 483 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
Guenmez 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
Metovid	Low	Low	Low	Low	Low	Low	Low
Mansour E et al	Low	Low	Low	Some Concerns	Low	Low	High
Zhang J et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - Lopinavir-ritonavir	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
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-El salam 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
Edalatfard 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
Edalatfard 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 Department)	High	Low	Low	Low	Low	High	High
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khamis F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BLAZE-1	High	Low	Low	Low	Low	High	High
PETAL	Low	Low	Low	Low	Low	Low	Low
Lanzoni G et al	High	Low	Low	Low	Low	High	High
Ruzhensova 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
EMPACKTA	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
ILJAD	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-C19-024-00	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-El salam 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
Roostbeh F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTIV-3/ITICO	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 (Cadeiani FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
JamalMoghadamSiakhali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedighyan 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 et 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	Low	Low	Low
Dabbous HM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATTRACT	Low	Some Concerns	Low	Low	Low	Low	Low
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
NITFM03200R	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
EIZein 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	Some Concerns	Some Concerns
Zarychanski	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Santos PSS et al	Low	Some Concerns	Low	Low	Low	Low	Low
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
Gaynildinova 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
Doael 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
Samimaghani 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
Siarni 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	Some Concerns	Some Concerns
SAVE-MORE	Low	Some Concerns	Low	Low	Low	Low	Low
Winchester S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elghohary 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-El salam 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	Some Concerns	Some Concerns
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	High	Some Concerns	Low	Some Concerns	Low	High	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
Abdulmir 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 Pietro F et al	Low	Low	Low	Low	Low	Low	Low
ARD-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
COVIT0Z-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	Low	Low	Low	Low	Low	Low
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	Some Concerns	Low	Some Concerns	Low	Low	High
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	Some Concerns	Some Concerns
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
UAHC	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
Fakharan 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
Gates MRI RESPOND-1	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV-2	Low	Low	Low	Low	Low	Low	Low
CARVIN	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Buonfrate et al	Low	Low	Low	Low	Low	Low	Low
McCreary M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Ghanei M et al	Low	Low	Low	Low	Low	Low	Low
Maskin et al	High	Low	Low	Low	Low	High	High
COL-COVID	Low	Low	Low	Low	Low	Low	Low
PRINCIPLE - Colchicine	Low	Low	Low	Low	Low	Low	Low
Hassaniiazad M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ramachandran R et al	Low	Low	Low	Low	Low	Low	Low
CPI-006-002	Low	Low	Low	Low	Low	Low	Low
Di-Doménico MB et al	Low	Low	Low	Low	Low	Low	Low
CT-PS9 1.2	High	Some Concerns	Low	Some Concerns	Low	High	High
ABC-110	High	Some Concerns	Low	Some Concerns	Low	High	High
CORONA	Low	Low	Low	Low	Low	Low	Low
STARS	High	Some Concerns	Low	Some Concerns	Low	High	High
ARTAN-C19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Babalola OE et al	High	Low	Low	Low	Low	High	High
HESPERIDIN	Low	Low	Low	Low	Low	Low	Low
Reszinate	High	Low	Low	Low	Low	High	High
Azizi H et al	High	Low	Some Concerns	Low	Low	High	High
FIGHT-COVID-19	Low	Low	Low	Low	Low	Low	Low
CANDIDATE	Low	Low	Low	Low	Low	Low	Low
BEMICOP	Low	Low	Low	Low	Low	Low	Low
HEP-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV4B	High	Low	High	Low	Low	High	High
COV-BARRIER-IMV	High	Some Concerns	Low	Some Concerns	Low	High	High
DEFINE	Low	Low	Low	Low	Low	Low	Low
SEV-COVID	Low	Low	Low	Low	Low	Low	Low
SARPAC	High	Low	High	Low	Low	High	High
Elamir YM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al	Low	Low	Low	Low	Low	Low	Low
PROCOV-19-2020	High	Some Concerns	Low	Some Concerns	Low	High	High
Haghighi S et al	Low	Low	Low	Low	Low	Some Concerns	Some Concerns
RUXCOVID	Low	Low	Low	Low	Low	Low	Low
ACTT-3	Low	Low	Low	Low	Low	Low	Low
Ameri A et al	Low	Low	Low	Low	Low	Low	Low
Maghbooli Z et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
INTEREST	High	Some Concerns	Low	Some Concerns	Low	High	High
Oilynyk O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
EB-P12-01	High	Some Concerns	Low	Some Concerns	Low	High	High
Mobarak S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Leal F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zhu R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CONTAIN	High	Some Concerns	Low	Some Concerns	Low	High	High
COV-AID-3	Low	Low	Low	Low	Low	Low	Low
Somersan-Karakaya	Low	Low	Low	Low	Low	Low	Low

COVID-19-MCS	High	Some Concerns	Low	Some Concerns	Low	High	High
Yildiz E et al	High	Low	Low	Low	Low	High	High
CYTOCOVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Algahtani FD et al	Low	Low	Low	Low	Low	Low	Low
ALPS-COVID	Low	Low	Low	Low	Low	Low	Low
R10933-10987-COV-20145	High	Some Concerns	Low	Some Concerns	Low	High	High
VCACS	High	Some Concerns	Low	Some Concerns	Low	High	High
CVD-04-CD-001	Low	Low	Low	Low	Low	Low	Low
PennCCP2	Low	Some Concerns	Low	Some Concerns	Low	Low	Low
Torghii N et al	Low	Low	Low	Low	Low	Low	Low
Isa F et al	High	Low	Low	Low	Low	High	High
MOVE-OUT	High	Some Concerns	Low	Some Concerns	Low	High	High
Weinreich_2	High	Some Concerns	Low	Some Concerns	Low	High	High
Beigmohammadi MT et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sarhan RM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
AP-014	Low	Low	Low	Low	Low	Low	Low
Asaradon M et al	Low	Low	Low	Low	Low	Low	Low
Kharazmi AB et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COMBAT-COVID	Low	Low	Low	Low	Low	Low	Low
ACPRECOV	High	Some Concerns	Low	Some Concerns	Low	High	High
X-Covid 19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Holubar M et al	Low	Low	Low	Low	Low	Low	Low
Malaysian Favipiravir Study							
George C et al	Low	Low	Low	Low	Low	Low	Low
TSUNAMI	High	Some Concerns	Low	Some Concerns	Low	High	High
CONV-ert & CoV-Early	High	Some Concerns	Low	Some Concerns	Low	High	High
Raghavan K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shohan et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Main findings

Corticosteroids

See Summary of findings Table 1, Appendix 1

We identified 19 RCTs including 9,603 participants in which systemic corticosteroids (dexamethasone, methylprednisolone, or hydrocortisone) were compared against standard of care or other treatments. Thirteen of these trials provided information on mortality for the corticosteroids against standard of care comparison. The RECOVERY trial was the biggest with 2,104 patients assigned to dexamethasone and 4,321 to standard of care. All 13 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 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate certainty ⊕⊕⊕○ (Figure 2)
- Corticosteroids probably reduce invasive mechanical ventilation requirement, RR 0.87 (95%CI 0.73 to 1.04); RD -2.2% (95%CI -4.7% to 0.7%); Moderate certainty ⊕⊕⊕○

- Corticosteroids may improve time-to-symptom resolution, RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⊕⊕○○
- Corticosteroids may not significantly increase the risk of severe adverse events, RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕○○
- Results were consistent with trials in which corticosteroids were used to treat non COVID-19 patients with ARDS. No significant differences between subgroups of studies using different corticosteroids were observed. (Figures 3 and 4)
- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) may not reduce mortality compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.96 (95%CI 0.65 to 1.42); RD -0.6% (95%CI -5.6% to 6.7%); 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

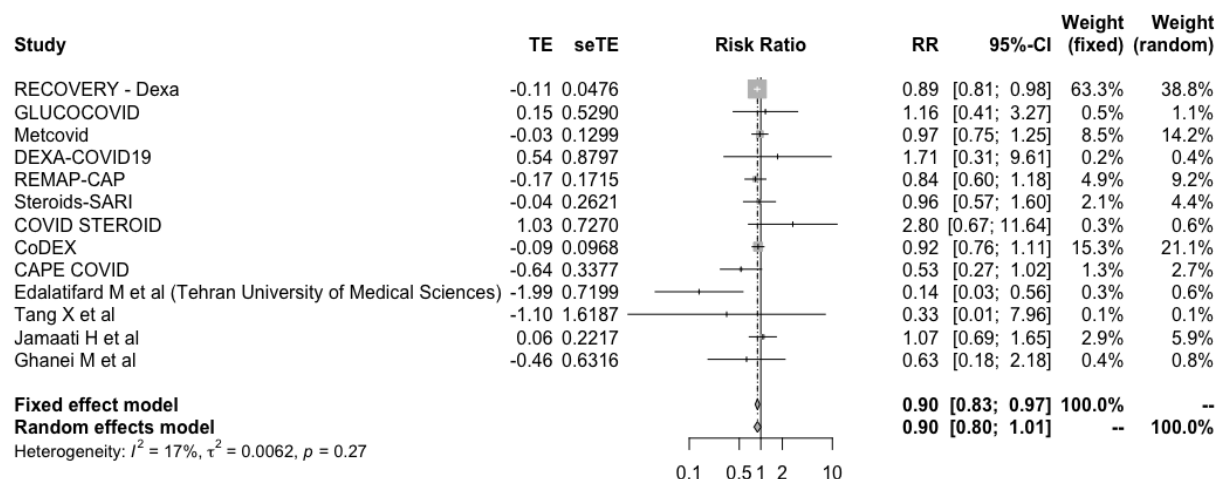


Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

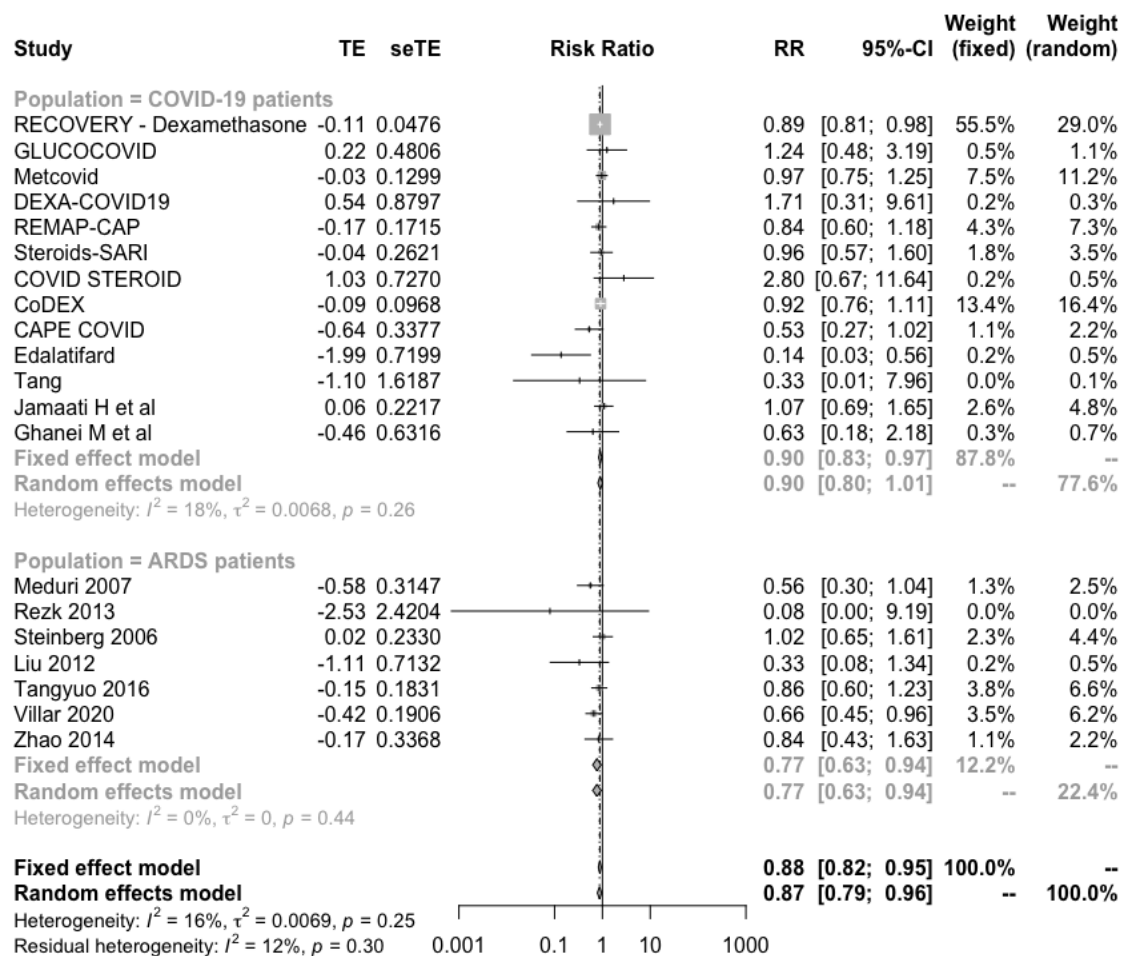


Figure 4. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

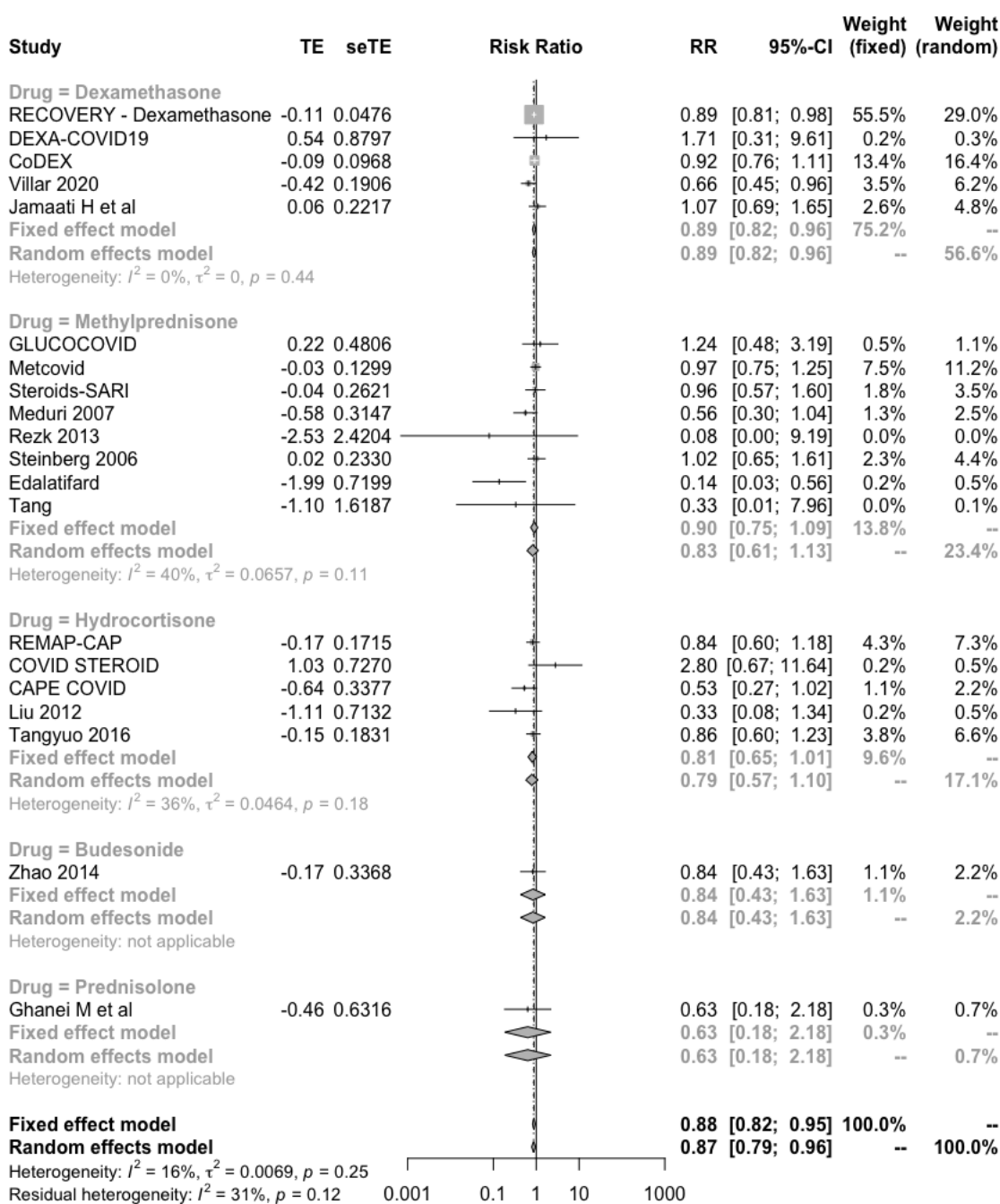
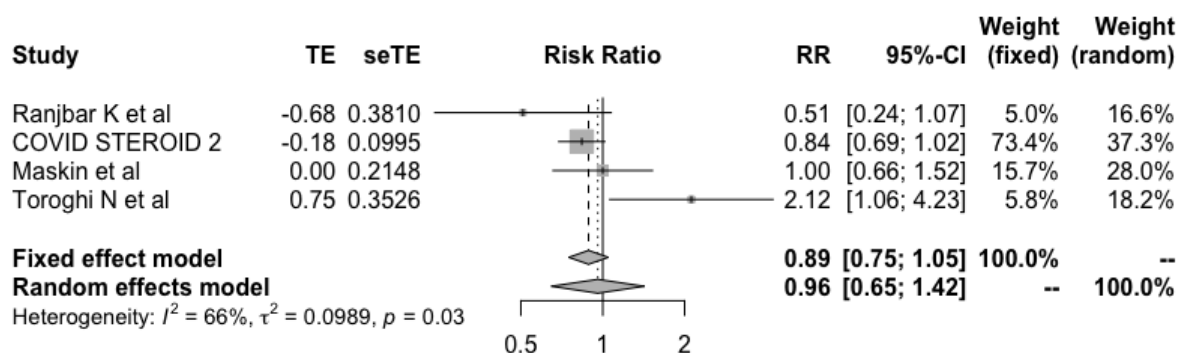


Figure 5. All-cause mortality in RCTs comparing high-dose corticosteroids (i.e., dexamethasone 12 mg a day) with standard-dose corticosteroids (i.e., dexamethasone 6 mg a day) in patients with COVID-19



Remdesivir

[See Summary of findings Table 2, Appendix 1](#)

We identified eight RCTs including 8,105 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 not reduce mortality, RR 0.97 (95%CI 0.85 to 1.10); RD -0.5% (95%CI -2.4% to 1.6%); Low certainty ⊕⊕○○ (Figure 6)
- Remdesivir may reduce invasive mechanical ventilation requirement, RR 0.79 (95%CI 0.51 to 1.23); RD -3.6% (95%CI -8.5% to 4%); Low certainty ⊕⊕○○ (Figure 7)
- Remdesivir may improve time to symptom resolution, RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low certainty ⊕⊕○○ (Figure 8)
- Remdesivir may 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

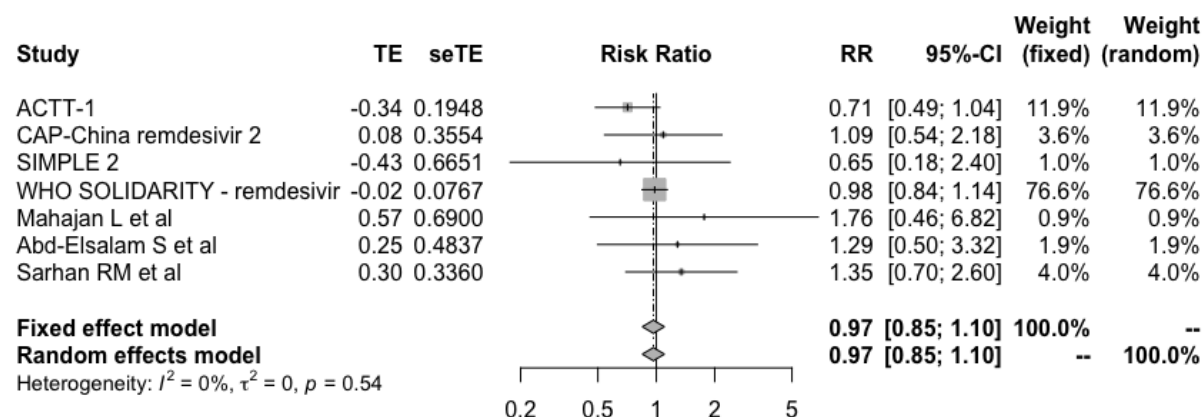


Figure 7. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

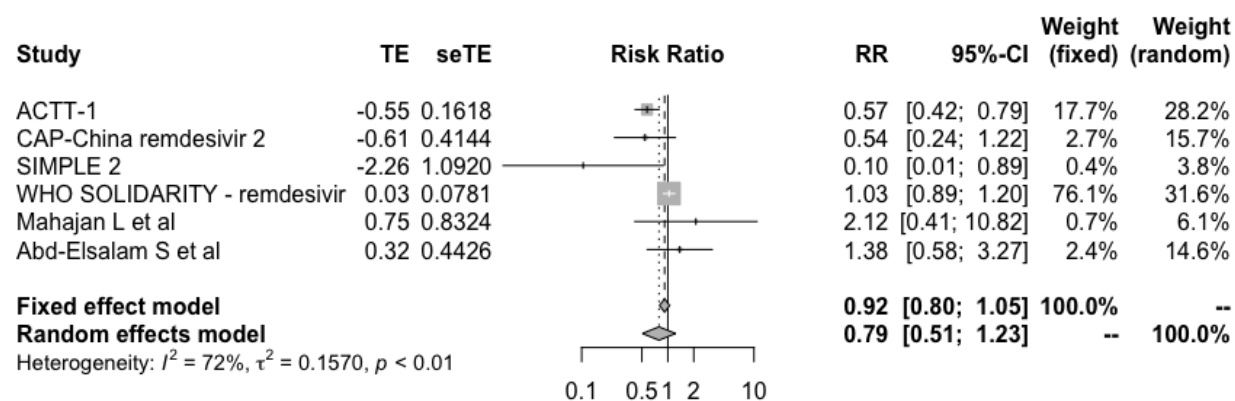
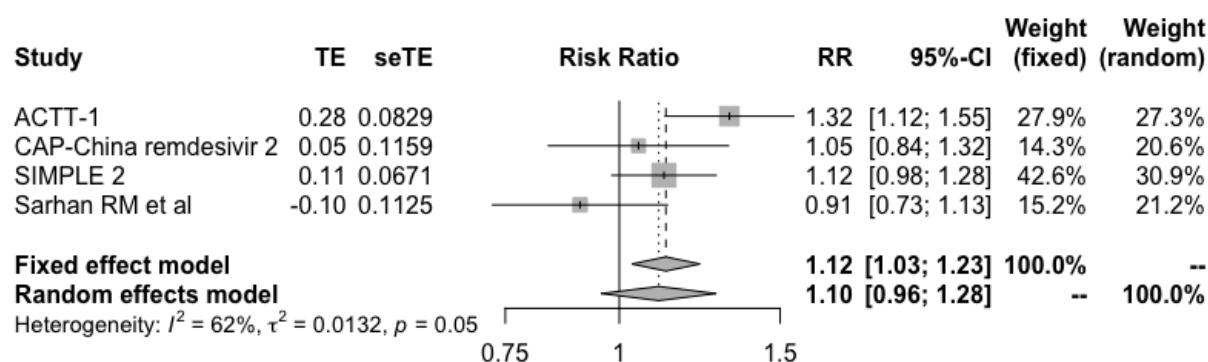


Figure 8. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

[See Summary of findings Table 3, Appendix 1](#)

We identified 51 RCTs including 22,276 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 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% 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

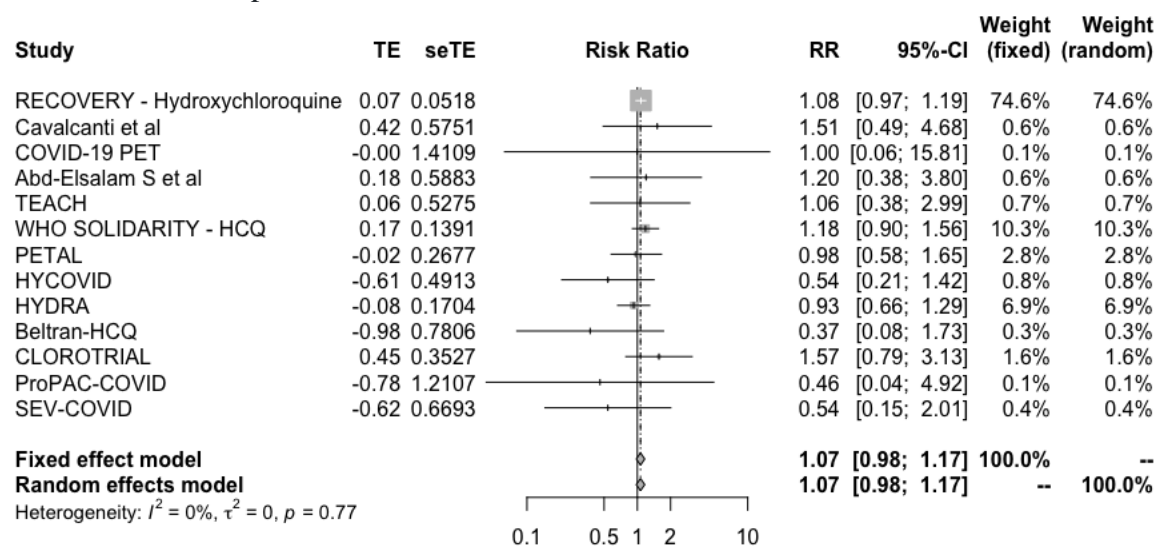
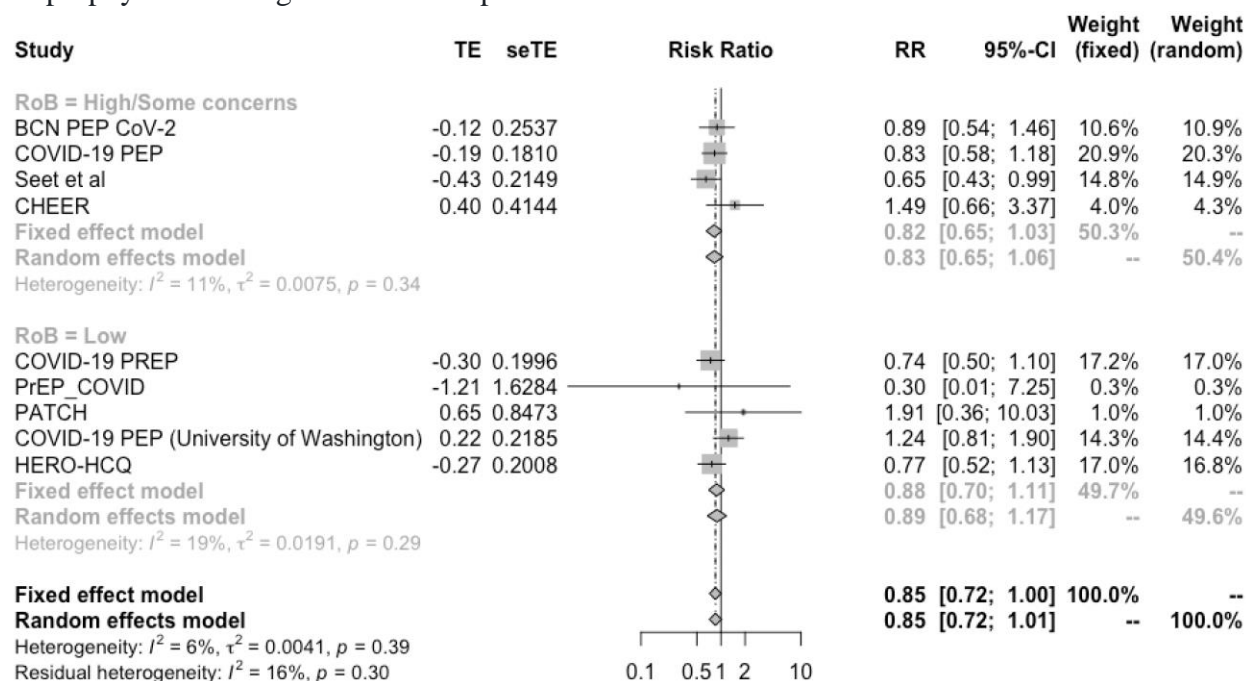


Figure 10. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



In addition, we identified a systematic review¹⁰ 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).

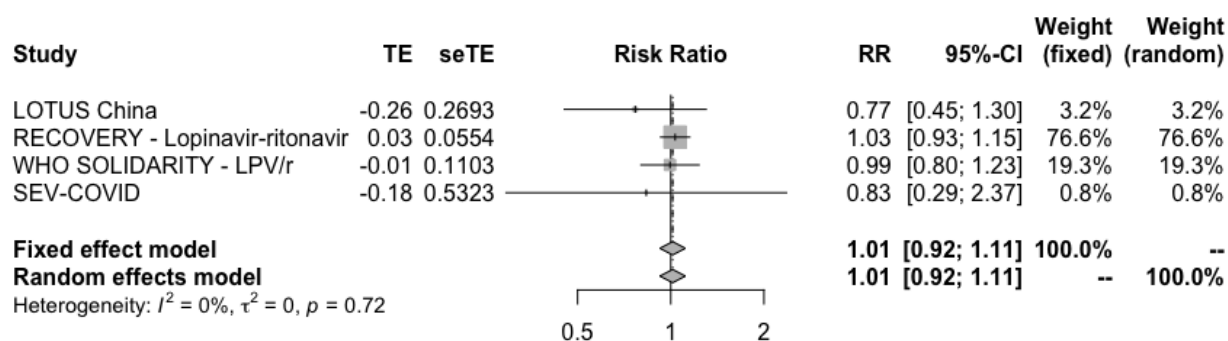
Lopinavir-ritonavir

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

We identified 17 RCTs including 10,327 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 27 RCTs including 19,262 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 (23/27) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 7.9% 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 to three 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 1.16); RD 0.8% (95%CI -1% to 2.8%); High certainty ⊕⊕⊕⊕ (based on low risk of bias studies)
- Convalescent plasma probably does not improve symptom resolution or improvement, RR 0.99 (95% CI 0.95 to 1.04); RD -0.6% (95%CI -3% to 2.4%); 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 have an important effect on hospitalizations, RR 0.89 (95% CI 0.68 to 1.16); RD -0.8% (95%CI -2.3% to 1.2%); Low certainty ⊕⊕○○

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

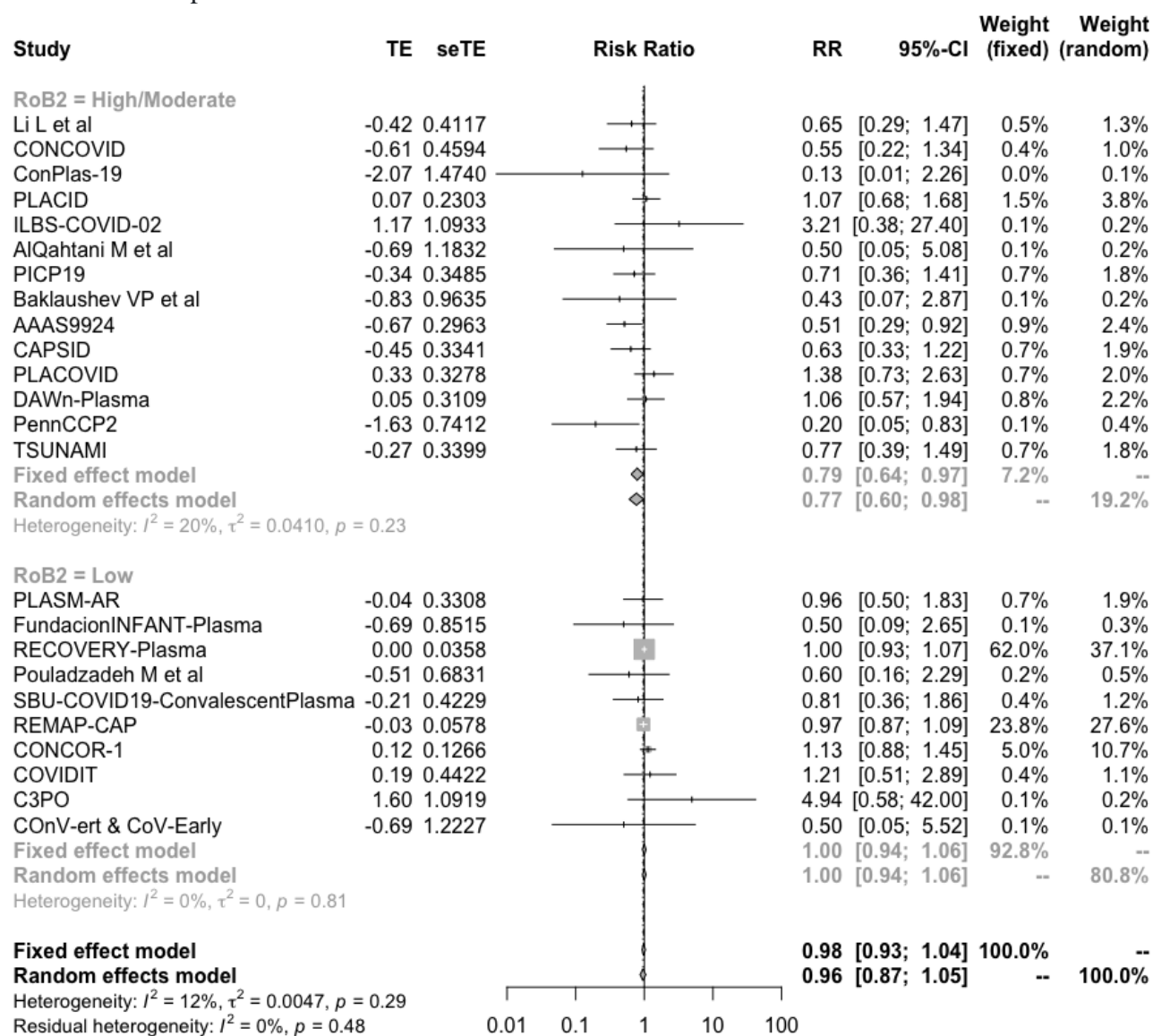
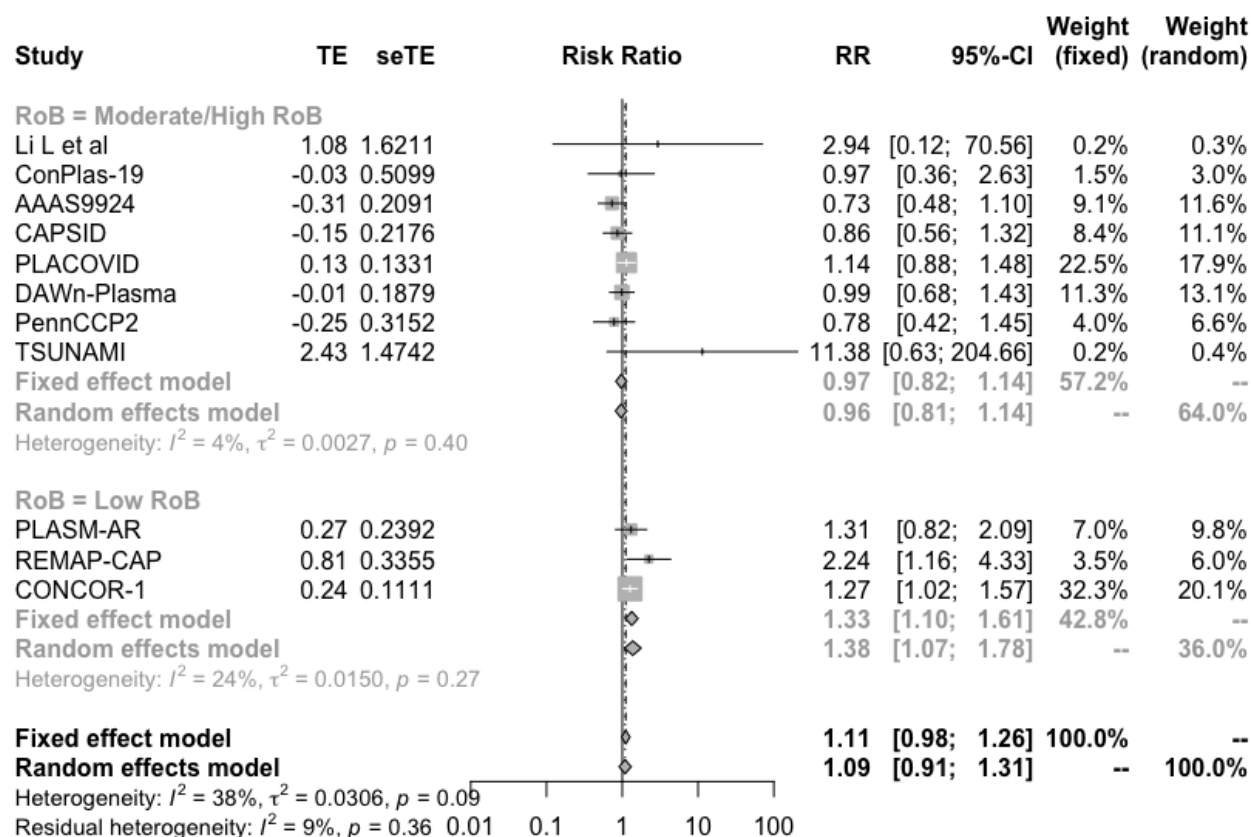


Figure 13. Severe adverse events in RCTs comparing convalescent plasma with standard of care for treatment of patients with COVID-19



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 $\oplus\circ\circ\circ$ 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 reduces mortality, RR 0.85 (95%CI 0.79 to 0.93); RD -2.4% (95%CI -3.4% to -1.1%); High 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

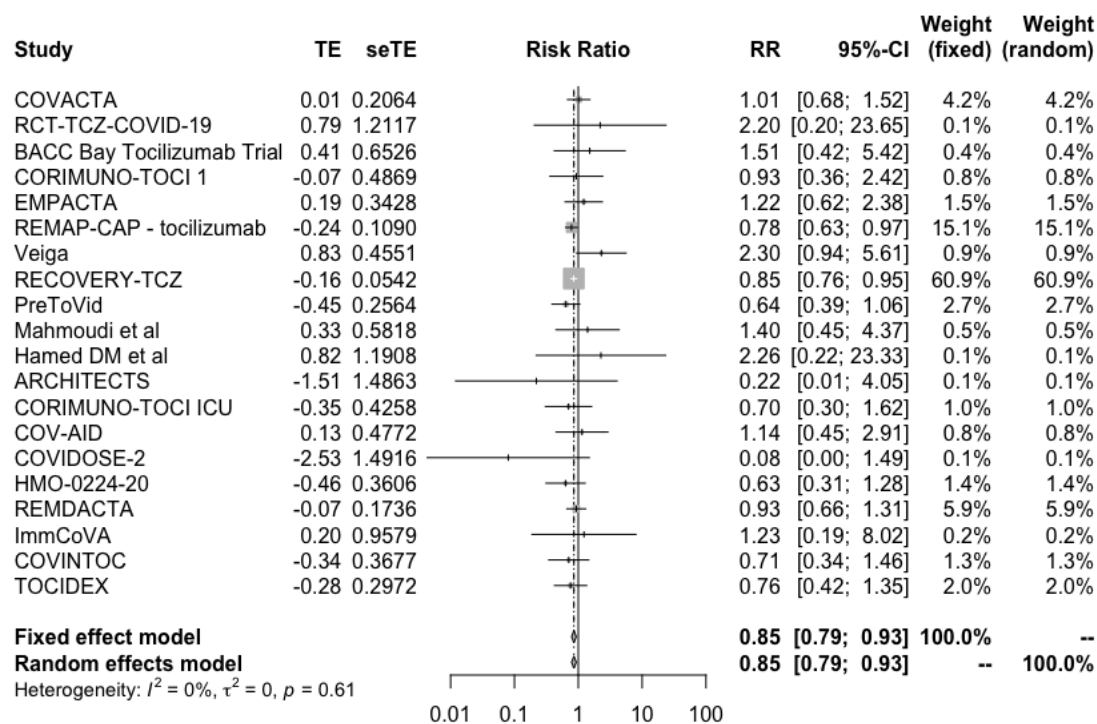
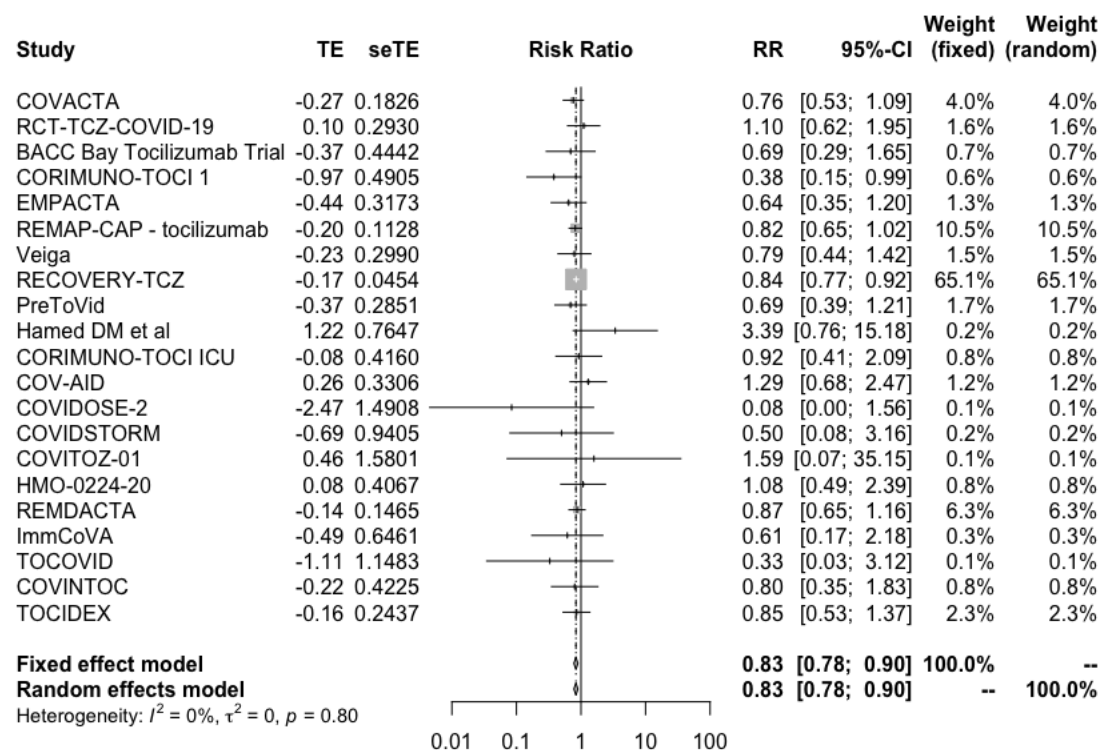


Figure 15. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



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 ($p=0.52$).

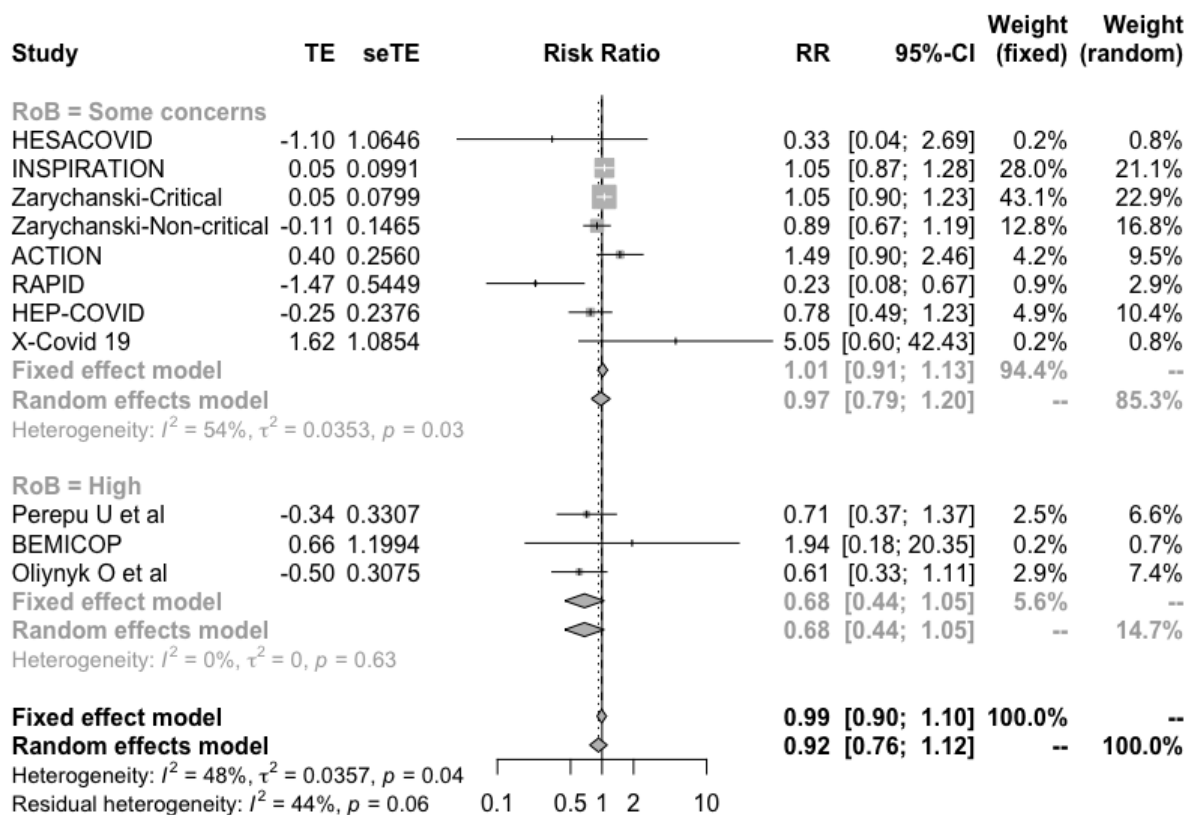
Anticoagulants

[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 thirteen RCTs including 6,637 patients that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day), or anticoagulants versus standard of care in patients with mild ambulatory disease. All studies included hospitalized patients with COVID-19. Our results showed:

- In moderate to critical patients, anticoagulants in intermediate dose or full dose may not reduce mortality in comparison with prophylactic dose, RR 0.97 (95%CI 0.79 to 1.2); RD -0.5% (95%CI -3.4% to 3.2%); Low certainty ⊕⊕○○ (excluding high risk of bias studies) (Figure 16)
- In moderate to critical patients, anticoagulants in intermediate dose may reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.82 (95%CI 0.33 to 2); RD -1.2% (95%CI -4.7% to 7%); Low certainty ⊕⊕○○
- In moderate to critical patients, anticoagulants in full dose reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.56 (95%CI 0.44 to 0.72); RD -3.1% (95%CI -3.9% to -1.9%); High certainty ⊕⊕⊕⊕
- In moderate to critical patients, anticoagulants in intermediate dose or full dose probably increase major bleeding in comparison with prophylactic dose, RR 1.76 (95%CI 1.19 to 2.62); RD 1.4% (95%CI 0.4% to 3.1%); Moderate certainty ⊕⊕⊕○
- In mild ambulatory patients, anticoagulants in prophylactic dose may not improve time to symptom resolution, RR 1.08 (95%CI 0.92 to 1.27); RD 4.8% (95%CI -4.8% to 16.4%); Low certainty ⊕⊕○○
- In mild ambulatory patients it is uncertain if anticoagulants in prophylactic dose increase or decrease clinically important bleeding and hospitalization; Very low certainty ⊕○○○

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



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.

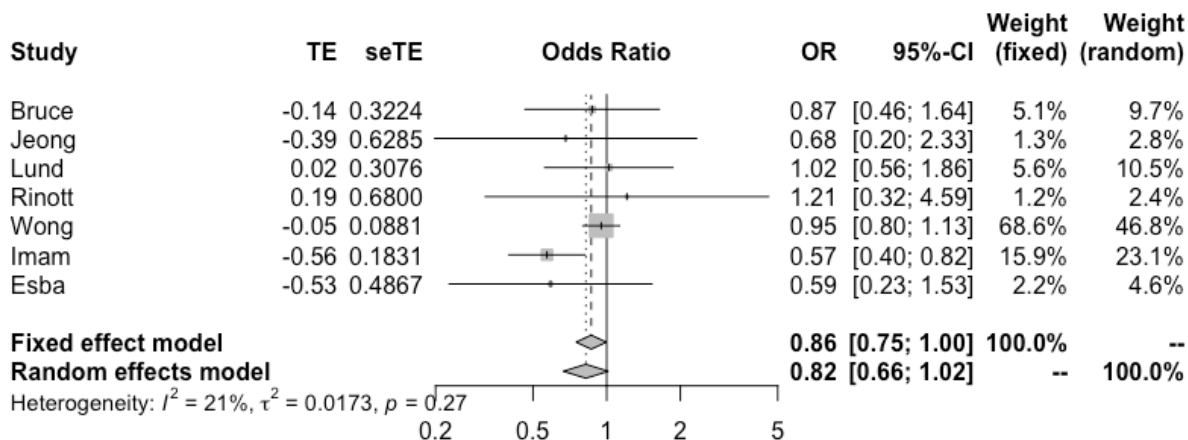
NSAIDs

[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

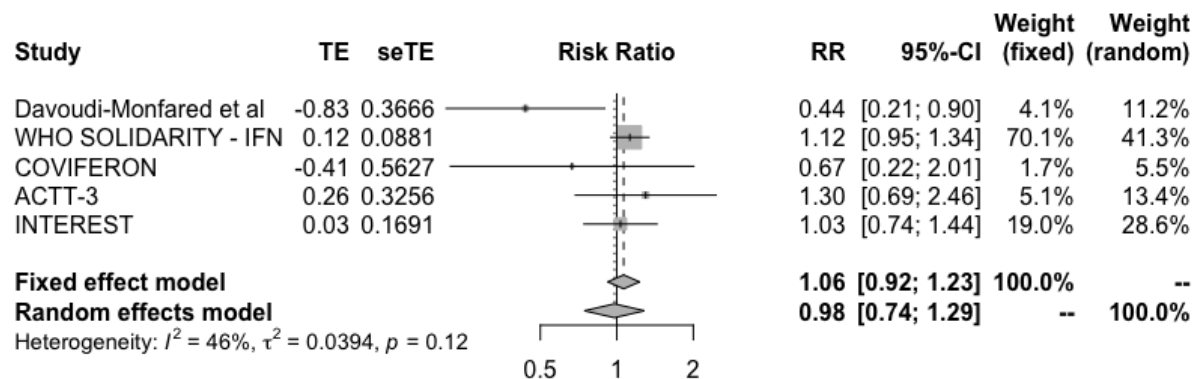
[See Summary of findings Table 9, Appendix 1](#)

We identified six RCTs including 5,752 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 0.98 (95%CI 0.74 to 1.29); RD -0.3% (95%CI -4.2% to 4.6%); Moderate certainty ⊕⊕⊕○ (Figure 18)

- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 0.97 (95%CI 0.83 to 1.14); RD -0.5% (95%CI -2.9% to 2.4%); Moderate certainty ⊕⊕⊕○
- Interferon beta-1a (subcutaneous) probably does not increase symptom resolution or improvement; RR 0.96 (95%CI 0.92 to 0.99); RD -2.6% (95%CI -4.8% to -3.2%); Moderate certainty ⊕⊕⊕○
- Interferon beta-1a probably does not increase severe adverse events, RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕○
- Interferon beta-1a (inhaled) may improve time to symptom resolution, HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕○○

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



Bamlanivimab +/- etesevimab (monoclonal antibody)

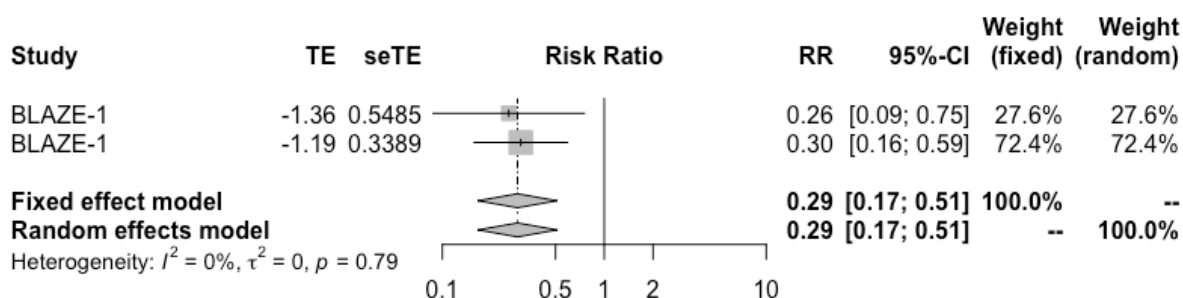
[See Summary of findings Table 10, Appendix 1](#)

We identified eight RCTs including 5,464 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.

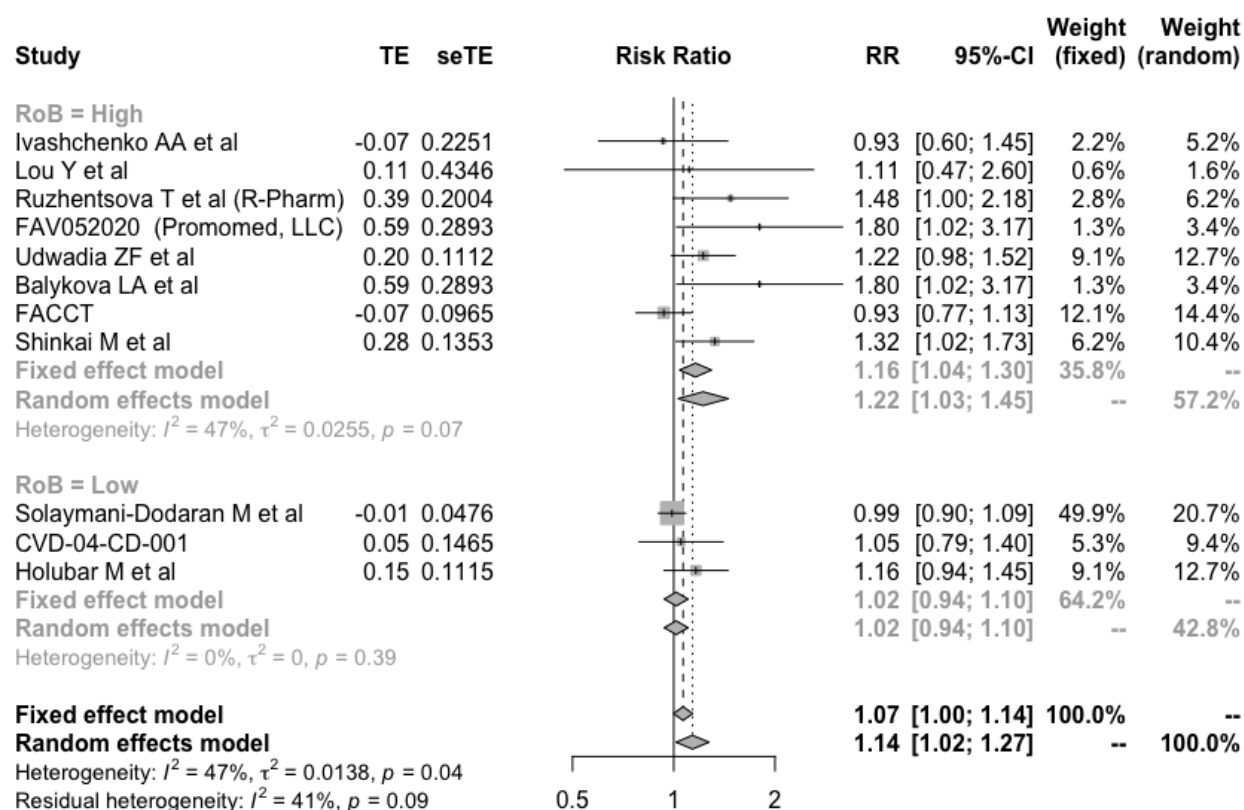
Favipiravir

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

We identified 19 RCTs including 3,473 patients in which favipiravir was compared against standard of care or other treatments. Nine 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 increase mortality; RR 1.17 (95%CI 0.82 to 1.67); RD 2.7% (95%CI -2.8% to 10.7%); Low certainty ⊕⊕○○
- Favipiravir may increase mechanical ventilation requirements; RR 1.27 (95%CI 0.91 to 1.76); RD 4.7% (95%CI -1.6% to 13.1%); Low certainty ⊕⊕○○
- Favipiravir probably does not increase symptom resolution or improvement, RR 1.02 (95%CI 0.94 to 1.1); RD 1.2% (95%CI -3.6% to 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 0.83 (95%CI 0.42 to 1.65); RD -1.7% (95%CI -5.9% to 6.6%); Very low certainty ⊕○○○
- It is uncertain if favipiravir affects hospitalizations in patients with non-severe disease; RR 0.45 (95%CI 0.1 to 2.13); RD -4% (95%CI -6.6% to 8.4%); 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 33 RCTs including 5,785 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 clinically 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 1.29 (95%CI 0.44 to 3.85); RD 2.9% (95%CI -5.7% to 29%); Very low certainty ⊕○○○
- Ivermectin may reduce hospitalizations in non-severe patients, RR 0.67 (95%CI 0.39 to 1.14); RD -2.4% (95%CI -4.5% to 1%); Low certainty ⊕⊕○○

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

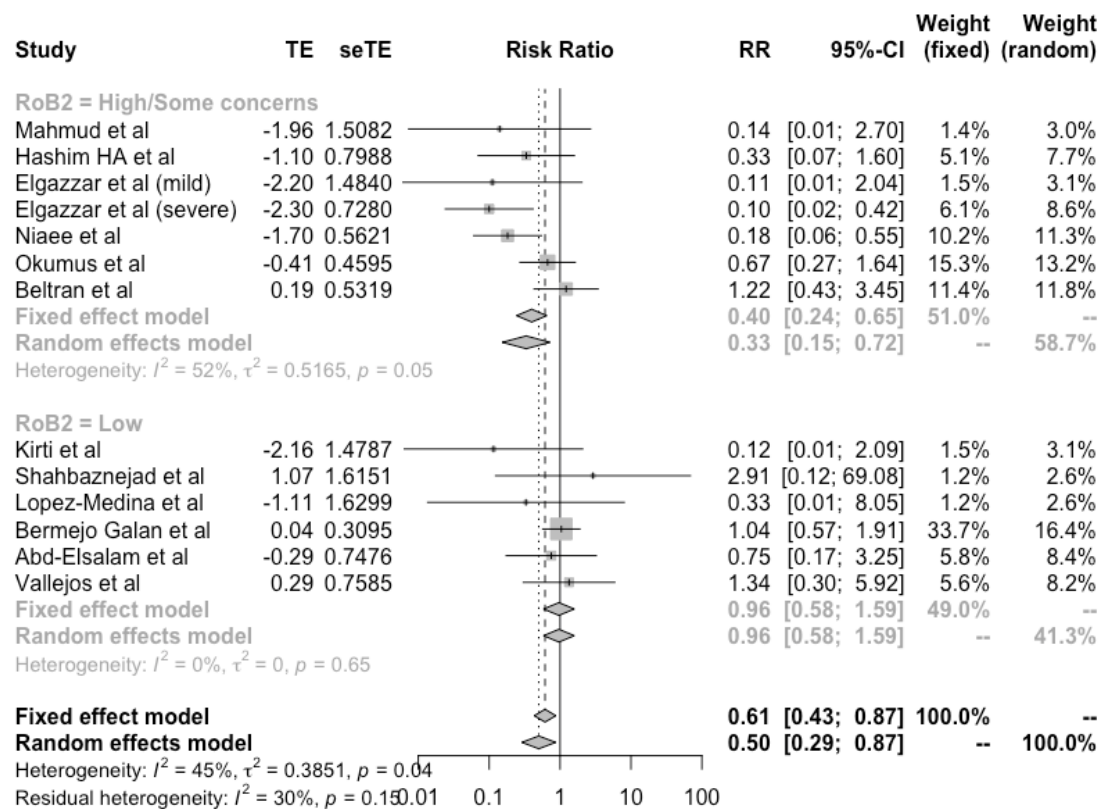
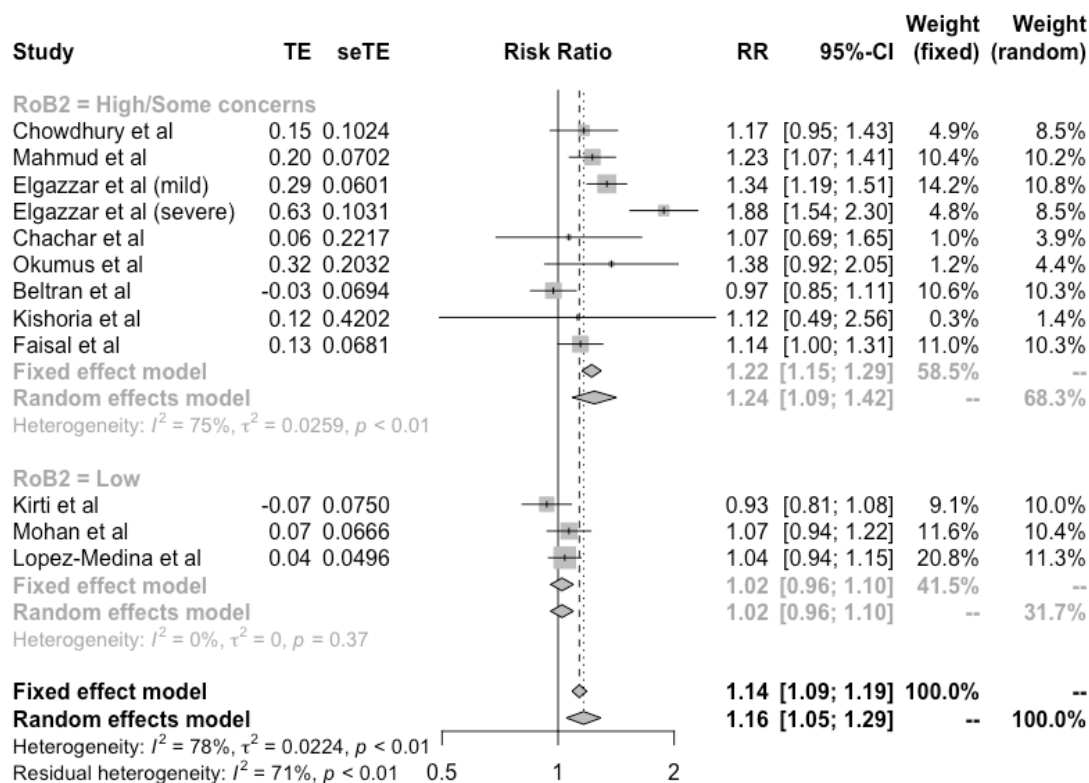


Figure 22. Symptom resolution or improvement in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



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

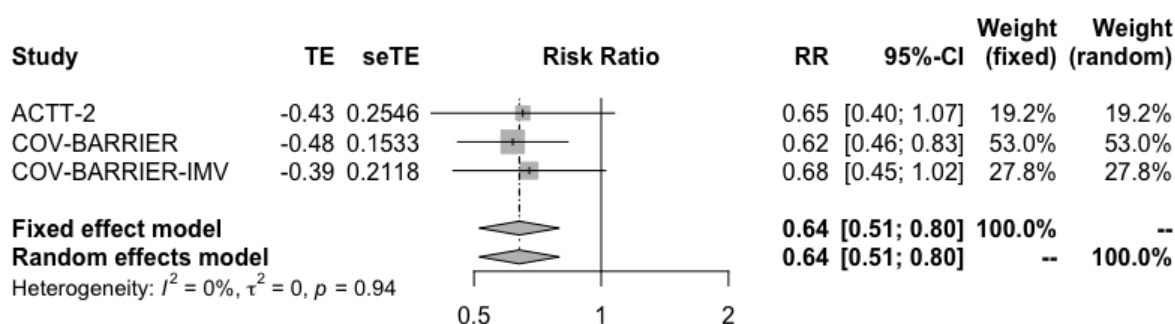
[See Summary of findings Table 13, Appendix 1](#)

We identified three RCTs including 2,659 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 probably reduces mortality, RR 0.64 (95%CI 0.51 to 0.8); RD -5.7% (95%CI -7.8% to -3.2%); 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 improves time to symptom resolution, RR 1.27 (95%CI 1.13 to 1.42); RD 16.3% (95%CI 7.9% to 25.5%); Moderate certainty ⊕⊕⊕○
- Baricitinib probably does not increase severe adverse events, RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⊕⊕⊕○

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



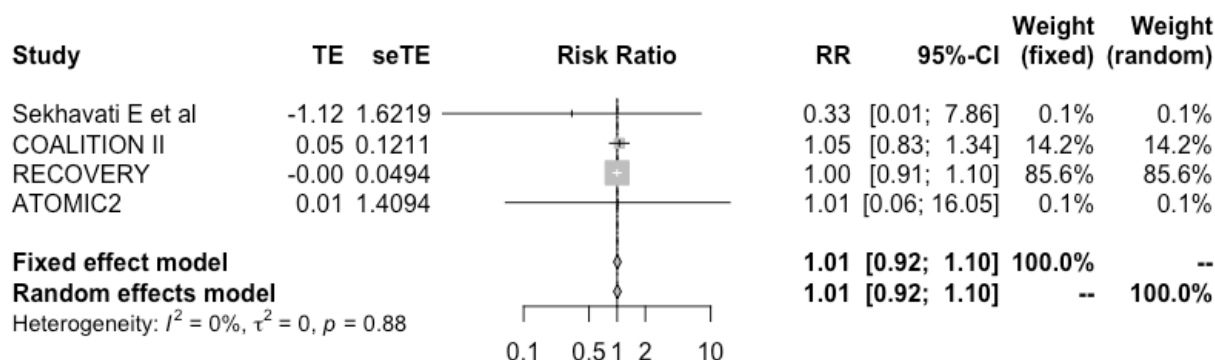
Azithromycin

[See Summary of findings Table 14, Appendix 1](#)

We identified ten RCTs including 10,429 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

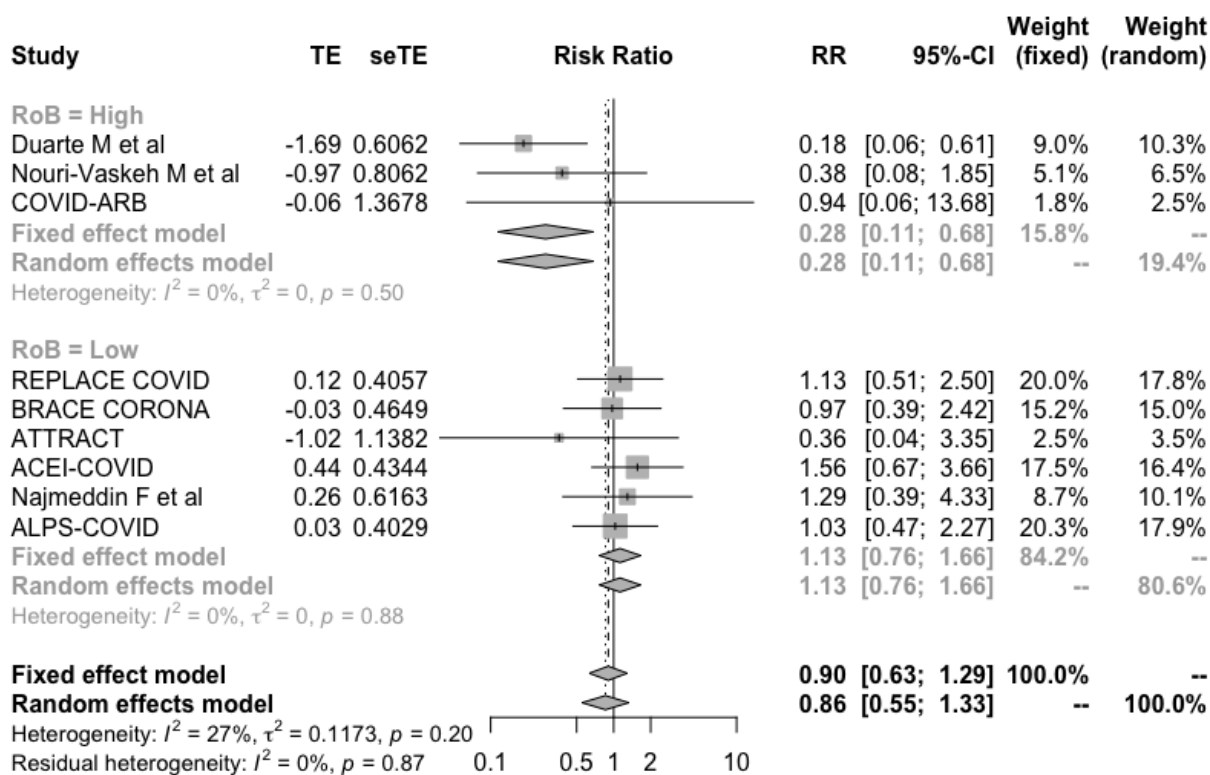


ACEI/ARB initiation or continuation

We identified ten RCTs including 1,752 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 1.13 (95%CI 0.76 to 1.66); RD 2% (95%CI -3.8% to 10.6%); Low certainty ⊕⊕○○ (Figure 25) (based on low risk of bias studies)
- ACEI/ARB discontinuation may reduce mechanical ventilation requirements, RR 0.89 (95%CI 0.66 to 1.22); RD -1.9% (95%CI -5.9% to 3.8%); Low certainty ⊕⊕○○

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



Colchicine

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

We identified seven RCTs including 16,497 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 1.07); RD 0% (95%CI -1.1% to 1.1%); 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 does not increase symptom resolution or improvement, RR 1 (95%CI 0.97 to 1.02); RD 0% (95%CI -1.8% to 1.2%); High certainty ⊕⊕⊕⊕
- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕
- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕○○○
- Colchicine may reduce hospitalizations in patients with recent onset disease, RR 0.81 (95%CI 0.63 to 1.04); RD -1.4% (95%CI -2.7% to 0.3%); Low certainty ⊕○○○

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

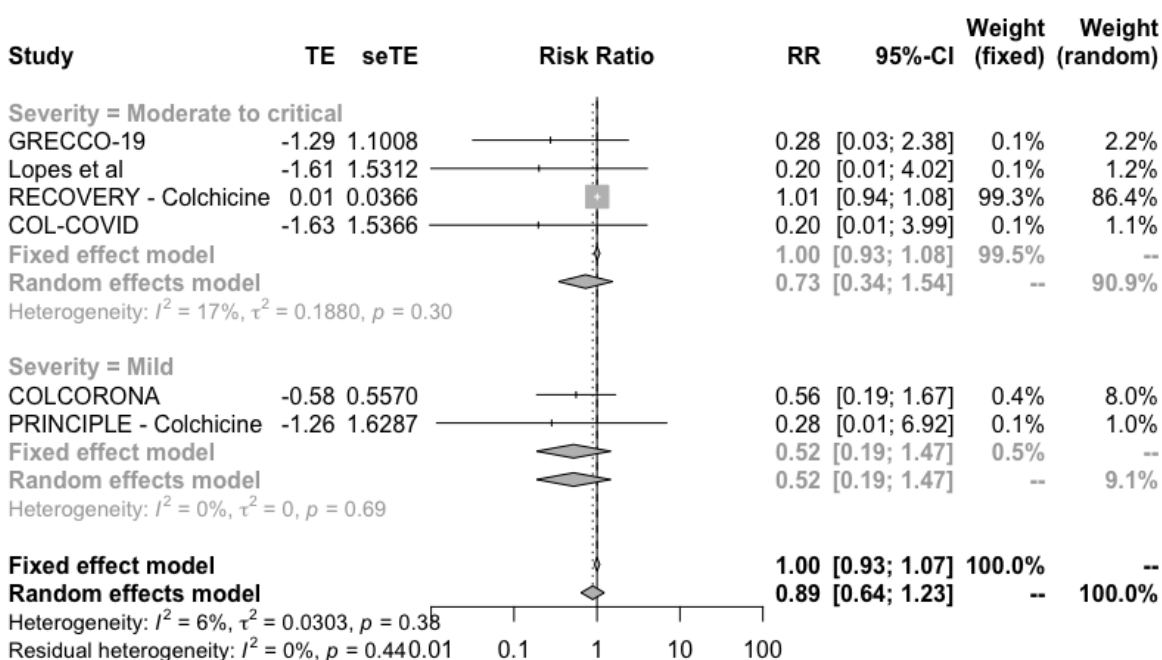
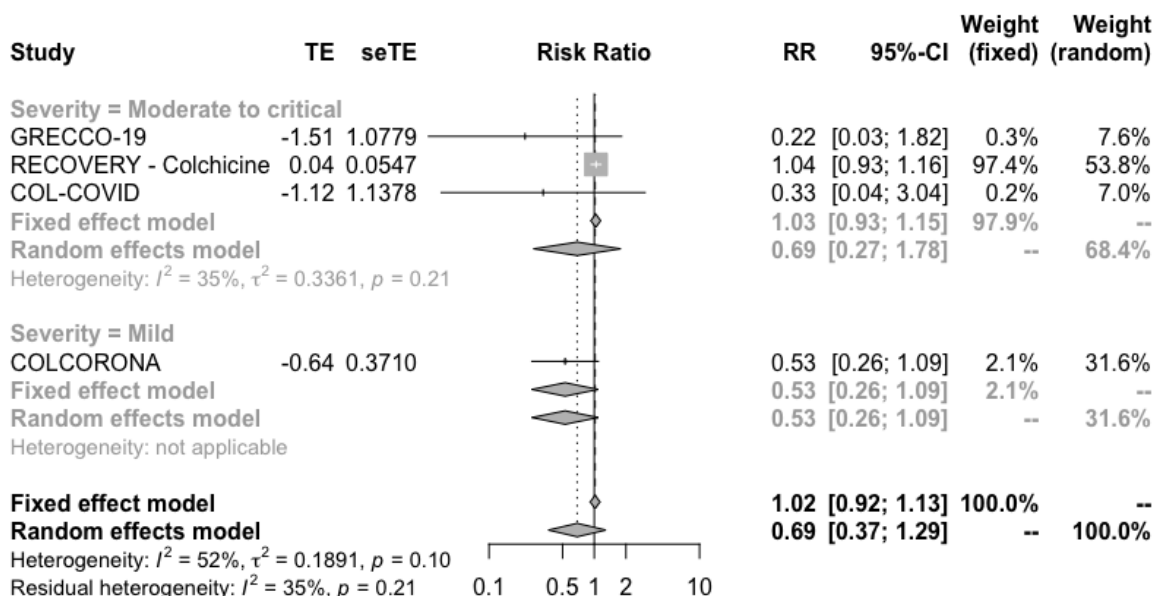


Figure 27. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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 because of a small number of events.

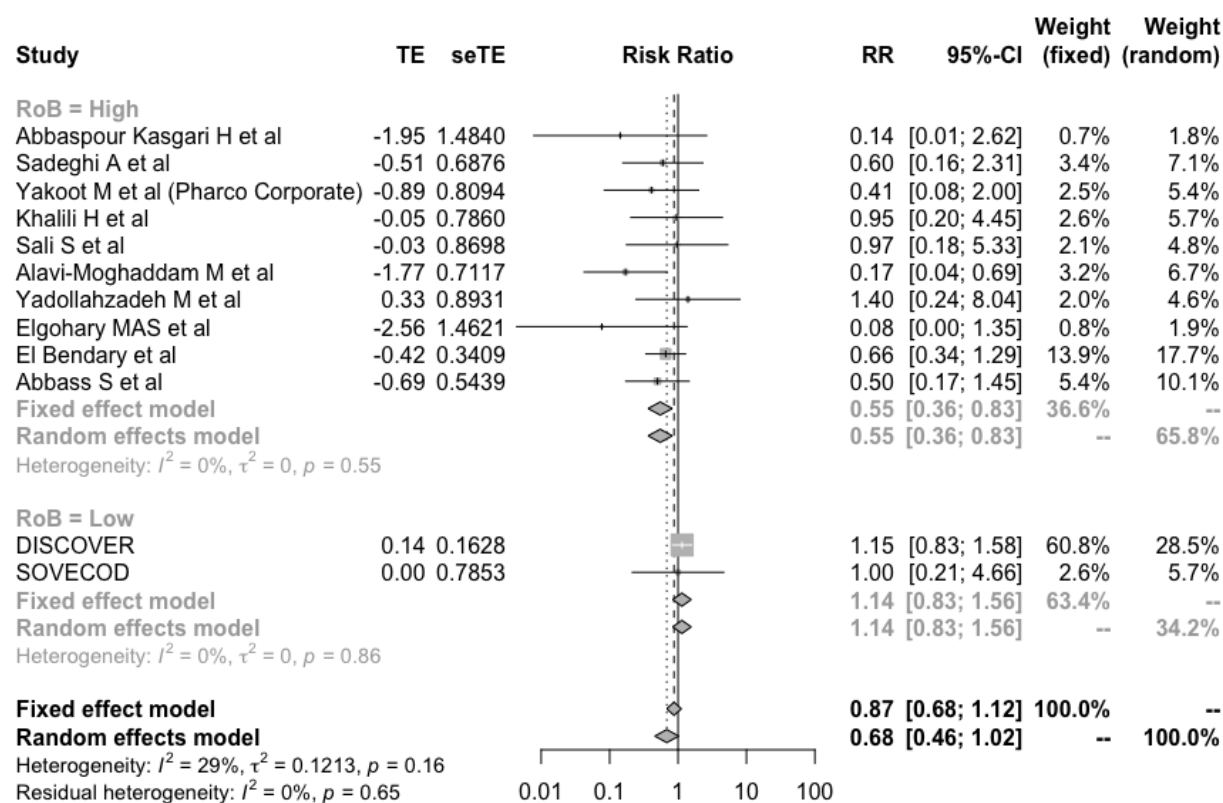
Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir

[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 1.14 (95%CI 0.83 to 1.56); RD 2.2% (95%CI -2.7% to 9%); Low certainty ⊕⊕○○ (Figure 28) (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mechanical ventilation requirements, RR 1.02 (95%CI 0.59 to 1.76); RD 0.3% (95%CI -7.1% to 13.1.7%); Low certainty ⊕⊕○○ (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir probably does not improve time to symptom resolution, RR 1.01 (95%CI 0.95 to 1.08); RD 0.6% (95%CI -3% to 4.8%); Moderate certainty ⊕⊕⊕○ (based on low risk of bias studies)

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 eight RCTs including 20,436 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 may decrease mortality, RR 0.83 (95%CI 0.64 to 1.04); RD -2.7% (95%CI -5.8% to 0.6%); Low certainty ⊕⊕○○
- In seronegative patients REGEN-COV probably decreases mortality, RR 0.8 (95%CI 0.71 to 0.89); RD -3.2% (95%CI -4.6% to -1.8%); Moderate certainty ⊕⊕⊕○ (Figure 29)
- Overall REGEN-COV may decrease mechanical ventilation, RR 0.79 (95%CI 0.54 to 1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕○○
- In seronegative patients REGEN-COV probably reduces mechanical ventilation, RR 0.82 (95%CI 0.74 to 0.9); RD -3.1% (95%CI -4.5% to -1.7%); Moderate certainty ⊕⊕⊕○
- Overall REGEN-COV may increase symptom resolution, RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕⊕○
- In seronegative patients REGEN-COV probably increases symptom resolution, RR 1.12 (95%CI 1.05 to 1.18); RD 7.2% (95%CI 3% to 10.9%); Moderate certainty ⊕⊕⊕○
- REGEN-COV reduces symptomatic infections in exposed individuals, RR 0.43 (95%CI 0.31 to 0.59); RD -9.9% (95%CI -12% to -7.1%); High certainty ⊕⊕⊕⊕
- REGEN-COV probably does not increase severe adverse events, RR 0.54 (95%CI 0.27 to 1.07); RD -4.7% (95%CI -7.4% to 0.7%); Moderate certainty ⊕⊕⊕○
- REGEN-COV probably reduces hospitalization, RR 0.30 (95%CI 0.20 to 0.46); RD -5.2% (95%CI -5.9% to -4%); Moderate certainty ⊕⊕⊕○ (Figure 30)

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

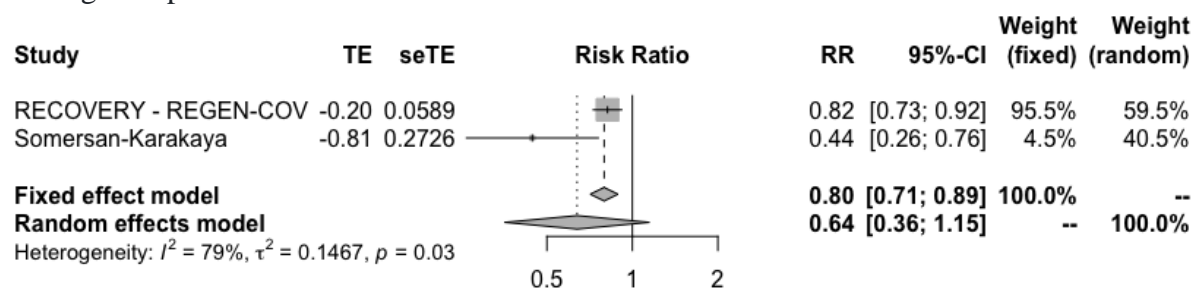
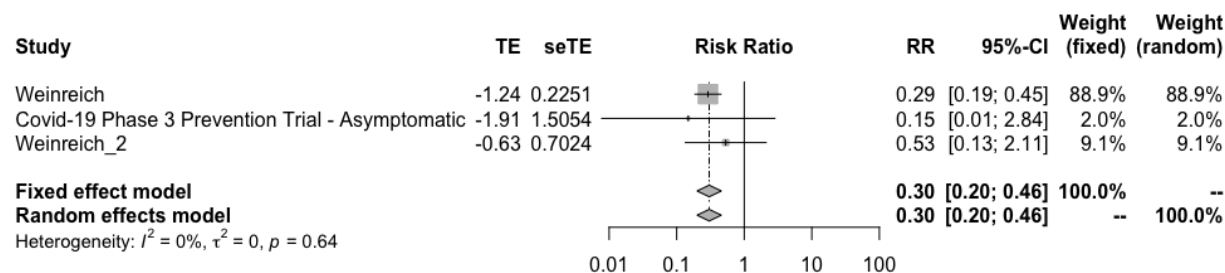


Figure 30. Hospitalization in randomized studies comparing REGEN-COV vs standard of care in patients with COVID-19



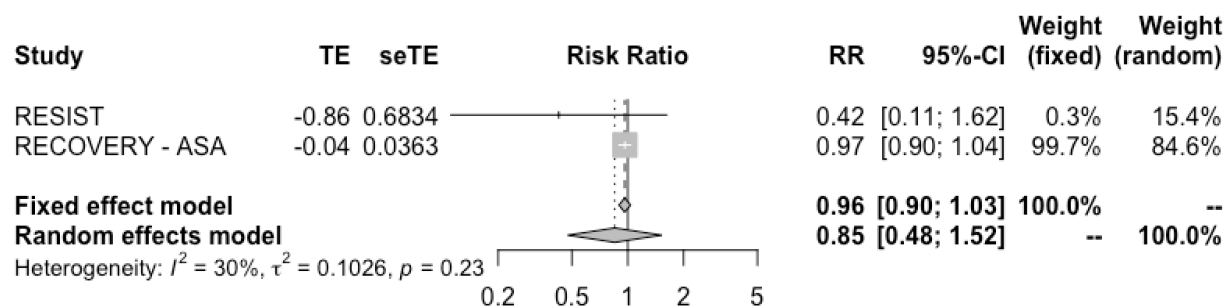
In addition, one study that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab in non-severe patients with risk factors for severity reported no important differences in hospitalizations.

Aspirin

We identified three RCTs including 15,612 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 $\oplus\oplus\oplus\circ$ (Figure 31)
- 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 $\oplus\oplus\oplus\circ$
- 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 $\oplus\oplus\oplus\circ$

Figure 31. 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:

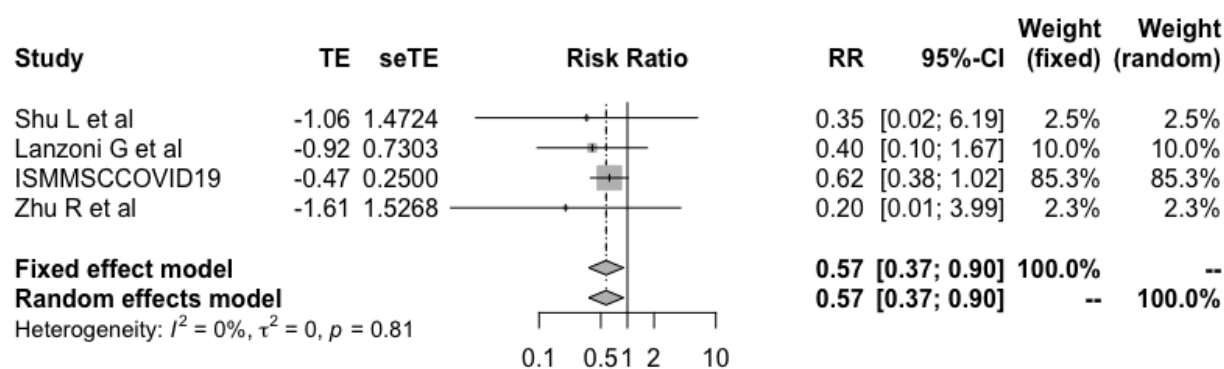
- Sotrovimab probably reduces hospitalizations, RR 0.14 (95%CI 0.04 to 0.48); RD -6.3% (95%CI -7.1% to -3.8%); Moderate certainty ⊕⊕⊕○
- Severe adverse events, RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕○○

Mesenchymal stem-cell transplantation

We identified five RCTs including 263 patients with severe to critical COVID-19, in which mesenchymal stem-cell transplantation was compared against standard of care. Our results showed:

- Mesenchymal stem-cell transplantation may reduce mortality, RR 0.57 (95%CI 0.37 to 0.90); RD -6.7% (95%CI -10.1% to -1.6%); Low certainty ⊕⊕○○ (Figure 32)

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

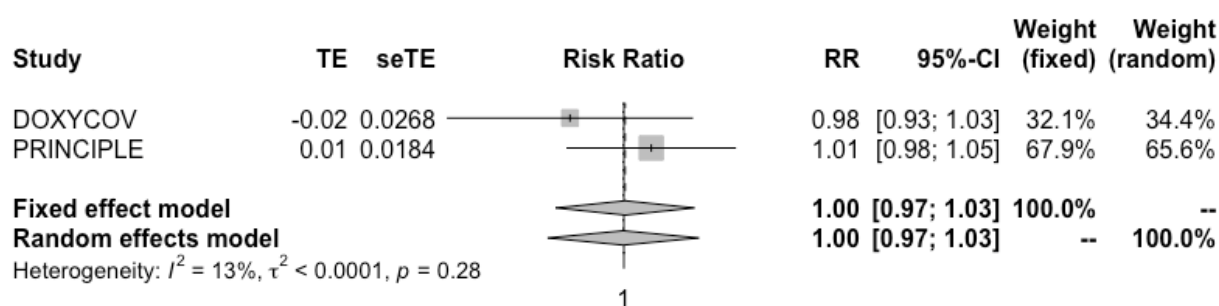


Doxycycline

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



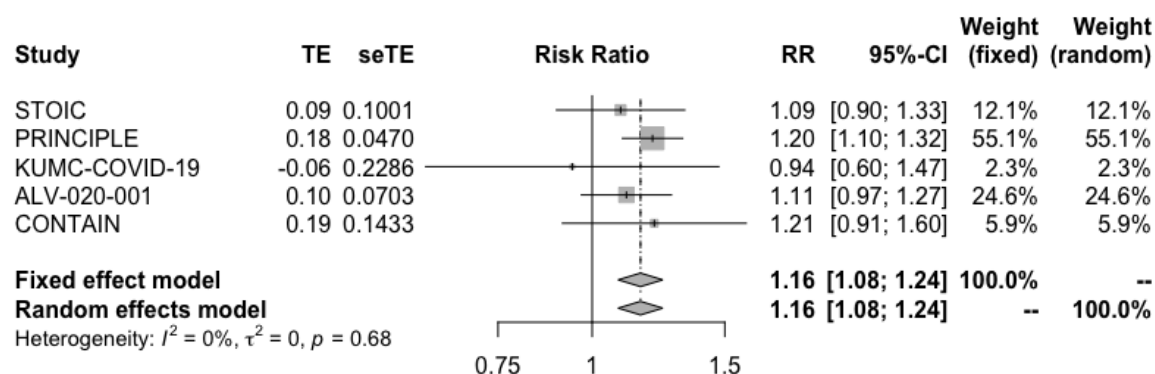
Inhaled corticosteroids

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

We identified five RCTs including 2,660 patients with mild COVID-19, in which inhaled corticosteroids were compared against standard of care. Our results showed:

- It is uncertain if inhaled corticosteroids reduce or increase mortality, RR 0.74 (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 34)
- It is uncertain if inhaled corticosteroids reduce or increase hospitalizations, RR 0.85 (95%CI 0.58 to 1.26); RD -1.1% (95%CI -3.1% to 1.9%); Very low certainty ⊕○○○

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



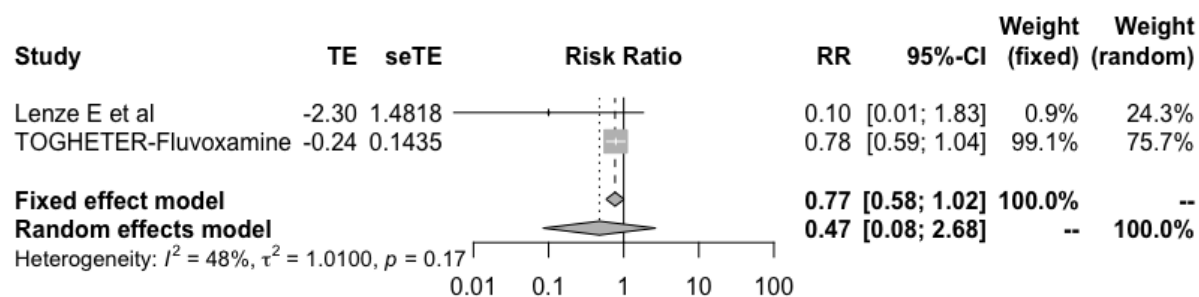
Fluvoxamine

[See Summary of findings Table 19, Appendix 1](#)

We identified two RCTs including 1,649 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 0.69 (95%CI 0.36 to 1.27); RD -5% (95%CI -10.2% to 4.3%); Very low certainty ⊕○○○
- It is uncertain if fluvoxamine reduces or increase mechanical ventilation, RR 0.77 (95%CI 0.45 to 1.3); RD -3.7% (95%CI -8.8% to 4.8%); Very low certainty ⊕○○○
- Fluvoxamine probably reduces hospitalizations, RR 0.77 (95%CI 0.78 to 1.02); RD -1.7% (95%CI -3.1% to 0.1%); Moderate certainty ⊕⊕⊕○ (Figure 35)
- Fluvoxamine may not increase severe adverse events, RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕○○

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



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
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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.	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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AMP5A (inhaled)

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

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

<p>AP-014 trial,¹⁶ Roshon et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 19 assigned to AMP5A (inhaled) four nebulization a day for 5 days and 21 assigned to SOC</p>	<p>Mean age 64 ± 15, male 62.5%</p>	<p>Corticosteroids 78%, remdesivir 40%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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Anakinra

It is uncertain if anakinra improves clinical important outcomes. 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 ; ¹⁷ 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 ; ¹⁸ 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	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
COV-AID-3 trial ; ¹⁹ Declercq et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 112 assigned to anakinra 100mg a day for 28 days and 230 assigned to SOC	Mean age 65.5, male 77.4%, hypertension 46.4%, diabetes 27.7%, COPD %, CHD 20.5%, CKD 10.8%	Corticosteroids 62.3%, remdesivir 5%, hydroxychloroquine 11.7%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to	

				symptoms and adverse events outcomes results.	
Kharazmi et al ; ²⁰ peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 15 assigned to anakinra 100mg a day for up to 14 days and 15 assigned to SOC	Mean age 54.1, male 63.3%, hypertension 33.3%, diabetes 36.6%, CHD 26.6%	Corticosteroids 63.3%, remdesivir 20%, lopinavir-ritonavir 63.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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
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RCT

REPLACE COVID trial ; ²¹ 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 1.13 (95%CI 0.76 to 1.66); RD 2% (95%CI -3.8% to 10.6%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 0.89 (95%CI 0.66 to 1.22); RD -1.9% (95%CI - 5.9% to 3.8%); Low certainty ⊕⊕○○ Symptom resolution
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<p>BRACE CORONA trial;²² Lopes et al; Peer reviewed; 2020</p>	<p>Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB</p>	<p>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%,</p>	<p>Corticosteroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%</p>	<p>Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.</p>	<p>or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
<p>ACEI-COVID trial;²³ Bauer et al; peer reviewed; 2021</p>	<p>Patients with mild to severe COVID-19 infection. 100 assigned to continuation of ACEI/ARB and 104 assigned to discontinuation of ACEI/ARB</p>	<p>Mean age 72 ± 11, male 63%, hypertension 98%, diabetes 33%, CHD 22%</p>	<p>Remdesivir 6.8%</p>	<p>Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>ATTRACT trial;²⁴ Tornling et al; peer reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200 mg a day for 7 days and 55 assigned to SOC</p>	<p>Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%</p>	<p>Corticosteroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events</p>	

<p>Nouri-Vaskeh et al;²⁵ Peer reviewed; 2020</p>	<p>Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan 50 mg a day for 14 days and 39 assigned to Amlodipine 5 mg a day for 14 days</p>	<p>Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	
<p>SURG-2020-28683 trial;²⁶ Puskarich et al; Preprint; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 58 assigned to losartan 25 mg a day for 10 days and 59 assigned to SOC</p>	<p>Age (35-54) 46%, male 51.4%, hypertension 7.7%, diabetes 6%, COPD %, asthma 10.2%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events</p>	
<p>COVID-ARB trial;²⁷ Geriak et al; peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 16 assigned to losartan 25 mg a day for 10 days and 15 assigned to SOC</p>	<p>Median age 53, male %, hypertension 38.7%, diabetes 25.8%, CHD 3.2%, obesity 41.9%</p>	<p>Corticosteroids 22.6%, remdesivir 29%, hydroxychloroquine 9.7%, , azithromycin 16.1%, convalescent plasma 6.5%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	
<p>Duarte et al;²⁸ peer reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19 infection. 71 assigned to Telmisartan 80 mg twice daily and 70 assigned to SOC</p>	<p>Mean age 66 ± 17, male 53.2%, hypertension 44.3%, diabetes 19%, chronic lung disease 11.4%, asthma 1.3%, CHD NR%, CKD 3.2%, cerebrovascular disease 6.9%, obesity 15.2%</p>	<p>Corticosteroids 50.6%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	

				Significant number of exclusions post randomization. Stop early for benefit in the context of multiple interim analysis.	
Najmeddin et al ; ²⁹ peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to continuation of ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB	Mean age 66.3 ± 9.9, male 46.9%, diabetes 50%, COPD 1.6%, CHD 25%, CKD 1.6%, cancer 4.7%,	Corticosteroids 42.2%, remdesivir 10.9%, , azithromycin 9.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes: 10.9% lost to follow-up	
ALPS-COVID trial ; ³⁰ Puskarich et al; preprint; 2021	Patients with moderate COVID-19 infection. 101 assigned to ACEI/ARB losartan 100 mg a day and 104 assigned to SOC	Mean age 55, male 60%, hypertension 42%, diabetes 22.9%, COPD 11.7%, asthma 13.2%, CHD 7.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Anticoagulants

There are specific recommendations on the use of antithrombotic agents⁸ for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) may not decrease mortality in comparison with prophylactic dose (i.e., enoxaparin 40 mg a day). Anticoagulants in intermediate or full dose probably decrease venous thromboembolic events but probably increase major bleeding in comparison with prophylactic dose.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
HESACOVID trial ; ³¹ Bertoldi Lemos et al; peer reviewed; 2020	Patients with critical COVID-19. Ten assigned to low molecular weight	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, coronary heart disease	Corticosteroids 70%, hydroxy-chloroquine 25%, azithromycin 90%	Some concerns for mortality and invasive mechanical ventilation; high for symptom	Mortality: RR 0.97 (95%CI 0.79 to 1.2); RD -0.5% (95%CI -3.4% to 3.2%); Low

	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)	10%, immunosuppression 5%		resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	certainty ⊕⊕○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
REMAP-CAP, ACTIV-4a, ATTACC trial ; ³² Zarychanski et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 534 assigned low molecular weight heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and 564 assigned to prophylactic dose (i.e., enoxaparin 40 mg a day)	Mean age 61 ± 12.5, male 70%, diabetes 32.7%, COPD 24.1%, CHD 6.9%, CKD 9.6%,	Corticosteroids 79.3%, remdesivir 30.8%, tocilizumab 1.8%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	Symptomatic infection (prophylaxis studies): No information Venous thromboembolic events (intermediate dose): RR 0.82 (95%CI 0.33 to 2); RD -1.2% (95%CI -4.7% to 7%); Low ⊕⊕○○
INSPIRATION trial ; ³³ Sadehipour et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 276 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 286 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 62 ± 21, male 57.8%, hypertension 44.3%, diabetes 27.7%, COPD 6.9%, CHD 13.9%, CKD %, cerebrovascular disease 3%	Corticosteroids 93.2%, remdesivir 60.1%, lopinavir-ritonavir 1%, tocilizumab 13.2%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	Venous thromboembolic events (therapeutic dose): RR 0.56 (95%CI 0.44 to 0.72); RD -3.1% (95%CI -3.9% to -1.9%); Moderate ⊕⊕⊕○ Major bleeding: RR 1.76 (95%CI 1.19 to 2.62); RD 1.4% (95%CI 0.4% to 3.1%); Moderate ⊕⊕⊕○
Perepu et al ; ³⁴ 2021	Patients with severe to critical COVID-19 infection. 87 assigned to low molecular	Median age 64 ± 62, male 56%, hypertension 60%, diabetes 37%, COPD 23%, CHD 31%,	Corticosteroids 75%, remdesivir 61%, azithromycin 21%, convalescent plasma	High for mortality and mechanical ventilation; high for symptom resolution, infection,	Hospitalization: No information

	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)	cancer 12%, obesity 49%	27%	and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP, ACTIV-4a, ATTACC trial ; ³⁵ Zarychanski et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 1171 assigned to enoxaparin 1 mg/kg twice a day and 1048 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Mean age 59 ± 14, male 58.7%, hypertension 51.8%, diabetes 29.7%, COPD 21.7%, CHD 10.6%, CKD 6.9%, immunosuppressive therapy 9.7%	Corticosteroids 61.7%, remdesivir 36.4%, tocilizumab 0.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
ACTION trial ; ³⁶ Lopes et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 311 assigned to enoxaparin 1 mg/kg twice a day or rivaroxaban 20 mg a day and 304 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 56.6 ± 14.3, male 60%, hypertension 49.1%, diabetes 24.4%, COPD 3.1%, asthma 4.7%, CHD 4.6%, cancer 2.6%,	Corticosteroids 83%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Although patients and carers were aware of the intervention arm assigned, outcome assessors were blinded.	
RAPID trial ; ³⁷ Sholzberg et al; peer	Patients with severe COVID-19 infection.	Mean age 60 ± 14.5, male 56.8%,	Corticosteroids 69.4%	Some concerns for mortality and	

reviewed; 2021	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	hypertension 43.8%, diabetes 34.4%, COPD 13.5%, asthma %, CHD 7.3%, CKD 7.1%, cerebrovascular disease 4.1%, cancer 6.9%,		mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.
HEP-COVID trial ; ³⁸ Spyropoulos et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 129 assigned to enoxaparin 1mg/kg twice a day and 124 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 66.7 ± 14, male 53.8%, hypertension 59.9%, diabetes 37.3%, COPD 6.7%, CHD 8.7%, CKD 3.6%, cerebrovascular disease 3.2%, cancer 2%	Corticosteroids 81%, remdesivir 70.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events
BEMICOP trial ; ³⁹ Marcos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 33 assigned to bemiparin 115 IU/Kg once daily and 32 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin	Mean age 62.7 ± 13, male 63.1%, hypertension 33.8%, diabetes 7.7%, COPD 16.9%, asthma %, CHD 6.2%, cancer 3.1%,	Corticosteroids 95.4%, remdesivir 13.8%, tocilizumab 23.1%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.

	40 mg a day) or unfractionated heparin prophylactic dose				
Oliylyk et al ; ⁴⁰ peer reviewed; 2021	Patients with severe COVID-19 infection. 84 assigned to enoxaparin 100 anti-Xa IU/kg twice a day or unfractionated heparin 80 U/kg/h intravenously, followed by a maintenance dose of 18 U/kg/h and 42 assigned to enoxaparin enoxaparin 50 anti-Xa IU/kg a day	Mean age 70.6, male 60.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
X-Covid 19 trial ; ⁴¹ Morici et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91 assigned to enoxaparin 40 mg twice a day and 92 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 59 ± 21, male 62.8%, hypertension 36.1%, diabetes 13.7%, COPD 5.5%, CKD 1.6%, cerebrovascular disease 2.7%	Corticosteroids 45.9%, remdesivir 21.8%, tocilizumab 1.1%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTIV-4B trial ; ⁴² Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 278 assigned to apixaban 2.5 to 5mg	Median age 54 ± 13, male 40.9%, hypertension 35.3%, diabetes 18.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	Mortality: No information Invasive mechanical

	twice a day and 136 assigned to SOC			and adverse events	ventilation: No information
Gates MRI RESPOND-1 trial ; ⁴³ Ananworanich et al; peer reviewed; 2021	Patients with mild covid-19 and risk factors for severity. 222 assigned to rivaroxaban 10mg a day and 222 assigned to SOC	Median age 49, male 39.3%, hypertension 51.8%, diabetes 27.7%, COPD 6.1%, immunosuppressive therapy 3.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Symptom resolution or improvement: RR 1.08 (95%CI 0.92 to 1.27); RD 4.8% (95%CI -4.8% to 16.4%); Low ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information Venous thromboembolic events (intermediate dose): No information Clinically important bleeding: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○

Aprepitant

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

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

Mehboob et al ; ⁴⁴ preprint; 2020	Patients with mild to critical COVID-19 infection. 10 assigned to aprepitant 80 mg	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	Mortality: No information Invasive mechanical ventilation: No
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	once a day for 3-5 days and 8 assigned to standard of care			infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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
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RCT

ARTI-19 trial , ⁴⁵ 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
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					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 , ⁴⁶ 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 ⊕⊕⊕○
RECOVERY-ASA trial , ⁴⁷ Horby et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 7351 assigned to aspirin 150 mg a day and 7541 assigned to SOC	Median age 59.2 ± 14.2, male 61.5%, diabetes 22%, COPD 19%, asthma %, CHD 10.5%, CKD 3%,	Corticosteroids 94%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Symptom resolution or improvement: RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information
ACTIV-4B trial , ⁴² Connors et al; peer	Patients with mild COVID-19 infection.	Median age 54 ± 13, male 40.9%,	NR	Low for mortality and mechanical ventilation;	Adverse events: No

reviewed; 2021	144 assigned to aspirin 81mg a day and 136 assigned to SOC	hypertension 35.3%, diabetes 18.3%		low for symptom resolution, infection and adverse events	information Hospitalization: Very low certainty ⊕○○○
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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
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RCT

Miller et al. ⁴⁸ 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
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Aviptadil

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE
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					certainty of the evidence
RCT					
COVID-AIV trial : ⁴⁹ Jihad et al; preprint (now retracted); 2021	Patients with severe to critical COVID-19 infection. 136 assigned to avertedil 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
Azelastine (inhaled) Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
CARVIN trial : ⁵⁰ Klussmann et al; preprint; 2021	Patients with mild COVID-19 infection. 56 assigned to azelastine (inhaled) 0.02 to 0.1% twice a day for 11 days and 28	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: No information Invasive mechanical ventilation: No information

	assigned to SOC				<p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Azithromycin

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

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

Sekhavati et al. ⁵¹ peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to azithromycin 500 mg twice daily and 55 assigned to standard of care	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Mortality: RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕○</p> <p>Invasive mechanical ventilation: RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⊕⊕⊕○</p>
Güvenmez et al. ⁵² peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for	<p>Symptom resolution or improvement: RR</p>

	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			symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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
COALITION II trial ; ⁵³ Furtado et al; peer-reviewed; 2020	Patients with severe COVID-19. 214 assigned to azithromycin 500 mg once a day for 10 days and 183 assigned to standard of care	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, coronary heart disease 5.8%, chronic kidney disease 11%, cerebrovascular disease 3.8%, immunosuppression %, cancer 3.5%, obesity %	Corticosteroids 18.1%, lopinavir-ritonavir 1%, oseltamivir 46%, ATB 85%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Adverse events: RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕○○○ Hospitalization: RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -3.6% to 6.4%); Low certainty ⊕⊕○○
RECOVERY trial ⁵⁴ 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 ; ⁵⁵ preprint ; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	

	Clarithromycin 1000 mg a day for 7 days and 99 assigned to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
PRINCIPLE trial ; ⁵⁶ 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 ; ⁵⁷ 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 ; ⁵⁸ 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	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse	

		1%, cancer 0.4%,		events Notes: Significant loss to follow-up.	
Ghanei et al. ⁵⁹ peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to Lopinavir-Ritonavir 200/50mg twice a day for 7 days and 110 assigned to azithromycin 500mg once followed by 250mg a day for 5 days	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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
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RCT

Ren et al. ⁶⁰ peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 10 assigned to azvudine 5 mg once a day and 10 assigned to standard of care	Median age 52 ± 59, male 60%, hypertension 5%, diabetes 5%, coronary heart disease 5%	Antivirals 100%, antibiotics 40%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No</p>
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					information Hospitalization: No information
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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
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RCT

Lou et al ; ⁶¹ 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
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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)
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					care) and GRADE certainty of the evidence
RCT					
BLAZE-1 trial ; ⁶² Chen et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700 mg, 2800 mg, or 7000 mg once and 143 assigned to standard of care	Mean age 45 ± 68, male 55%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: RR 1.02 (95%CI 0.99 to 1.06); RD 1.2% (95%CI 3.6% to 5.4%); Moderate certainty ⊕⊕⊕○
ACTIV-3/TICO trial ; ⁶³ Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000 mg once and 151 assigned to SOC	Median age 71 ± 22, male 66%, hypertension 49%, diabetes 29%, COPD %, asthma 9%, CHD 4%, CKD 11%, obesity 52%	Corticosteroids 49%, remdesivir 95%	Low for mortality and adverse events; high for symptom resolution. Notes: Significant loss to follow-up for symptom improvement/resolution outcome.	Symptomatic infection (prophylaxis studies): RR 0.56 (95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Moderate certainty ⊕⊕⊕○
Gottlieb et al ; ⁶⁴ Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700-7000 mg once, 112 assigned to bamlanivimab + etesevimab and 156 assigned to SOC	Mean age 44.7 ± 15.7, male 45.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	Adverse events: RR 1.16 (95%CI 0.76 to 1.78); RD 1.6% (95%CI -0.2% to -7.9%); Low certainty ⊕⊕○○
BLAZE-2 trial ; ⁶⁵ 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	Hospitalization: RR 0.29 (95%CI 0.17 to 0.51); RD -5.2% (95%CI -6.1% to -3.6%); Low certainty ⊕⊕○○

BLAZE-1 trial , ⁶⁶ 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 , ⁶⁷ 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 , ⁶⁸ 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%, immunosuppressive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
ACTIV-2 trial , ⁶⁹ Choudhary et al; preprint; 2021	Patients with mild COVID-19 infection. 159 assigned to bamlanivimab 700 to 7000mg and 158 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.	

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 ; ⁷⁰ 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 0.64 (95%CI 0.51 to 0.8); RD -5.7% (95%CI -7.8% to -3.2%); 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 ⊕⊕○○
COV-BARRIER trial ; ⁷¹ Marconi et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 764 assigned to baricitinib 4 mg for 14 days and 761 assigned to SOC	Mean age 57.6 ± 14.1, male 63.1%, hypertension 47.9%, diabetes 30%, COPD 4.6%, obesity 33%	Corticosteroids 79.3%, remdesivir 18.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	Symptom resolution or improvement: RR 1.27 (95%CI 1.13 to 1.42); RD 16.3% (95%CI 7.9% to 25.5%); Moderate certainty ⊕⊕⊕○
COV-BARRIER-IMV trial ; ⁷² Wesley et al; preprint; 2021	Patients with critical COVID-19 infection. 51 assigned to baricitinib 4 mg a day for 14 days and 50 assigned to SOC	Mean age 58.6 ± 13.8, male 54.5%, hypertension 54.5%, diabetes 35.6%, COPD 3%, obesity 56.4%	Corticosteroids 86.1%, remdesivir 2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⊕⊕⊕○

					Hospitalization: No information
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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
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RCT

Padmanabhan et al ; ⁷³ 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
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Beta glucans

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

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

Raghavan et al ; ⁷⁴	Patients with mild to	Mean age 41.2	NR	High for mortality and	Mortality: No
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peer reviewed; 2021	moderate COVID-19 infection. 16 assigned to beta glucans 3 to 13 gr a day and 8 assigned to SOC			mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	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
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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
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RCT

Rybakov et al; ⁷⁵ 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
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					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 ; ⁷⁶ peer-reviewed; 2020	Patients with severe to critical COVID-19. 12 assigned to bromhexine hydrochloride 32 mf three times a day for 14 days and 6 assigned to standard of care	Median age 52 ± 15.5, male 77.8%, hypertension 33.3%, diabetes 11.1%	Corticosteroids 22.2%, interferon 77.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
Ansarin et al ; ⁷⁷ 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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Mikhaylov et al. ⁷⁸ 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. ⁷⁹ Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 48 assigned to bromhexine 32 mg a day for 14 days and 52 assigned to SOC	Mean age 52 ± 16, male 46%, hypertension 39%, diabetes 33%, COPD 7%, asthma 6%, CHD 9%, CKD 5%, cerebrovascular disease 2%, cancer 6%,	Lopinavir-ritonavir 100%, interferon 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.

Calcitriol

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

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

Elamir et al. ⁸⁰ peer reviewed; 2021	Patients with moderate COVID-19 infection. 25 assigned to calcitriol 0.5 µg daily for 14 days and 25 assigned to SOC	Mean age 66.5, male 30%, hypertension 60%, diabetes 40%, COPD 16%, cancer 4%, obesity 20%	Corticosteroids 50%, remdesivir 52%, convalescent plasma 12%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information
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				Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>CamoCO-19 trial;^{S1} Gunst et al; peer reviewed; 2021</p>	<p>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</p>	<p>Median age 61 ± 23, male 60%, hypertension 34%, diabetes 17%, COPD 10%, asthma 13%, CHD 19%, cancer 14%, obesity 33%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very</p>
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					low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

CAN-COVID trial ; ⁸² Caricchio et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 223 assigned to canakinumab 450-750 mg/kg once and 223 assigned to SOC	Median age 59, male 58.8%, hypertension 55.7%, diabetes 36.1%, COPD 7.3%, asthma 7.7%, CHD 20.3%, CKD 8.8%, cerebrovascular disease 5.9%	Corticosteroids 36.3%, remdesivir 20.7%, hydroxychloroquine 13.2%, azithromycin 37.4%, convalescent plasma 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information
Three C trial ; ⁸³ 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	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Cannabidiol

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

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

CANDIDATE trial ; ⁸⁴ Crippa et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 49 assigned to cannabidiol 300mg a day for 14 days and 42 assigned to SOC	Mean age 39.7, male 32.7%, hypertension 4.4%, diabetes 2.2%, COPD %, asthma 3.3%, cancer 1.1%, obesity 6.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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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
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RCT

Perlin et al ; ⁸⁵ preprint; 2021	Patients with mild to moderate COVID-19 infection. 31 assigned	Mean age 58.5 ± 14, male 69.5%	Corticosteroids 91.5%, remdesivir 68.2%	High for mortality and mechanical ventilation; High for symptom	Mortality: Very low certainty ⊕○○○
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	to CERC-002 16 mg/kg once and 31 assigned to SOC			resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	<p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ⁸⁶ 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 ; ⁸⁷ 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; ⁵⁵ preprint; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to clarithromycin 1000 mg a day for 7 days and 99 assigned to SOC	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 ; ⁸⁸ Altay et al; preprint; 2020	Patients with mild to moderate COVID-19. 71 assigned to cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 22 assigned to standard of care	Mean age 35.6 ± 47, male 60%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Outcome assessors not blinded. Possible reporting bias.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
COVID-19-MCS trial ; ⁸⁹ Altay et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 229 assigned to Cofactors (L-Carnitine, N-Acetylcysteine, Nicotinamide, Serine) and 75 assigned to SOC	Mean age 36.3, male 57.6%, hypertension 9.2%, diabetes 6.2%	Hydroxychloroquine 81.9%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Colchicine

Colchicine probably does not reduce mortality and mechanical ventilation requirements nor improve time to symptom resolution; In mild ambulatory patients it may reduce hospitalizations but the certainty of the evidence is low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
GRECCO-19 trial ; ⁹⁰ 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 1.07); RD 0% (95%CI -1.1% to 1.1%); 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 ⊕⊕⊕○
Lopes et al ; ⁹¹ preprint; 2020	Patients with moderate to severe COVID-19 infection. 19 assigned to colchicine 0.5 mg three times a day, for 5 days followed by 0.5 mg twice daily for 5 days and 19 assigned to standard of care	Median age 50.75 ± 26.2, male 40%, diabetes 31.4%, chronic lung disease 14.2%, coronary heart disease 40%	Corticosteroids 40%, hydroxychloroquine 100%, azithromycin 100%, heparin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Symptom resolution or improvement: RR 1 (95%CI 0.97 to 1.02); RD 0% (95%CI -1.8% to 1.2%); High certainty ⊕⊕⊕⊕ Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕
Salehzadeh et al ; ⁹² 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.	Pulmonary embolism: RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕⊕○○
Tardif et al; ⁹³ 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	Hospitalization: RR 0.81 (95%CI 0.63 to 1.04); RD -1.4% (95%CI -2.7% to 0.3%); Low certainty ⊕⊕○○
RECOVERY- Colchicine trial; ⁹⁴ Horby et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 5610 assigned to colchicine 500 mg twice a day for 10 days and 5730 assigned to SOC	Mean age 63.4 ± 13.8, male 69.5%, diabetes 25.5%, COPD 21.5%, asthma %, CHD 21%, CKD 3%	Corticosteroids 94%	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COL-COVID trial; ⁹⁵ Figal et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 52 assigned to colchicine 1.5 gr once followed by 1 gr a day for 7 days and 51	Mean age 51 ± 12, male 52.4%, hypertension 27.2%, diabetes 14.6%, COPD 1%, CHD 2.9%, CKD 6.8%, cerebrovascular disease 1.9%,	Corticosteroids 74.8%, remdesivir 32%, lopinavir-ritonavir 1%, tocilizumab 9.7%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	assigned to SOC	immunosuppressive therapy %, cancer %, obesity 21.4%		study. Concealment of allocation probably inappropriate.	
PRINCIPLE - Colchicine trial ; ⁹⁶ Dorward et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 156 assigned to colchicine 500µg a day for 14 days and 133 assigned to SOC	Mean age 61, male 50%, hypertension 19.5%, diabetes 10.9%, COPD or asthma 32.2%, CHD 8%, cerebrovascular disease or other neurological diseases 5.2%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, hospitalization and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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
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RCT

Gaitan-Duarte et al ; ⁹⁷ 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):
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					<p>No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

Li et al. ⁹⁸ 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.	<p>Mortality: RR 1 (95%CI 0.94 to 1.06); RD 0% (95%CI -1% to 1%); High certainty ⊕⊕⊕⊕</p> <p>Invasive mechanical ventilation: RR 1.05 (95% CI 0.94 to 1.16); RD 0.8% (95%CI -1% to 2.8%); High certainty ⊕⊕⊕⊕</p>
CONCOVID trial ; Gharbharan et al. ⁹⁹ 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	<p>Symptom resolution or improvement: RR 0.99 (95% CI 0.95 to 1.04); RD -0.6% (95%CI -3% to 2.4%); Moderate certainty ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies):</p>

				symptoms and adverse events outcomes results.	No information
Avendaño-Solá et al , ¹⁰⁰ preprint; 2020	Patients with severe COVID-19. 38 assigned to convalescent plasma 250-300 ml once and 43 assigned to standard of care	Mean age 60.8 ± 15.5, male 54.3%, hypertension 39.5%, diabetes 20.9%, chronic lung disease 12.3%, asthma NR%, coronary heart disease 18.5%, chronic kidney disease 4.9%	Corticosteroids 56.8%, remdesivir 4.94%, hydroxychloroquine 86.4%, lopinavir-ritonavir 41.9%, tocilizumab 28.4%, azithromycin 61.7%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Adverse events: RR 1.38 (95% CI 1.07 to 1.78); RD 3.9% (95%CI 0.7% to 8%); Moderate certainty ⊕⊕⊕○ Hospitalization: RR 0.89 (95% CI 0.68 to 1.16); RD -0.8% (95%CI -2.3% to 1.2%); Low certainty ⊕⊕○○
PLACID trial , ¹⁰¹ 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 , ¹⁰² 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 , ¹⁰³ Bajpai et al; preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to	Mean age 48.2 ± 9.8, male 75.9%,	Hydroxychloroquine 100%, azithromycin 100%,	Low for mortality and mechanical ventilation; high for symptom	

	convalescent plasma 500 ml twice and 15 assigned to standard of care			resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
AlQahtani et al ; ¹⁰⁴ 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 ; ¹⁰⁵ 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 ; ¹⁰⁶ 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 ; ¹⁰⁷ Horby et al; Other; 2020	Patients with severe to critical COVID-19 infection. 5795 assigned to CP 275 ml a day for two days and 5763 assigned to SOC	Median age 63.5 ± 14.7, male 64.2%, diabetes 26%, COPD 24%, CHD 22%	Corticosteroids <1%, lopinavir-ritonavir <1%, azithromycin 10%, colchicine 14%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Baklaushev et al ; ¹⁰⁸ 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 ; ¹⁰⁹ Peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 150 assigned to CP one infusion and 73 assigned to SOC	Median age 61 ± 23, male 65.9%, hypertension 33.6%, diabetes 36.8%, COPD 9%, CHD 37.7%, CKD 9.4%, obesity 48.8%	Corticosteroids 81%, remdesivir 6%, hydroxychloroquine 6%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Sensitivity analysis including loss to follow-up patients significantly modified results. At the time	

				mortality was measured the number of patients on IMV was significantly higher in the intervention arm.	
Beltran Gonzalez et al ; ¹¹⁰ preprint; 2021	Patients with severe to critical COVID-19 infection. 130 assigned to CP 200 ml a day for 2 days and 60 assigned to IVIG	Mean age 58 ± 25, male 62.6%, hypertension 35.2%, diabetes 34.7%, COPD 4.7%, CHD 3.1%, CKD 3.1%, cerebrovascular disease 1.05%, cancer 0.53%, obesity 41.5%	Corticosteroids 82.6%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Pouladzadeh et al ; ¹¹¹ 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 ; ¹¹² 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 ; ¹¹³ 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 ; ¹¹⁴ 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 ; ¹¹⁵ 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 ; ¹¹⁶ 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 ; ¹¹⁷ Sekine et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 80 assigned to CP 300 ml twice and 80 assigned to SOC	Median age 60.5 ± 20, male 58.1%, hypertension 61.3%, diabetes 39.4%, COPD 13.8%, CHD 21.9%, obesity 56.9%	Corticosteroids 98.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVIDIT trial ; ¹¹⁸ 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 ; ¹¹⁹ 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 ; ¹²⁰ Devos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection.	Mean age 62 ± 14, male 68.7%, hypertension %, diabetes 29.6%, COPD	Corticosteroids 66.4%, remdesivir 14.8%, hydroxychloroquine	Low for mortality and mechanical ventilation; high for symptom	

	320 assigned to CP 200 to 250 ml once or twice and 163 assigned to SOC	9.4%, asthma 10.1%, CHD 14.1%, CKD 13.4%,	1.4%, lopinavir-ritonavir 0.4%, tocilizumab 0.6%,	resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
PennCCP2 trial , ¹²¹ Bar et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 40 assigned to CP two units and 39 assigned to SOC	Mean age 63 , male 45.6%, hypertension 67.1%, diabetes 40.5%, COPD 29.1%, CHD 29.1%, CKD 32.9%, immunosuppression 13.9%, cancer 26.6%, obesity 45.6%	Corticosteroids 83.5%, remdesivir 81%, hydroxychloroquine 2.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
TSUNAMI trial , ¹²² Manichetti et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 231 assigned to CP 200ml a day for 1 to 3 days and 239 assigned to SOC	Median age 64 ± 20, male 64.3%, hypertension 37.8%, diabetes 19.2%, COPD 5.7%, CKD 4.7%, cancer 3.6%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
COV-ert & CoV-Early trial , ¹²³ Millat-Martinez et al; other; 2021	Patients with mild to moderate COVID-19 infection. 390 assigned to CP 200 to 300 ml once and 392 assigned to SOC	Median age 58 ± 11, male 66.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

Balcells et al; ¹²⁴ 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
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Non-RCT

Joyner et al; ¹²⁵ 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%
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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
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RCT					
DARE-19 trial ; ¹²⁶ Kosiborod et al; peer reviewed; 2021	Patients with moderate COVID-19 infection and cardiometabolic risk factors. 625 assigned to dapagliflozin 10 mg for 30 days and 625 assigned to SOC	Mean age 61.4 ± 13.5, male 57.4%, hypertension 84.8%, diabetes 50.9%, COPD 4.6%, CHD 7.2%, CKD 6.6%, obesity 48.1%	Corticosteroids 28.4%, remdesivir 18%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Mortality: RR 0.76 (95%CI 0.51 to 1.12); RD -3.8% (95%CI -7.8% to 1.9%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: RR 1.02 (95%CI 0.98 to 1.06); RD 1.2% (95%CI -1.2% to 3.6%); Moderate certainty ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Darunavir-cobicistat

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
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RCT					
DC-COVID-19	Patients with mild	Mean age 47.2 ± 2.8,	NR	High for mortality and	Mortality: No

trial ; ¹²⁷ Chen et al; peer-reviewed; 2020	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	male NR, diabetes 6.6%, coronary heart disease 26.6%		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
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Dimethyl sulfoxide (DSMO) (nasal spray)

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

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

Hosseinzadeh et al ; ¹²⁸ 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):
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					<p>Very low certainty ⊕○○○</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
<p>Doxycycline</p> <p>Uncertainty in potential benefits and harms. Further research is needed.</p>					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
<p>DOXYCOV trial,¹²⁹ Sobngwi et al; preprint; 2021</p>	<p>Patients with mild COVID-19 infection. 92 assigned to doxycycline 200 mg a day for 7 days and 95 assigned to SOC</p>	<p>Mean age 39 ± 13, male 52.4%, hypertension 1.1%, asthma 1.6%</p>	NR	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: RR 1 (95%CI 0.97 to 1.03); RD 0% (95%CI -1.8% to 1.8%); High certainty ⊕⊕⊕⊕</p>
<p>PRINCIPLE trial,¹³⁰ Butler et al; peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 61.1 ± 7.9, male 44.1%, hypertension 41.5%, diabetes 18%, COPD 37.3%, CHD 14.2%, cerebrovascular disease 6.2%</p>	NR	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: RR 1.13 (95%CI 0.73 to 1.74); RD 0.5%</p>

					(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 ; ¹³¹ Cadejani et al; preprint; 2020	Patients with mild COVID-19. 64 assigned to dutasteride (dosage not reported) and 66 assigned to standard of care	Mean age 42 ± 12, male 100 %, diabetes 11%, COPD 0%, asthma 1%, coronary heart disease 1%, cancer 0%, obesity 15.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
EAT-DUTA AndroCoV trial ; ¹³² Cadejani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 43 assigned to dutasteride 0.5 mg a day for 30 days and 44 assigned to SOC	Mean age 41.9 ± 12.4, male 100%, hypertension 21.8%, diabetes 9.2%, COPD 0%, asthma 1.1%, CHD 1.1%, cancer 0%, obesity 10.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Significant lost to follow-up.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○
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 ; ¹³³ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○</p> <p>Adverse events: No information</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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
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RCT					
Gaitan-Duarte et al ; ¹³⁴ 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	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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No</p>

	SOC			introduced bias to symptoms and adverse events outcomes results.	<p>information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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. ¹³⁵ 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 , ¹³⁶ 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 INCREASE mortality and 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; ¹³⁷ 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 1.17 (95%CI 0.82 to 1.67); RD 2.7% (95%CI -2.8% to 10.7%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 1.27 (95%CI 0.91 to 1.76); RD 4.7% (95%CI -1.6% to 13.1%); Low certainty ⊕⊕○○
Ivashchenko et al ¹³⁸ peer-reviewed; 2020	Patients with moderate COVID-19 infection. 20 assigned to favipiravir 1600 mg once followed by 600 mg twice a day for 12 days, 20 assigned to favipiravir and 20 assigned to standard of care	Mean age not reported	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Symptom resolution or improvement: RR 1.02 (95%CI 0.94 to 1.1); RD 1.2% (95%CI -3.6% to 6%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.83 (95%CI 0.42 to 1.65); RD -1.7% (95%CI -5.9% to 6.6%); Very low certainty ⊕○○○
Lou et al; ⁶¹ 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.	Hospitalization: RR 0.45 (95%CI 0.1 to 2.13); RD -4% (95%CI -6.6% to 8.4%); Very low certainty ⊕○○○
Doi et al , ¹³⁹ 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 , ¹⁴⁰ 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 , ¹⁴¹ 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 ; ¹⁴² 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 ; ¹⁴³ 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 ; ¹⁴⁴ 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 ; ¹⁴⁵ peer-reviewed; 2020	Patients with moderate to severe COVID-19. 100 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 14 days and 100 assigned to SOC	Mean age 49.7 ± 13, male 50%, hypertension 28.5%, diabetes 9%, COPD 5%, asthma %, CHD 6%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Solaymani-Dodaran et al ; ¹⁴⁶ 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 ; ¹⁴⁷ 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 ; ¹⁴⁸ 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 ; ¹⁴⁹ peer reviewed; 2021	Patients with moderate COVID-19 infection. 107 assigned to favipiravir 3200 mg once followed by 1600 mg a day for 14 days and 49 assigned to SOC	Mean age 46.2, any comorbidities 75.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
FIGHT-COVID-19 trial ; ¹⁵⁰ Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800mg a day or	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.

	Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day or favipiravil 6000mg followed by 2400mg + Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day for 7 to 14 days.				
CVD-04-CD-001 trial ; ¹⁵¹ Shenoy et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 175 assigned to favipiravir 3600mg on day 1 followed by 1600mg a day for 10 days and 178 assigned to SOC	Mean age 51.9 ± 12.5, male 67.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Holubar et al ; ¹⁵² preprint; 2021	Patients with mild to moderate COVID-19 infection. 59 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 10 days and 57 assigned to SOC	Mean age 43 ± 12, male 51.9%, hypertension 8.6%, diabetes 8.6%, COPD 4.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Malaysian Favipiravir Study trial ; ¹⁵³ Chuah et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 250 assigned to favipiravir 3601 mg once followed by 1600 mg a day for 5 days and 250 assigned to SOC	Mean age 62.5 ± 8, male 48.4%, hypertension 80.2%, diabetes 49.8%, COPD 1.4%, asthma 7.4%, CHD 15%, CKD 1.4%, immunocompromised therapy 0.4%, cancer 1.4%, obesity 20.6%	Corticosteroids 24.6%, tocilizumab 2%, vaccinated 0.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse	

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
Febuxostat Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Davoodi et al. ¹⁵⁴ peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to HCQ	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○ Hospitalization: No information
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 ; ¹⁵⁵ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to finasteride 5 mg a day for 7 days and 40 assigned to SOC	Mean age 72 ± 14, male 100%, hypertension 66.3%, diabetes 25%, COPD 12.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p> <p>Hospitalization: No information</p>
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 ; ¹⁵⁶ peer-reviewed; 2020	Patients with mild to moderate COVID-19. 80 assigned to fluvoxamine	Median age 45.5 ± 20.5, male 28.2%, hypertension 19.7%, diabetes 11%, asthma	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical</p>

	incremental dose to 100 mg three times a day for 15 days and 72 assigned to standard of care	17.1%, obesity 56.6%		and adverse events	ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information
TOGHETER-Fluvoxamine trial ; ¹⁵⁷ Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 741 assigned to Fluvoxamine 100mg a day for 10 days and 756 assigned to SOC	Median age 50 ± 18, male 42.5%, hypertension 13.2%, diabetes 16.5%, COPD 0.6%, asthma 1.9%, CHD 1.1%, CKD 0.3%, obesity 0.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes:	Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕○○ Hospitalization: RR 0.77 (95%CI 0.78 to 1.02); RD -1.7% (95%CI -3.1% to 0.1%); 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
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RCT

Strich et al ; ¹⁵⁸ 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	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
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	SOC				<p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

Shogenova et al. ¹⁵⁹ 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	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p>
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					Hospitalization: No information
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Hesperidin

Hesperidin may not improve symptom resolution, however the certainty of the evidence was low. Further research is needed.

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

HESPERIDIN trial ; ¹⁶⁰ Dupuis et al; preprint; 2021	Patients with mild COVID-19 infection. 104 assigned to hesperidin 1000 mg once a day and 107 assigned to SOC	Mean age 41 ± 12.1, male 44.9%, hypertension 10.6%, diabetes 3.2%, COPD 0.9%, asthma 13.5%, CHD 0%, cerebrovascular disease 0%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: RR 0.87 (95%CI 0.57 to 1.34); RD -7.9% (95%CI -26.1% to 20.6%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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Hemadsorption

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CYTOCOV-19 trial ; ¹⁶¹ Jarczak et al; preprint; 2021	Patients with critical COVID-19 infection. 12 assigned to hemadsorption and 12 assigned to SOC	Mean age 64.5 , male 75%, hypertension 66.6%, diabetes 33.3%, CHD 4%, CKD 25%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Hydroxychloroquine and chloroquine

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 ; ¹⁶² Borba et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 41 assigned to chloroquine 600 mg	Mean age 51.1 ± 13.9, male 75.3%, hypertension 45.5%, diabetes 25.5%, chronic	Azithromycin 100%, oseltamivir 89.7%	Low for mortality and invasive mechanical ventilation; low for symptom resolution,	Mortality: RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI - 0.3% to 2.7%);

	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	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%,		infection, and adverse events	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 ⊕⊕⊕○
Huang et al ; ¹⁶³ 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.	Moderate certainty ⊕⊕⊕○ Symptom resolution or improvement: RR 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% to 6.1%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): RR 0.85 (95%CI 0.72 to 1.01); RD -2.6% (95%CI -4.9% to 0.2%); Low certainty ⊕⊕○○
RECOVERY-Hydroxychloroquine trial ; ¹⁶⁴ Horby et al; preprint; 2020	Patients with Mild to critical COVID-19 infection. 1561 assigned to hydroxychloroquine 800 mg once followed by 400 mg twice a day for 9 days and 3155 assigned to standard of care	Mean age 65.3 ± 15.3, male %, diabetes 26.9%, chronic lung disease 21.9%, asthma NR%, coronary heart disease 25.4%, chronic kidney disease 7.8%, HIV 0.4%	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	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 ; ¹⁶⁵ 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	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	

	for 6 days and 1198 assigned to standard of care			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 ; ¹⁶⁶ 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 ; ¹⁶⁷ Cavalcanti et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 159 assigned to hydroxychloroquine 400 mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to standard of care	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%, diabetes 19.1%, chronic lung disease 1.8%, asthma 16%, coronary heart disease 0.8%, chronic kidney disease 1.8%, cancer 2.9%, obesity 15.5%	Corticosteroids 1.5%, ACE inhibitors 1.2%, ARBs 17.4%, NSAID 4.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Kamran SM et al ; ¹⁶⁸ Kamran et al; preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to	Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%	NR	High for symptom resolution, infection, and adverse events

	hydroxychloroquine 400 mg twice a day once then 200 mg twice a day for 4 days and 151 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
COVID-19 PET trial ; ¹⁶⁹ 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 ; ¹⁷⁰ 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; ¹⁷¹ 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; ¹⁷² 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; ¹⁷³ 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; ¹⁷⁴ preprint; 2020	Patients with mild to severe COVID-19 infection. 21 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg twice a day for 6 days and 12 assigned to standard of care	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HC-nCoV trial; ¹⁷⁵ Jun et al; peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 15 assigned	Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%,	Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%	High for mortality and invasive mechanical ventilation; high for	

	to hydroxychloroquine 400 mg once a day for 5 days and 15 assigned to standard of care	chronic lung disease 3.3%		symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
Abd-Elsalam et al ; ¹⁷⁶ 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 ; ¹⁷⁷ Rajasingham et al; peer-reviewed; 2020	Patients exposed to COVID-19. 989 assigned to hydroxychloroquine 400 mg twice in one day followed by 400 mg once weekly for 12 weeks or 400 mg twice weekly for 12 weeks and 494 assigned to standard of care	Median age 41 ± 15, male 49%, hypertension 14%, asthma 10%	NR	Low for infection, and adverse events
TEACH trial ; ¹⁷⁸ 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	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart	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

	twice a day for 2 to 5 days and 61 assigned to standard of care	disease 26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%		Notes: Concealment of allocation probably inappropriate.
PrEP COVID trial ; ¹⁷⁹ 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 ; ¹⁸⁰ 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 ; ¹⁸¹ Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 947 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 10 days and 906 assigned to standard of care	Age < 70 years 61%, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%, chronic kidney disease %	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.
Davoodi et al ; ¹⁵⁴ peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection.	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%,	NR	High for mortality and invasive mechanical ventilation; high for

	30 assigned to febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	chronic lung disease 1.9%		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; ¹⁸² 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 , ¹⁸³ Self et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 242 assigned to hydroxychloroquine 800 mg on day 1 followed for 200 mg twice a day for 5 days and 237 assigned to standard of care	Median age 58.5 ± 24.5, male 56%, hypertension 52.8%, diabetes 34.6%, COPD 8.1%, asthma %, coronary heart disease %, chronic kidney disease 8.8%,	Corticosteroids 18.4%, remdesivir 21.7%, azithromycin 19%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
HAHPS trial , ¹⁸⁴ 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	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

	azithromycin			between study arms
HYCOVID trial ; ¹⁸⁵ 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 ; ¹⁸⁶ 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 ; ¹⁸⁷ peer reviewed; 2020	Patients with mild to moderate COVID-19. 44 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 10 days and 48 assigned to CQ	Mean age 35.5 ± 16.8, male 48.9%, comorbidities 18.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
HYDRA trial ; ¹⁸⁸ 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 ; ¹⁸⁹	Patients with mild COVID-19. 60	Median age 37 ±, male 43.3%, hypertension	NR	Low for mortality and mechanical ventilation;

Johnston et al; peer-reviewed; 2020	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	20.9%, diabetes 11.6%, COPD 9.3%, asthma 1.6%, immunosuppressive therapy 0.8%, obesity 76%		low for symptom resolution, infection, and adverse events	
Purwati et al , ¹⁹⁰ 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 , ¹⁹¹ Preprint; 2020	Patients with moderate to severe COVID-19. 33 assigned to HCQ 800 mg once followed by 400 mg a day for 5 days and 37 assigned to SOC	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
PATCH 1 trial , ¹⁹² 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 ; ¹⁹³ 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 ; ¹⁹⁴ 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 ; ¹⁹⁵ Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to HCQ 800 mg once followed by 400 mg a day for 9 days and 227 assigned to SOC	Mean age 53, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
CLOROTRIAL trial ; ¹⁹⁶ 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 ; ¹⁹⁷ 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 ; ¹⁹⁸ 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 ; ¹⁹⁹ 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 assigned to SOC	Median age 32 ± 27, male 72%, hypertension 2.8%, diabetes 2.8%, COPD %, CHD 0.9%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ALBERTA HOPE-Covid19 trial ; ²⁰⁰ 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	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	

	SOC				
HERO-HCQ trial ; ²⁰¹ 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 ; ²⁰² 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 to SOC	Mean age 36.5 ± 9.6, male 40.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Babalola et al ; ²⁰³ preprint; 2021	Patients with mild to severe COVID-19 infection. 31 assigned to HCQ + AZT 200/500 mg a day for 3 days and 30 assigned to SOC	Mean age 40.4 ± 1.9, male 63%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
FIGHT-COVID-19 trial ; ¹⁵⁰ Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably	

	HCQ 800mg a day or Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day or favipiravil 6000mg followed by 2400mg + Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day for 7 to 14 days.			inappropriate.	
SEV-COVID trial ; ²⁰⁴ Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 37 assigned to Hydroxychloroquine 400 mg twice on first day followed by 400 mg per oral daily for 10 days + Ribavirin (1.2 g orally as a loading dose followed by 600mg orally every 12 hours) for 10 days and 40 assigned to SOC	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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 , ²⁰⁵ preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric oxygen	Median age 65.4 ± 7.8, male 60%, hypertension 72%, diabetes 60%, COPD %, asthma 8%,	Corticosteroids 92%, tocilizumab 24%, convalescent plasma 80%	High for mortality and mechanical ventilation; High for symptom resolution, infection,	Mortality: Very low certainty ⊕○○○ Invasive mechanical

	two sessions a day for 4 days and 9 assigned to SOC	CHD 24%, cancer 4%, obesity 8%		and adverse events Notes: Blinding and concealment are probably inappropriate.	ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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
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RCT

Ali et al. ²⁰⁶ 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
Parikh et al. ²⁰⁷ preprint; 2021	Patients with moderate to severe	Mean age 52 ± 10.1, male 73.3%	NR	High for mortality and mechanical ventilation;	

	COVID-19 infection. 30 assigned to C-IVIG 30ml twice and 30 assigned to SOC			high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

Mansour et al. ²⁰⁸ 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 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
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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
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RCT

VASCEPA COVID-19 CARDIOLINK-9 trial ; ²⁰⁹ 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
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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
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RCT

Vlaar et al. ; ²¹⁰ peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1 800 mg IV with a	Mean age 60 ± 9, male 73%, hypertension 30%, diabetes 27%, obesity 20%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No
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	maximum of seven doses and 15 assigned to standard of care			infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

COUNTER-COVID trial ; ²¹¹ 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
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					1.05 (95%CI 0.84 to 1.32); RD 0.5% (95%CI -1.6% to 3.3%); Low certainty ⊕⊕○○ Hospitalization: No information
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Indomethacin

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

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

Ravichandran et al ; ²¹² 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
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Infliximab

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

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

CATALYST trial ; ²¹³ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

Lopardo et al ; ²¹⁴ peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005	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,	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical</p>
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	4 mg/kg in two doses on days 1 and 3 and 123 assigned to SOC			and adverse events	<p>ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: RR 1.06 (95%CI 0.96 to 1.66); RD 3.6% (95%CI -2.4% to 10.3%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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Interferon alpha-2b and interferon gamma
Uncertainty in potential benefits and harms. Further research is needed.

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

ESPERANZA trial ; ²¹⁵ Esquivel-Moynelo et al; preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to interferon alpha-2b plus interferon gamma twice a week for two weeks (standard care) and 33 assigned to	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%, coronary heart disease 6.3%, any comorbidities 50.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, antibiotics 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No</p>
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	interferon alpha-2b three times a week (IM)			study. Concealment of allocation is probably inappropriate.	information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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Interferon beta-1a

IFN beta-1a probably does not reduce mortality 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 ; ²¹⁶ preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three times a week and 39 assigned to standard of care	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	Corticosteroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: RR 0.98 (95%CI 0.74 to 1.29); RD -0.3% (95%CI -4.2% to 4.6%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 0.97 (95%CI 0.83 to 1.14); RD -0.5% (95%CI -2.9% to 2.4%); Moderate certainty ⊕⊕⊕○
WHO SOLIDARITY ; ¹⁸¹ 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.	Symptom resolution or improvement: RR 0.96 (95%CI 0.92 to 0.99); RD -2.6% (95%CI -4.8% to -3.2%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information
COVIFERON trial ; ²¹⁷ 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	Adverse events: RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕○

	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.	Hospitalization: No information
Darazam et al; ²¹⁸ 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.	
ACTT-3 trial; ²¹⁹ Kalil et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 487 assigned to interferon beta-1a 44 µg a day for up to four days and 482 assigned to SOC	Mean age 58.7 ± 15.9, male 58%, hypertension 58%, diabetes 37%, COPD 11%, asthma 13%, CKD 12%, obesity 58%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
INTEREST trial; ²²⁰ Ranieri et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 144 assigned to Interferon beta-1a 10 µg a day for 6 days and 152 assigned to SOC	Mean age 58, male 65.8%,	Corticosteroids 35.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Monk P et al. ²²¹ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Interferon beta-1b

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

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

Rahmani et al. ²²² peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to interferon beta-1b 250 mcg subcutaneously every	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%,	Corticosteroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low</p>
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	other day for two consecutive weeks and 33 assigned to standard of care	coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%		events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
COVIFERON trial ; ²¹⁷ 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
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RCT

Myasnikov et al ; ²²³ 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
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					<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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Interferon kappa plus TFF2

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

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

<p>Fu et al;²²⁴ peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 35.2 ± 11.2, male 63.7%, hypertension 5%, diabetes 3.7%</p>	<p>NR</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ²²⁵ 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
CARR-COV-02 trial ; ²²⁶ 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.	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○

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 ; ²²⁷ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ²²⁸ 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 ⊕⊕○○
Chowdhury et al ; ²²⁹ 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.	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 ⊕○○○
Podder et al ; ²³⁰ 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	Adverse events: RR 1.29 (95%CI 0.44 to 3.85); RD 2.9%

	care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	(95%CI -5.7% to 29%); Very low certainty ⊕○○○ Hospitalization: RR 0.67 (95%CI 0.39 to 1.14); RD -2.4% (95%CI -4.5% to 1%); Low certainty ⊕⊕○○
Hashim et al , ²³¹ 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 , ²³² 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); ²³³ preprint (now retracted); 2020	Patients with mild to moderate COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 55.2 ± 19.8, male 69.5%, hypertension 11.5%, diabetes 14.5%, COPD %, asthma 5.5%, coronary heart disease 4%, chronic kidney disease %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elgazzar et al (severe); ²³³ preprint	Patients with severe COVID-19. 100	Mean age 58.9 ± 19.5, male 71%, hypertension	NR	High for mortality and mechanical ventilation;	

(now 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); ²³³ preprint (now 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 ; ²³⁴ 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 ; ²³⁵ 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 ; ²³⁶ 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 ; ²³⁷ 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 ; ²³⁸ 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 ; ²³⁹ 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. ²⁴⁰ 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 ²²⁵ 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. ²⁴¹ 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. ²⁴² 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. ²⁴³ 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. ; ²⁴⁴ peer-reviewed (now retracted); 2020	Patients with mild (asymptomatic) COVID-19 infection. 50 assigned to ivermectin 9 to 12 mg or 150 µg/kg once and 50 assigned to SOC	Mean age 31.6 ± 7.7, male 50%, hypertension 8%, diabetes 6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Randomization process and concealment of allocation is probably inappropriate.
Bukhari et al. ; ²⁴⁵ 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. ; ²⁴⁶ 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. ¹⁹¹ 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. ²⁴⁷ 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. ¹⁹³ 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. ²⁴⁸ 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. , ²⁴⁹ 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. ; ¹⁹⁴ 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. , ²⁵⁰ 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 ; ²⁵¹ 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 ; ²⁵² 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 ; ²⁵³ peer reviewed; 2021	Patients with mild COVID-19 infection. 250 assigned to ivermectin 24-36 mg and 251 assigned to SOC	Mean age 42.5 ± 15.5, male 52.7%, hypertension 23.8%, diabetes 9.6%, COPD 2.8%, asthma 7.2%, CHD 1.8%, cancer 1.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
COVER trial ; ²⁵⁴ Buonfrate et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 61 assigned to ivermectin 600 to 1200 µg/kg once a day for 5 days and 32 assigned to SOC	Median age 47 ± 27, male 58.1%, diabetes 9.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events

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
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					certainty of the evidence
RCT					
Aref et al. ²⁵⁵ peer reviewed; 2021	Patients with mild COVID-19 infection. 57 assigned to inhaled (inh) ivermectin and 57 assigned to SOC	Mean age 45 ± 19, male 71.9%, hypertension 17.5%, diabetes 12.3%, COPD 0.9%, cerebrovascular disease 3.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Randomization and concealment of allocation is probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
Intravenous immunoglobulin (IVIG) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and 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. ²⁵⁶ preprint; 2020	Patients with severe COVID-19 infection. 16 assigned to IVIG 0.5 g/kg/day for 3 days and 17 assigned to	Mean age 54 ± NR, male 60.6%, hypertension 33.3%, diabetes 36.3%, chronic lung disease 12%,	Corticosteroids 78.7%, remdesivir 51.5%, convalescent plasma 15.2%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low</p>

	standard of care	coronary heart disease 3%, chronic kidney disease 3%, immunosuppression 3%		events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	certainty ⊕○○○ Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
Gharebaghi et al. ²⁵⁷ 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. ²⁵⁸ 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. ²⁵⁹ 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.	
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KB109 (microbiome modifier)

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

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

Haran et al. , ²⁶⁰ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT					
Coppola et al ; ²⁶¹ 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
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RCT					
PROBCO trial ; ²⁶² Endam et al; preprint; 2021	Patients with mild recently diagnosed COVID-19 infection. 12 assigned to <i>Lactococcus lactis</i> (intranasal) two nasal irrigations a day and 11 assigned to SOC	Mean age 30.4 ± 9.1, male 30%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○

					<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
<p>Lactoferrin Uncertainty in potential benefits and harms. Further research is needed.</p>					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Algahtani et al. ²⁶³ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 36 assigned to lactoferrin 200 to 400 mg a day and 18 assigned to SOC	Mean age 48.6, male 60.3%	NR	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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. , ²⁶⁴ 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
Wang et al. , ²⁶⁵ peer-reviewed; 2020	Patients with moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day followed by 20 mg a day for 8 days and 24 assigned to standard of care	Median age 55.7 ± 21.5, male 50%, hypertension 27.2%, diabetes 4.5%, chronic lung disease 4.5%, coronary heart disease 2.3%, cancer 2.3%	Corticosteroids 34.1%, hydroxychloroquine 56.8%, lopinavir-ritonavir 11.4%, umifenovir 75%, IVIG 20.4%, ATB 63.6%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information 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
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RCT					
LIVE-AIR trial , ²⁶⁶ Temesgen et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 236 assigned to lenzilumab 1800 mg once and 243 assigned to SOC	Mean age 60.5 ± 13.9, male 64.7%, hypertension 66%, diabetes 53.4%, COPD 7.3%, asthma 10.6%, CHD 13.6%, CKD 14%,	Corticosteroids 93.7%, remdesivir 72.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Mortality: RR 0.72 (95%CI 0.44 to 1.19); RD -4.5% (95%CI -9% to 3%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: RR 0.71 (95%CI 0.48 to 1.04); RD -5% (95%CI -9% to 0.7%); Low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.82 (95%CI 0.62 to 1.07); RD -1.8% (95%CI -3.9% to 0.7%); Low certainty ⊕⊕⊕○</p> <p>Hospitalization: No information</p>
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					

Roostaie et al ; ²⁶⁷ 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 ⊕○○○
Asgardoon et al ; ²⁶⁸ preprint; 2021	Patients with mild to moderate COVID-19 infection. 185 assigned to levamisole 50 mg a day for 10 days and 180 assigned to SOC	Median age 40 ± 18.75, male 56.1%, hypertension 8.8%, diabetes 9.4%, CHD 1.6%	Hydroxychloroquine 11.2%,	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○ Hospitalization: No information

Levilimab

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

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

CORONA trial ; ²⁶⁹ Lomakin et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 103 assigned to levilimab 364mg once (subcutaneous) and 103 assigned to SOC	Mean age 58.3 ± 11.8, male 52.9%, CHD 15.5%,	Corticosteroids 7.3%, hydroxychloroquine 67.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement:
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					<p>Mortality: RR 1.48 (95%CI 1.13 to 1.93); RD 29.1% (95%CI -7.9% to 56.4%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>Guvenmez et al.⁵² peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 58.7 ± 16, male 70.8%,</p>	<p>NR</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
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					<p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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 ; ²⁷⁰ Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to lopinavir-ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Corticosteroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Mortality: RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -1.3% to 1.8%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕
ELACOI trial ; ²⁷¹ Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, intravenous immunoglobulin 6.3%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Symptom resolution or improvement: RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ 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 ⊕⊕○○
RECOVERY- Lopinavir-ritonavir trial ; ²⁷² 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.	Hospitalization: Very low certainty ⊕○○○
Huang et al; peer-reviewed; ¹⁶³ 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; ²⁷³ 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; ²⁷⁴ 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 ; ¹⁸¹ 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 ; ²⁷⁵ 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 ; ²⁷⁶ 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; ²⁷⁷ 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; ²⁷⁸ 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; ¹⁹⁵ Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 244 assigned to lopinavir-ritonavir 1600 mg/400 mg once followed by 800 mg/200 mg a day for 9 days and 227 assigned to SOC	Mean age 53 ± 76, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
COPEP trial; ²⁷⁹ Labhardt et al;	Patients exposed to COVID-19 infection.	Median age 39 ± 22, male 50.6%,	NR	Low for mortality and mechanical ventilation;

preprint; 2021	209 assigned to lopinavir-ritonavir 400/10 mg a day for 5 days and 109 assigned to SOC	hypertension 8.2%, diabetes 3.1%, COPD 7.8%, CHD 2.5%, cancer 0.6%,		high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Ghanei et al ; ⁵⁹ peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to Lopinavir-Ritonavir 200/50mg twice a day for 7 days and 110 assigned to azithromycin 500mg once followed by 250mg a day for 5 days	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
FIGHT-COVID-19 trial ; ¹⁵⁰ Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800mg a day or Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day or favipiravil 6000mg followed by 2400mg + Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day for	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.

	7 to 14 days.				
SEV-COVID trial ; ²⁰⁴ Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 24 assigned to Lopinavir ritonavir + ribavirin Lopinavir (200 mg) + Ritonavir (50 mg) two tablets twice daily + Ribavirin (1.2 g orally as a loading dose followed by 600 mg orally every 12 hours) for 10 days and 24 assigned to SOC	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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
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RCT

COVID-RT-01 trial ; ²⁸⁰ 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
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					<p>(prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
<p>Mavrilimumab Uncertainty in potential benefits and harms. Further research is needed.</p>					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
<p>MASH-COVID trial;²⁸¹ Cremer et al; peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 21 assigned to mavrilimumab 6 mg/kg once and 19 assigned to SOC</p>	<p>Mean age 56.7 ± 23.8, male 65%, hypertension 55%, diabetes 43%, COPD 8%, CKD 8%, cerebrovascular disease 3%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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. , ²⁸² 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
Davoodian et al. , ²⁸³ 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	Adverse events: No information Hospitalization: No information
Alizadeh et al. , ²⁸⁴ 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.	Adverse events: No information Hospitalization: No information

Mousavi et al; ²⁸⁵ 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.	
Hasan et al; ²⁸⁶ peer reviewed; 2021	Patients with severe COVID-19 infection. 82 assigned to melatonin 10mg a day for 14 days and 76 assigned to SOC	Mean age 56.3 ± 7.7, male 72.2%, hypertension 53.2%, diabetes 29.7%, asthma 10.1%, cerebrovascular disease 15.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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
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RCT

Shu et al; ²⁸⁷ 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	Mortality: RR 0.57 (95%CI 0.37 to 0.90); RD -6.7% (95%CI -10.1% to -1.6%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: Very low certainty ⊕○○○
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				allocation is probably inappropriate.	Symptom resolution or improvement: Very low certainty ⊕○○○
Shi et al. , ²⁸⁸ preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem cell three infusions with 4.0×10^7 cells each and 35 assigned to standard of care	Mean age 60.3 ± 8.4 , male 56%, hypertension 27%, diabetes 17%, COPD 2%	Corticosteroids 22%	Low for mortality and mechanical ventilation	Symptomatic infection (prophylaxis studies): No information Adverse events: No information
Lanzoni et al. , ²⁸⁹ preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell $100 \pm 20 \times 10^6$ UC- MSC twice and 12 assigned to standard of care	Mean age 58.7 ± 17.5 , male 54.1%, hypertension 66.7%, diabetes 45.8%, coronary heart disease 12.5%, , cancer 4.2%, obesity 66.6%	Corticosteroids 90.4%, remdesivir 66.7%, hydroxychloroquine 12.5%, tocilizumab 20.8%, convalescent plasma 29.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	Hospitalization: No information
Dilogo et al. , ²⁹⁰ peer reviewed; 2021	Patients with critical COVID-19 infection. 20 assigned to mesenchymal stem cell one 100 ml infusion and 20 assigned to SOC	age >60, 45%, male 75%, hypertension 42.5%, diabetes 50%, CHD 25%, CKD 17.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Zhu et al. , ²⁹¹ peer reviewed; 2021	Patients with Severe COVID-19 infection. 29 assigned to mesenchymal stem cell 1×10^6 cells per kilogram body weight, once and 29 assigned to SOC	Median age 65, male 37.9%, hypertension 25.8%, diabetes 13.8%, COPD 1.7%, CHD 10.3%, cerebrovascular disease 8.6%	Corticosteroids 67.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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
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RCT

Hamidi-Alamdari et al. ²⁹² peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to methylene blue 1 mg/kg every 12 to 8 h for 14 days and 40 assigned to SOC	Mean age 54 ± 13, male 52.5%, hypertension 17.5%, diabetes 10%	Corticosteroids 87.5%, azithromycin 92.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

Borges et al. ²⁹³ peer reviewed; 2020	Patients with mild to moderate COVID-19.	Mean age 33.2 ± 16, male 53.3%, COPD	NR	High for mortality and mechanical ventilation;	Mortality: No information
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	30 assigned to metisoprinol 1500 mg/kg/day for 14 days and 30 assigned to SOC	10%, CKD 16.6%, cancer 3.3%,		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
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Metoprolol

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
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RCT

MADRID-COVID trial ; ²⁹⁴ 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
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					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; ²⁹⁵ 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
AGILE trial; ²⁹⁶ Khoo et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 12 assigned to molnupiravir 600-1600 mg a day and 6 assigned to SOC	Median age 56 ± 58, male 27.8%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
Fischer et al; ²⁹⁷ 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	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

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; ²⁹⁸ 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 ⊕○○○
GARGLES trial; ²⁹⁹ Mohamed et al; preprint; 2020	Patients with COVID-19. 10 assigned to mouthwash with povidone iodine or essential oils 3 times a day and 10 assigned to mouthwash with water or no mouthwash	Median age 28.9, male 80%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information
KILLER trial; ³⁰⁰ 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. ³⁰¹ 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. ³⁰² 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. ³⁰³ Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to mouthwash with β-cyclodextrin-citrox three times a day and 78 assigned to SOC	Mean age 43.8 ± 15.5, male 45.7%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Huang et al. ³⁰⁴ 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. ³⁰⁵ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 34 assigned to mouthwash cetylpyridinium chloride, zinc, chlorhexidine, hydrogen peroxide and 9 assigned to SOC	Mean age 54.7, male 74.4%, hypertension 30.2%, diabetes 23.2%, COPD 11.6%, CHD 18.6%, CKD 11.6%, obesity 13.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Di-Domênico et al. ³⁰⁶ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 63 assigned to mouthwash with hydrogen peroxide 1% three time a day and nasal wash with hydrogen peroxide 0.5% and 43 assigned to SOC	Age >60 17%, male 39.6%, hypertension 22.6%, diabetes 11.3%, COPD 5.7%, CHD 3.8%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant number of patients excluded post-randomization resulting in potential imbalances in baseline risks	
ACPREGCOV trial ³⁰⁷ Damião Costa et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to Mouthwash 15 mL of 0.12% chlorhexidine gluconate and 50 assigned to SOC	Mean age 39 ± 12, male 50%, hypertension 17%, diabetes 4%, obesity 25%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Mupadolimab

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

Study; publication status	Patients and interventions	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE
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	analyzed				certainty of the evidence
RCT					
Miller et al. , ³⁰⁸ preprint; 2021	Patients with moderate to severe COVID-19 infection. 29 assigned to mupadolimab 1-2 mg/kg and 11 assigned to SOC	Median age 55, male 57.5%, any comorbidities 45%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○

Mycobacterium w

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ARMY-1 trial , ³⁰⁹ 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

					<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

de Alencar et al. ³¹⁰ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p>
Gaynitdinova et al. ³¹¹ 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.	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p>
Taher et al. ³¹² peer	Patients with mild to	Mean age 57.6 ± 18.7,	Corticosteroids 69.6%,	High for mortality and	Hospitalization: No information

reviewed; 2021	moderate COVID-19 infection. 47 assigned to NAC 40 mg/kg a day for 3 days and 45 assigned to SOC	male 58.7%, diabetes 23.9%, COPD 15.2%, asthma %, CHD 28.2%,	hydroxychloroquine 90.2%, azithromycin 51.1%,	mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
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Nafamostat Mesylate

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

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

DEFINE trial , ³¹³ Quinn et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 21 assigned to nafamostat 0.2 mg/kg/hr for 7 days and 21 assigned to SOC	Mean age 63.6, male 59.5%, hypertension 38.1%, diabetes 21.4%, COPD %, asthma 9.5%, CHD 14.3%, CKD 4.8%, immunosuppression 7.1%, cancer 9.5%, obesity %	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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 ; ²¹³ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
Nano-curcumin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hassaniyazad et al ; ³¹⁴ peer reviewed; 2021	Patients with mild to severe COVID-19	Mean age 48.5 ± 10.9, male 55%	Corticosteroids 87.5%, hydroxychloroquine	High for mortality and mechanical ventilation;	Mortality: No information

	infection. 20 assigned to nano-curcumin 160mg a day for 14 days and 20 assigned to SOC		45%, lopinavir-ritonavir 52.5%,	high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

Kimura et al. , ³¹⁵ 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 ⊕○○○
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Yildiz et al. ³¹⁶ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 50 assigned to nasal hypertonic saline and 50 assigned to SOC	Mean age 38.8 ± , male 58%, hypertension 12%, diabetes 6%, COPD/asthma 4%, CHD 15%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
George et al. ³¹⁷ preprint; 2021	Patients with mild COVID-19 infection. 20 assigned to nasal hypertonic saline (Caesium rich hypertonic salts) and 20 assigned to SOC	Age range 22-45		Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Neem (*Azadirachta indica* A. Juss)

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

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

Nesari et al. ³¹⁸ 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
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					<p>(prophylaxis studies): Very low certainty ⊕○○○</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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Niclosamaide

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

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

Abdulmir et al. , ³¹⁹ 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	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 ; ³²⁰ Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + <i>Nigella sativa</i> 1 g + 80 mg/kg three times a day for 13 days and 156 assigned to SOC	> 60 age 52 ±, male 56.8%, hypertension 31.6%, diabetes 36.7%	Corticosteroids 26.5%, azithromycin 73.8%, ivermectin 36.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
Koshak et al ; ³²¹ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 91 assigned to <i>Nigella sativa</i> 500 mg twice a day for 10 days and 92 assigned to SOC	Mean age 36 ± 11, male 53%, hypertension 9%, diabetes 8%, asthma 4%, CHD 0.5%, obesity 25%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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 ; ³²² Rocco et al;	Patients with mild COVID-19. 194	Age range 18 - 77, male 47%, comorbidities	NR	Low for mortality and mechanical ventilation;	Mortality: Very low certainty ⊕○○○

preprint; 2020	assigned to nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	13.2%		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.	Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
Fontanesi et al , ³²³ 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.	Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○
Silva et al , ³²⁴ 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 , ³²⁵ 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	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	

	to SOC				
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. ³²⁶ 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 ⊕○○○ Hospitalization: No information
Winchester et al. ³²⁷ peer-reviewed; 2021	Patients with mild COVID-19 infection. 40 assigned to nitric oxide nasal spray (NONS) 4 sprays 5 to 6 times a day for 9 days and 40 assigned to SOC	Mean age 44, male 36.7%, hypertension 6.3%, diabetes 6.3%, COPD 1.2%, CHD 0%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Adverse events: Very low certainty ⊕○○○ 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
RCT					
Mobarak et al. ³²⁸ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 39 assigned to naproxen 1000 mg a day and 38 assigned to SOC	Mean age 47, male 55.8%, hypertension 9%, diabetes 17%, CHD 13%, CKD 5.2%, obesity 1.3%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
Non-RCT					
Eilidh et al. ³²⁹ 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).	<p>Mortality: OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕○○○</p>

<p>Jeong et al;³³⁰ preprint; 2020</p>	<p>Patients with moderate to severe COVID-19 infection. 354 received NSAID and 1470 received alternative treatment schemes</p>	<p>Age >65 36%, male 41%, hypertension 20%, diabetes 12%, chronic lung disease 16%, asthma 6%, chronic kidney disease 2%, cancer 6%</p>	<p>NR</p>	<p>High for mortality and invasive mechanical ventilation</p> <p>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).</p>	
<p>Lund et al;³³¹ peer-reviewed; 2020</p>	<p>Patients with mild to severe COVID-19 infection. 224 received NSAID and 896 received alternative treatment schemes</p>	<p>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%</p>	<p>Corticosteroids 7.1%</p>	<p>High for mortality and invasive mechanical ventilation</p> <p>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</p>	

				prescription drugs, and phase of the outbreak.	
Kinott et al. , ³³² 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. , ³³³ 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. , ³³⁴ 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. ³³⁵ 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).	
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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
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RCT

Zheng et al. ²⁷³ 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	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
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	29 assigned to lopinavir-ritonavir				<p>(prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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Nutritional support

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

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

Leal et al; ³³⁶ preprint; 2021	Patients with severe COVID-19 infection. 40 assigned to nutritional support with spirulin, folic acid, glutamine, vegetable protein, vitamin C, zinc, selenium, vitamin D, resveratrol, Omega-3, L-Arginine, magnesium and probiotics and 40 assigned to SOC	Mean age 52.7 ± 10.8, male 65%, CHD 33.7%, obesity 33.7%	NR	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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					
Sedighyan et al. , ³³⁷ 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
Doaei et al. , ³³⁸ 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
Opaganib Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ABC-110 trial , ³³⁹ Winthrop et al;	Patients with moderate to severe	Median age 58 ± 29.8, male 64.3%	Corticosteroids 92.8%, remdesivir 45.2%	Low for mortality and mechanical ventilation;	Mortality: Very low certainty ⊕○○○

preprint; 2021	COVID-19 infection. 22 assigned to Opaganib 1000mg a day for 14 days and 18 assigned to SOC			low for symptom resolution, infection, and adverse events	<p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

OSCAR trial ; ³⁴⁰ Patel et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 386 assigned to otilimab 90 mg once and 393 assigned to SOC	Mean age 59.6 ± 12, male 71.6%, hypertension 49.7%, diabetes 36.7%, CHD 11.9%	Corticosteroids 83%, remdesivir 34%, tocilizumab 1.2%, convalescent plasma 6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection</p>
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					<p>(prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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
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RCT

<p>PROBIOZOID trial;³⁴¹ Araimo et al; peer-reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19. 14 assigned to ozone 250 ml ozonized blood and 14 assigned to standard of care</p>	<p>Mean age 61.7 ± 13.2, male 50%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
<p>SEOT trial;³⁴² Shah et al; Peer reviewed; 2020</p>	<p>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</p>	<p>Mean age 43.8 ± 9, male 80%, diabetes 10%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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					
PEGL20.002 trial ; ³⁴³ Pandit et al; Peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to pegylated interferon alfa 1 µg/kg once and 19 assigned to SOC	Mean age 49.2 ± 13.5, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
Bushan et al ; ³⁴⁴ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 119 assigned to Peg Interferon Alfa 1 µg/kg subcutaneous [SC] injection once and 123 assigned to SOC	Mean age 49.9 ± 15.3, male 70.8%	Corticosteroids 59.9%, remdesivir 21.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Peg-interferon (IFN) lambda

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ILLAD trial ; ³⁴⁵ 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	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
COVID-Lambda trial ; ³⁴⁶ 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	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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. ³⁴⁷ peer-reviewed; 2020	Patients with severe to critical COVID-19. 26 assigned to pentoxifylline 400 mg three times a day while hospitalized and 12 assigned to standard of care	Mean age 57.5 ± 11.7, male 55.2%, hypertension 39.4%, diabetes 50%, obesity 55.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information
Azizi et al. ³⁴⁸ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to pentoxifylline 1200mg a day for 10 days and 32 assigned to SOC	Mean age 59, male 35%, hypertension 18%, diabetes 32%, CHD 12.5%, cerebrovascular disease 5.5%	Corticosteroids 55.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information 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 ; ³⁴⁹ Lattaman et al; preprint; 2021	Patients with moderate COVID-19 infection. 20 assigned to PNB001 200 mg a day for 14 days and 20 assigned to SOC	Mean age 52, 65% male	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

Polymerized type I collagen (PT1C)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mendez-Flores et al ; ³⁵⁰ preprint; 2021	Patients with mild to moderate COVID-19 infection. 44 assigned to PT1C 25 mg intramuscular for 3 days followed by 12.5 mg for another 4 days and 43 assigned to SOC	Mean age 48.5 ± 14.1, male 41.6%, hypertension 20.2%, diabetes 16.9%, COPD 2.3%, asthma 4.5%, CHD 0%, cancer 0%, obesity 28.1%	Corticosteroids 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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. ¹⁹⁴ 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 ; ³⁵¹ 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: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: No information Hospitalization: No information
PROCOV-19-2020 trial ; ³⁵² Ivashkin et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 99 assigned to probiotics three times a day for 14 days and 101 assigned to SOC	Mean age 64 ± , male 46%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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. ³⁵³ 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 ; ³⁵⁴ Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 g a day and 5 assigned to standard of care	Mean age 28.5 ± 3.85, male 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Propolis

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

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

Bee-Covid trial ; ³⁵⁵ 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
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Prostacyclin

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

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

COMBAT-	Patients with critical	Mean age 67, male	NR	Low for mortality and	Mortality: Very low certainty ⊕○○○
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<p>COVID trial,³⁵⁶ Johansson et al; peer reviewed; 2021</p>	<p>COVID-19 infection. 41 assigned to prostacyclin 1 ng/kg/min for 3 days and 39 assigned to SOC</p>	<p>66.2%, hypertension 61.2%, COPD 12.5%, CKD 2.5%,</p>		<p>mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Proxalutamide

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cadegiani et al. ³⁵⁷ 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%); Very 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%); Very low certainty ⊕○○○
AB-DRUG-SARS-004 trial ³⁵⁸ Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 171 assigned to proxalutamide 200 mg a day for 15 days and 65 assigned to SOC	Mean age 45.3 ± 13, male 54.2%, hypertension 22.5%, diabetes 8.9%, COPD 0%, asthma 5%, CKD 0.4%, cancer 17%, obesity 15.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	Symptom resolution or improvement: RR 2.62 (95%CI 1.82 to 3.75); RD 98.2% (95%CI -49.6% to 100%); Very low certainty ⊕○○○
KP-DRUG-SARS-003 trial ³⁵⁹ 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	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○
AB-DRUG-SARS-005 trial ³⁶⁰	Patients with mild to moderate COVID-19	Mean age 44.2 ± 12.1, male 0%, hypertension	NR	High for mortality and mechanical ventilation;	Hospitalization: RR 0.07 (95%CI 0.01 to

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.	0.52); RD -6.9% (95%CI -7.3% to -3.6%); Very low certainty ⊕○○○
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Pyridostigmine

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

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

PISCO trial ; ³⁶¹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 , ³⁶² peer review; 2020	Patients with moderate to severe COVID-19. 49 assigned to Quercetin 1000 mg and 380 assigned to SOC	Age > 50 65.7%, male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma 13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information
Di Piero et al , ³⁶³ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to quercetin 400-600 mg a day for 14 days and 21 assigned to SOC	Mean age 49.3 ± 19.5, male 47.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Hospitalization: Very low certainty ⊕○○○
Shohan et al , ³⁶⁴ peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to quercetin 1000 mg a day for 7 days and 30 assigned to SOC	Mean age 51.8, male 56.6%, hypertension 20%, asthma 6.6%, CHD 15%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes:	Hospitalization: Very low certainty ⊕○○○

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 , ³⁶⁵ 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
RD-X19 (light therapy) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
EB-P12-01 trial , ³⁶⁶ Stasko et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to RD-X19 light dose	Median age 40 ± 20.6, male 52%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	Mortality: No information Invasive mechanical ventilation: No

	<p>of 16 J/cm² twice a day and 11 assigned to SOC</p>			<p>adverse events</p>	<p>information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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Recombinant super-compound interferon

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Li et al. , ³⁶⁷ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>

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 , ³⁶⁸ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p>
CT-P59 1.2 trial , ³⁶⁹ Kim et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 15 assigned to regdanvimab 20 to 80mg once and 3 assigned to SOC	Median age 52 ± 8, male 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	<p>Symptom resolution or improvement: RR 1.24 (95%CI 1.05 to 1.46); RD 4.2% (95%CI 9% to 80%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

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 ; ³⁷⁰ preprint; 2020	Patients with recent onset mild disease with risk factors for severe COVID-19 infection. 2091 assigned to REGEN-COV (casirivimab and imdevimab) 1.2 to 2.4 g single infusion and 2089 assigned to SOC	Median age 50 ± 21, male 48.7%, obesity 58%, comorbidities 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	Mortality: RR 0.83 (95%CI 0.64 to 1.04); RD -2.7% (95%CI -5.8% to 0.6%); Low certainty ⊕⊕○○ Mortality (seronegative): RR 0.8 (95%CI 0.71 to 0.89); RD -3.2% (95%CI -4.6% to -1.8%); Moderate certainty ⊕⊕⊕○
RECOVERY-REGEN-COV trial ; ³⁷¹ 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.	Invasive mechanical ventilation: RR 0.79 (95%CI 0.54 to 1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕○○ Invasive mechanical ventilation (seronegative): RR 0.82 (95%CI 0.74 to 0.9); RD -3.1% (95%CI -4.5% to -1.7%); Moderate certainty ⊕⊕⊕○
O'Brien et al ; ³⁷² preprint; 2021	Patients with early asymptomatic COVID-19 infection. 100 assigned to REGEN-COV	Mean age 40.9 ± 18, male 45.4%, diabetes 7.8%, CKD 2.5%, immunosuppressive therapy 1.5%, obesity	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	Symptom resolution or improvement: RR 1.06 (95%CI 1 to 1.12); RD 3.6%

	(Regeneron) 1.2 g once and 104 assigned to SOC	13.2%			(95%CI 0% to 7.2%); Low certainty ⊕⊕○○
O'Brien et al; ³⁷³ 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 (seronegative): RR 1.12 (95%CI 1.05 to 1.18); RD 7.2% (95%CI 3% to 10.9%); Moderate certainty ⊕⊕⊕○
OPTIMISE-C19 trial; ⁶⁸ 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%, immunosuppressive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	Symptomatic infection (prophylaxis studies): RR 0.43 (95%CI 0.31 to 0.59); RD -9.9% (95%CI -12% to -7.1%); High certainty ⊕⊕⊕⊕ Adverse events: RR 0.54 (95%CI 0.27 to 1.07); RD -4.7% (95%CI -7.4% to 0.7%); Low certainty ⊕⊕○○ Hospitalization: RR 0.30 (95%CI 0.20 to 0.46); RD -5.2% (95%CI -5.9% to -4%); Moderate certainty ⊕⊕⊕○
Somersan-Karakaya et al; ³⁷⁴ preprint; 2021	Patients with moderate to severe COVID-19 infection. 804 assigned to REGN-COV2 (Regeneron) 2.4 to 8 gr once and 393 assigned to SOC	Median age 62 ± , male 54.1%	Corticosteroids 74.8%, remdesivir 54.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
R10933-10987-COV-20145 trial; ³⁷⁵ Portal Celhay et al; preprint; 2021	Patients with mild COVID-19 infection. 584 assigned to REGN-COV2 (Regeneron) 300 - 2400 mg once and 77 assigned to SOC	Mean age 34.6, male 44.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Isa et al; ³⁷⁶ preprint;	Patients with COVID-	Median age 48 ± 22,	NR	Low for mortality and	

2021	19 infection. assigned to REGN-COV2 (Regeneron) and assigned to	male 55.1%, hypertension 14.7%, asthma 5.2%, CHD 0.8%, CKD 0.2%,		mechanical ventilation; low for symptom resolution, infection and adverse events	
Weinreich et al; ³⁷⁷ preprint; 2021	Patients with mild to moderate COVID-19 infection. 434 assigned to REGN-COV2 (Regeneron) 2400 TO 8000 mg once and 231 assigned to SOC	Median age 42 ± 21, male 47.1%, obesity 37.3%, Risk factor for hospitalization 60.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Remdesivir

Remdesivir may not reduce mortality, it may reduce 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
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RCT

ACTT-1 trial; Beigel et al; ³⁷⁸ 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 0.97 (95%CI 0.85 to 1.10); RD -0.5% (95%CI -2.4% to 1.6%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 0.79 (95%CI 0.51 to 1.23); RD -3.6% (95%CI -8.5% to 4%); Low certainty ⊕⊕○○ Symptom resolution or improvement: RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low
SIMPLE trial;	Patients with severe	Median age 61.5 ± 20,	NR	Low for mortality and	

Goldman et al; ³⁷⁹ peer-reviewed; 2020	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)	male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%		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.	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 certainty ⊕⊕○○
CAP-China remdesivir 2 trial ; ³⁸⁰ Wang et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 158 assigned to remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions and 79 assigned to standard of care	Median age 65 ± 7.5, male 60.5%, hypertension 43%, diabetes 23.7%, coronary heart disease 7.2%	Corticosteroids 65.6%, lopinavir-ritonavir 28.4%, IFN 32.2%, ATB 91.1%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	Hospitalization: No information
SIMPLE 2 trial ; Spinner et al; ³⁸¹ 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	Patients with	age < 70 years 61%, male	Corticosteroids 15.1%,	Low for mortality and	

<p>SOLIDARITY,¹⁸¹ Pan et al; preprint; 2020</p>	<p>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</p>	<p>62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%</p>	<p>convalescent plasma 0.5%, Anti IL6 2.1%</p>	<p>invasive mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	
<p>Mahajan et al;³⁸² peer reviewed; 2021</p>	<p>Patients with mild to severe COVID-19 infection. 34 assigned to remdesivir 200 mg once followed by 100 mg once a day for 5 days and 36 assigned to SOC</p>	<p>Mean age 57.7 ± 13.1, male 65.5%, hypertension 45.7%, diabetes 60%, asthma 1.4%, CHD 12.9%, CKD 4.3%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	
<p>Abd-Elsalam et al;³⁸³ peer reviewed; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 100 assigned to remdesivir 200mg once followed by 100mg a day for 10 days and 100 assigned to SOC</p>	<p>Mean age 53 ± 15, male 59.5%, hypertension 33%, diabetes 34%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Sarhan et al;³⁸⁴ peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 52 assigned to Remdesivir 200 mg once followed by 100</p>	<p>Mean age 57, male 72%, hypertension 61.7%, diabetes 47.6%, COPD 2.8%, asthma 13.1%, CHD 21.5%, CKD</p>	<p>Hydroxychloroquine 52.3%, tocilizumab 100%,</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p>	

	mg a day for 5 days plus tocilizumab and 56 assigned to HCQ 400mg once followed by 200mg a day for 5 days plus tocilizumab	4.7%,		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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Reseveratrol

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

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

McCreary et al. ³⁸⁵ preprint; 2021	Patients with mild COVID-19 infection. 50 assigned to resveratrol 4gr a day for 7 days and 50 assigned to SOC	Mean age 56 ± 9, male 43%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p>
Reszinate trial. ³⁸⁶ Kaplan et al; preprint; 2021	Patients with mild COVID-19 infection. 14 assigned to resveratrol + Zinc 4000/150 mg once a day for five days and 16 assigned to SOC	Mean age 42.4, male 40%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes:	<p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>

rhG-CSF (in patients with lymphopenia)

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

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

Cheng et al , ³⁸⁷ 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
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rhG-CSF (inhaled)

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

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

SARPAC trial , ³⁸⁸ Lambrecht et al; preprint; 2021	Patients with severe COVID-19 infection. 40 assigned to rhG-CSF (inhaled) 125 µg	Mean age 60 ± 20, male 61%, hypertension 17.1%, diabetes 17.1%, CHD 2.4%, CKD 2.4%,	Corticosteroids 22%, hydroxychloroquine 63.4%,	High for mortality and mechanical ventilation; high for symptom resolution, infection,	Mortality: Very low certainty ⊕○○○ Invasive mechanical
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	twice daily for 5 days and 41 assigned to SOC	cancer 4.9%,		and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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Ribavirin

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

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

Chen et al; ²⁷⁴ 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
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					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. ³⁸⁹ peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 86 assigned to ribavirin plus interferon beta-1b 400 mg every 12 hours (ribavirin), and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]) on alternate days, for 14 days and 41 assigned to standard of care	Median age 52 ± 15, male 54%, hypertension 18.3%, diabetes 13.3%, coronary heart disease 7.9% cerebrovascular disease 1.5%, cancer 1.5%	Corticosteroids 6.2%, ATB 53.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Ruxolitinib

Ruxolitinib may not improve time to symptom resolution. However the certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cao et al ; ³⁹⁰ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: RR 0.99 (95%CI 0.89 to 1.1); RD -0.6% (95%CI -6.6% to 6%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
RUXCOVID trial ; other; 2021	Patients with moderate to severe COVID-19 infection. 287 assigned to Ruxolitinib 10 mg a day for 14 to 28 days and 145 assigned to SOC	Mean age 56.5 ± 13.3, male 54.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: RR 0.99 (95%CI 0.89 to 1.1); RD -0.6% (95%CI -6.6% to 6%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 ; ³⁹¹ 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 0.98 (95%CI 0.85 to 1.13); RD -0.3% (95%CI -2.4% to 2.1%); 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 ⊕⊕○○
Lescure et al ; ³⁹² peer-reviewed; 2020	Patients with severe to critical COVID-19. 332 assigned to sarilumab 200-400 mg once and 84 assigned to SOC	Mean age 59 ± 18, male 62.7%, hypertension 42.5%, diabetes 26.4%, COPD 4.3%, asthma 4.1%, CHD 5.3%, CKD 4.3%, cancer 10.1%, obesity 20.7%	Corticosteroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	Symptom resolution or improvement: RR 0.99 (95%CI 0.94 to 1.05); RD -0.6% (95%CI -3.6% to 3%); Moderate certainty ⊕⊕⊕○
Sarilumab-COVID19 Study trial ; ³⁹³ Sivapalasingam, et al; preprint; 2021 (two studies reported)	Patients with severe to critical COVID-19 infection. 1148 assigned to sarilumab 200-400 mg once and 376 assigned to SOC	Critical patient population: Mean age 61 ± 20, male 68.4%, hypertension 52.1%, diabetes 18.7%, obesity 46.5%	Corticosteroids 34.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	Symptomatic infection (prophylaxis studies): No information Severe adverse events: RR 1.01 (95%CI 0.88 to 1.16); RD 0.1% (95%CI -1.2% to 1.6%); Moderate certainty ⊕⊕⊕○
CORIMUNO-SARI trial ; ³⁹⁴	Patients with moderate to severe	Median age 62, male %, hypertension 25.1%,	Steroids 20.1%, remdesivir 0%,	Low for mortality and mechanical ventilation;	

Mariette, et al, peer reviewed; 2021	COVID-19 infection. 68 assigned to sarilumab 400mg once and 76 assigned to SOC	diabetes 30.5%, COPD 6.3%, asthma 8%, CKD 11.8%, cancer 3%,	hydroxychloroquine 14.6%, azithromycin 39.6%	high for symptom resolution, infection, and adverse events	Hospitalization: No information
CORIMUNO-SARIICU trial ; ³⁹⁵ 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%, 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 ; ³⁹⁵ 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 ; ³⁹⁵ 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 ; ³⁹⁶ Sancho-Lopez et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 99 assigned to	Median age 60, male 70.2%, hypertension 40.8%, diabetes 16.4%, COPD 9.5%, CHD	Steroids 100%, remdesivir 1%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection,	

	sarilumab 200-400mg once and 102 assigned to SOC	12.4%, CKD 3%, cancer 3%, obesity 3.5%		and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
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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
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RCT

BISHOP trial ; ³⁹⁷ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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 , ³⁹⁸ 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 ; ³⁹⁵ 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. ³⁹⁹ 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; ²⁷⁷ peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: RR 1.14 (95%CI 0.83 to 1.56); RD 2.2% (95%CI -2.7% to 9%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 1.02 (95%CI 0.59 to 1.76); RD 0.3% (95%CI -7.1% to 13.1.7%); Low certainty ⊕⊕○○
Sadeghi et al; ⁴⁰⁰ peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 14 days and 33 assigned to standard of care	Median age 58 ± 13, male 20.21%, hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%, coronary heart disease 15.1%, cancer 4.5%, obesity 25.7%	Corticosteroids 30.2%, lopinavir-ritonavir 48.4%, antibiotics 89.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation is probably inappropriate.	Symptom resolution or improvement: RR 1.01 (95%CI 0.95 to 1.08); RD 0.6% (95%CI -3% to 4.8%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information
Yakoot et al; ⁴⁰¹ 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,	Hospitalization: Very low certainty ⊕○○○

	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.
Roozbeh et al; ⁴⁰² 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; ²⁷⁵ 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; ⁴⁰³ Mobarak et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 541 assigned to sofosbuvir/daclatasvir 400/60mg a day for 10 days and 542 assigned to SOC	Median age 58, male 54%, hypertension 34%, diabetes 26%, COPD 2.1%, asthma 4.8%, CHD 9.1%,	Steroids 69.9%, remdesivir 15.6%, hydroxychloroquine 12.8%, lopinavir-ritonavir 33.1%, azithromycin 22.1%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
Alavi-moghaddam et al; ⁴⁰⁴ 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. ; ²⁷⁸ 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. ; ⁴⁰⁵ 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. ; ⁴⁰⁶ 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 ; ⁴⁰⁷ 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 ; ⁴⁰⁸ 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 ; ⁴⁰⁹ 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					
<p>COMET-ICE trial;⁴¹⁰ Gupta et al; peer reviewed; 2021</p>	<p>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</p>	<p>Median age 53 ±, male 46%, diabetes 23%, COPD 4%, asthma 16%, CKD 0.7%, obesity 63%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events</p> <p>Notes: Stopped early for benefit.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕○○</p> <p>Hospitalization: RR 0.14 (95%CI 0.04 to 0.48); RD -6.3% (95%CI -7.1% to -3.8%); Moderate certainty ⊕⊕⊕○</p>

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. ³⁹⁹ 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 , ⁴⁶ 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 ; ⁴¹¹ 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.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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 not 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 ; ⁴¹² Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone 40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	Mean age 69.5 ± 11.5, male 61.9%, hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%, cerebrovascular disease 12.7%	Hydroxychloroquine 96.8%, lopinavir-ritonavir 84.1%, azithromycin 92%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Mortality: RR 0.90 (95%CI 0.80 to 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 0.87 (95%CI 0.73 to 1.04); RD -2.2% (95%CI -4.7% to 0.7%); Moderate certainty ⊕⊕⊕○
Metcovid trial ; ⁴¹³ Prado Jeronimo et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 194 assigned to methylprednisolone 0.5 mg/kg twice a day for 5 days and 199 assigned to standard of care	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease 0.5%, asthma 2.5%, coronary heart disease 6.9%, alcohol use disorder 27%, liver disease 5.5%	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	Symptom resolution or improvement: RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⊕⊕○○ Symptomatic infection (prophylaxis studies): No information
RECOVERY-Dexamethasone trial ; ⁴¹⁴ 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	Severe adverse events: RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to

	standard of care	2%, any comorbidities 56%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	1.7%); Low certainty ⊕⊕○○ Hospitalization: No information
DEXA-COVID19 trial ; ⁴¹⁵ 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 ; ⁴¹⁶ 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 ; ⁴¹⁷ 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 ; ⁴¹⁵ 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 ; ⁴¹⁸ 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 ; ⁴¹⁵ 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 ; ⁴¹⁹ 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. ⁴²⁰ 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. ⁴²¹ 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. ⁴²² 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. ⁴²³ 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.	
Ghanei et al ; ⁵⁹ peer reviewed; 2021	Patients with severe COVID-19 infection. 116 assigned to prednisolone 25mg a day for 5 days and 110 assigned to SOC	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ranjbar et al ; ⁴²⁴ 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 0.96 (95%CI 0.65 to 1.42); RD -0.6% (95%CI - 5.6% to 6.7%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information
COVID STEROID 2 trial ; ⁴²⁵ Munch et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 497 assigned to dexamethasone 12 mg a day for 10	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	Symptomatic infection (prophylaxis studies): No information Adverse events: RR

	days and 485 assigned to dexamethasone 6 mg a day for 10 days				0.85 (95%CI 0.61 to 1.19); RD -1.5% (95%CI -4% to 1.9%); Low certainty ⊕⊕○○
Maskin et al; ⁴²⁶ preprint; 2021	Patients with critical COVID-19 infection. 49 assigned to dexamethasone 16 mg a day for 5 days followed by 8 mg a day for 5 days and 49 assigned to dexamethasone 6mg a day for 10 days	Mean age 61.8 ± 13.4, male 70%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Hospitalization: No information
Toroghi et al; ⁴²⁷ peer reviewed; 2021	Patients with severe COVID-19 infection. 86 assigned to dexamethasone 16 to 24 mg a day and 47 assigned to dexamethasone 8 mg a day for up to 10 days	Mean age 58, male 60.2%, hypertension 36%, diabetes 22.5%, COPD 6%, CHD 17.3%, CKD 1.5%, cerebrovascular disease 6%, cancer 2.3%,	Remdesivir 75.2%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Steroids (inhaled corticosteroids)

Inhaled corticosteroids probably improve symptom resolution. Further research is needed.

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

<p>STOIC trial;⁴²⁸ Ramakrishnan et al; peer reviewed ; 2020</p>	<p>Patients with mild to moderate COVID-19. 71 assigned to inhaled budesonide 800 µg twice a day and 69 assigned to SOC</p>	<p>Mean age 45 ± 56, male 42.4%</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Hospitalization: RR 0.85 (95%CI 0.58 to 1.26); RD -1.3% (95%CI -2.8% to 0.6%); Low certainty ⊕○○○</p> <p>Adverse events: No information</p>
<p>PRINCIPLE trial;⁴²⁹ Yu et al; peer reviewed; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 787 assigned to inhaled budesonide 800µg twice daily for 14 days and 1069 assigned to SOC</p>	<p>Mean age 64.2 ± 7.6, male 48%, hypertension 44.3%, diabetes 21.4%, COPD 12.6%, CHD 15.8%, cerebrovascular disease 5.6%</p>	<p>NR</p>	<p>Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Significant loss to follow-up.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Hospitalization: RR 0.85 (95%CI 0.58 to 1.26); RD -1.3% (95%CI -2.8% to 0.6%); Low certainty ⊕○○○</p> <p>Adverse events: No information</p>
<p>Song et al;⁴³⁰ peer reviewed; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 35 assigned to inhaled ciclesonide 320 µg twice per day for 14 days and 26 assigned to SOC</p>	<p>Median age 53 ± 26, male 47%, hypertension 27.8%, diabetes 14.7%, cerebrovascular disease 3.3%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Hospitalization: RR 0.85 (95%CI 0.58 to 1.26); RD -1.3% (95%CI -2.8% to 0.6%); Low certainty ⊕○○○</p> <p>Adverse events: No information</p>
<p>ALV-020-001 trial;⁴³¹ Clemency et</p>	<p>Patients with mild COVID-19 infection.</p>	<p>Mean age 43.3 ± 16.9, male 44.8%,</p>	<p>NR</p>	<p>Low for mortality and mechanical ventilation;</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>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 ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Hospitalization: RR 0.85 (95%CI 0.58 to 1.26); RD -1.3% (95%CI -2.8% to 0.6%); Low certainty ⊕○○○</p> <p>Adverse events: No information</p>

al; peer reviewed; 2021	197 assigned to inhaled ciclesonide 640 µg a day for 30 days and 203 assigned to SOC	hypertension 22.3%, diabetes 7.5%, asthma 6.5%		low for symptom resolution, infection and adverse events	
CONTAIN trial , ⁴³² Ezer et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 105 assigned to inhaled ciclesonide 1200 µg + 200 µg intranasal a day and 98 assigned to SOC	Median age 35 ± 19, male 46.3%, hypertension 5.9%, diabetes 2.5%, asthma 5%, CHD 0.5%, cancer 1%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Steroids (nasal corticosteroids)

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

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

Yildiz et al , ³¹⁶ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 50 assigned to nasal steroids and 50 assigned to SOC	Mean age 37.8 ± , male 56%, hypertension 10%, diabetes 7%, COPD/asthma 8%, asthma %, CHD 14%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p>
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					Hospitalization: No information
Sulodexide Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ERSul trial , ⁴³³ 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 ; ⁴³⁴ Preprint; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to TD-0903 1-10 mg once a day for 7 days and 6 assigned to SOC	Mean age 57.1 ± 12.3, male 68%, hypertension 68%, diabetes 40%	Corticosteroids 92%, remdesivir 12%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Tenofovir + emtricitabine

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
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RCT					
ARO-CORONA trial ; ⁴³⁵ Parienti et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 30 assigned to tenofovir + emtricitabine 245/200 mg twice a day on day one followed by 245/200 mg a day for	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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p>

	7 days and 30 assigned to SOC			symptoms and adverse events outcomes results.	Symptomatic infection (prophylaxis studies): No information
ARTAN-C19 trial ; ⁴³⁶ Lima et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 81 assigned to tenofovir +/- emtricitabine 300/200mg once a day and 41 assigned to SOC	Mean age 38 ± 14.9, male 35%, hypertension 17%, diabetes 10%, asthma 6%, CHD 3%, cancer 1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	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
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RCT

Amra et al ; ⁴³⁷ 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
Haghighi et al ; ⁴³⁸ preprint; 2021	Patients with moderate to severe COVID-19 infection. 25 assigned to Thalidomide 100 mg a day for 14 days and 25	Median age 51 ± 18, male 68%, hypertension 24%, diabetes 16%, CHD 8%, cancer 14%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty

	assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	⊕○○○ Hospitalization: No information
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Tissue plasminogen activator (tPA)

Uncertainty in potential benefits and harms. Further research is needed

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

STARS trial . ⁴³⁹ Barret et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 25 assigned to tPa 50mg bolus with or without drip and heparin and 25 assigned to SOC	Mean age 61, male 74%, hypertension 36%, diabetes 34%, COPD 62%, asthma %, CHD 66%, immunosuppressive therapy 66%	Corticosteroids 52%, remdesivir 40%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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Tocilizumab

Tocilizumab reduces mortality and mechanical ventilation requirements without increasing severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
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RCT					
COVACTA trial ; Rosas et al; ⁴⁴⁰ peer-reviewed; 2020	Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned to standard of care	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, coronary heart disease 28%, obesity 20.5%	Corticosteroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	Mortality: RR 0.85 (95%CI 0.79 to 93); RD -2.4% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕
Wang et al ; ⁴⁴¹ preprint; 2020	Patients with moderate to severe COVID-19. 34 assigned to tocilizumab 400 mg once or twice and 31 assigned to standard of care	Median age 63 ± 16, male 50.8%, hypertension 30.8%, diabetes 15.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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 ⊕⊕○○
Zhao et al ; ¹⁴⁷ peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir plus tocilizumab	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	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 ⊕⊕⊕○
RCT-TCZ-COVID-19 trial ; ⁴⁴² Salvarani et al; peer-reviewed; 2020	Patients with severe COVID-19. 60 assigned to tocilizumab 8 mg/kg twice on day 1 and 66	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	Hospitalization: No information

	assigned to standard of care			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
BACC Bay Tocilizumab Trial ; ⁴⁴³ 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-TOCI1 trial ; ⁴⁴⁴ 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 ; ⁴⁴⁵ Salama et al; preprint; 2020	Patients with moderate to severe COVID-19. 249 assigned to tocilizumab 8 mg/kg once and 128 assigned to standard of care	Mean age 55.9 ± 14.4, male 59.2%, hypertension 48.3%, diabetes 40.6%, COPD 4.5%, asthma 11.4%, coronary heart disease 1.9%, cerebrovascular disease 3.4%, obesity 24.4%	Corticosteroids 59.4%, remdesivir 54.6%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
REMAP-CAP - tocilizumab trial ; ³⁹¹ Gordon et al; peer-	Patients with severe to critical COVID-19 infection. 353 assigned	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%,	Corticosteroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom

reviewed; 2020	to TCZ 8 mg/kg once or twice, 48 assigned to sarilumab 400 mg once and 402 assigned to SOC	CHD 10.2%, immunosuppressive therapy 1.4%, cancer %, obesity %		resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Veiga et al ; ⁴⁴⁶ 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 ; ⁴⁴⁷ 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 . ⁴⁴⁸ Rutgers et al; preprint; 2021	Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice	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 180 assigned to SOC			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Talaschian et al ; ⁴⁴⁹ 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 ; ⁴⁵⁰ 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 ; ³⁹⁵ other; 2021	Patients with severe to critical COVID-19 infection. 10 assigned to TCZ 8 mg/kg once or twice and 11 assigned to SOC	Median age 61 ±	Corticosteroids 95.2%, remdesivir 90.4%, convalescent plasma 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.

CORIMUNO-TOCLICU trial ; ³⁹⁵ 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 ; ³⁹⁵ 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 ; ³⁹⁵ 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 ; ³⁹⁵ other; 2021	Patients with severe to critical COVID-19 infection. 26 assigned to TCZ 8 mg/kg once and 13 assigned to SOC	Median age 66	Corticosteroids 77%, 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.	

COVITOX-01 trial; et al; ³⁹⁵ 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; ³⁹⁵ 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; ⁴⁵¹ Rosas et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 430 assigned to TCZ 8 mg/kg once or twice and 210 assigned to SOC	Median age 6, male 63.2%, hypertension 61.7%, diabetes 39.5%, CHD 23.4%	Corticosteroids 88.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ImmCoVA trial; ³⁹⁵ 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 ; ³⁹⁵ 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 ; ⁴⁵² 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 ; ⁴⁵³ 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 ; ⁴⁵⁴ Guimaraes et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 144 assigned to tofacitinib 10 mg twice a day for 14 days and 145 assigned to SOC	Mean age 56 ± 14, male 65.1%, hypertension 50.2%, diabetes 23.5%	Corticosteroids 78.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: RR 1.1 (95%CI 0.98 to 1.23); RD 6.1% (95%CI 1.2% to 13.9%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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

<p>Wu et al.;⁴⁵⁵ peer-reviewed; 2020</p>	<p>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</p>	<p>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%</p>	<p>Corticosteroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%, umifenovir 61.5%, ribavirin 28.9%,</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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. ¹³⁷ 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. ²⁷¹ 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.	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
Nojomi et al. ⁴⁵⁶ 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	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

	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. ⁴⁵⁷ 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 ⁴⁵⁸ 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.
UAIC trial ⁴⁵⁹ Darazam et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 51 assigned to umifenovir 600 mg a day for 10 days and 50 assigned to SOC	Mean age 61.2 ± 15.8, male 56.4%, hypertension 46.4%, diabetes 31.6%, COPD 10%, asthma 6.1%, CHD 11.2%, CKD 7.1%, cancer 1%	Corticosteroids 3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have

				introduced bias to symptoms and adverse events outcomes results.	
Ramachandran et al , ⁴⁶⁰ preprint; 2021	Patients with mild to moderate COVID-19 infection. 60 assigned to umifenovir 800 mg twice a day for 14 days and 63 assigned to SOC	Mean age 46.7 ± 1.9, male 74.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

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
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RCT

Zhang et al , ⁴⁶¹ 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
Kumari et al , ⁴⁶² 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	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

				study. Concealment of allocation is probably inappropriate.	low certainty ⊕○○○
Jamali Moghadam Siahkali et al ; ⁴⁶³ Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5 g a day for 5 days and 30 assigned to SOC	Mean age 59.2 ± 17, male 50%, hypertension 41.6%, diabetes 38.3%, COPD 10%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVIDAtoZ- Vit C trial ; ⁴⁶⁴ Thomas et al; peer reviewed; 2020	Patients with mild COVID-19. 48 assigned to Vit C 8000 mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Corticosteroids 8.4%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
VCACS trial ; ⁴⁶⁵ Tehrani et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 18 assigned to Vit C 8 gr a day for 5 days and 26 assigned to SOC	Mean age 59.5, male 59%, hypertension 40.9%, diabetes 34%, COPD 7%, CHD 22.7%, CKD 9.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Beigmohammadi et al , ⁴⁶⁶ peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin Vitamin D 600000 UI once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000mg a day in addition to others for 7 days. and 30 assigned to SOC	Mean age 52 ± 9, male 51.6%, hypertension 33.3%, diabetes 18.3%, asthma 13.3%, cancer 5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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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
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RCT

COVIDIOL trial ; Entrenas Castillo et al, ⁴⁶⁷ 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 Symptomatic infection (prophylaxis studies): No information
SHADE trial , ⁴⁶⁸ 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	Adverse events: Very low certainty ⊕○○○

				Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	Hospitalization: No information
Murai et al , ⁴⁶⁹ 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 , ⁴⁷⁰ 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 , ⁴⁷¹ 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.	
Maghbooli et al , ⁴⁷² peer reviewed; 2021	Patients with moderate to severe COVID-19 infection.	Mean age 49.1 ± 14.1, male 60.4%, hypertension 31.1%,	Corticosteroids 46.2%,	High for mortality and mechanical ventilation; high for symptom	

	53 assigned to Vit D3 25 µg a day for 30 days and 53 assigned to SOC	diabetes 23.6%, COPD 10.3%, CHD 12.3%, CKD 2.8%		resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Beigmohammadi et al. ⁴⁶⁶ peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin Vitamin D 600000 UI once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000mg a day in addition to others for 7 days. and 30 assigned to SOC	Mean age 52 ± 9, male 51.6%, hypertension 33.3%, diabetes 18.3%, asthma 13.3%, cancer 5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

XAV-19 (swine glyco-humanized polyclonal antibodies)

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

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

POLYCOR trial ⁴⁷³ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic</p>
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					<p>infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Zinc

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

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

<p>Hassan et al;⁴⁷⁴ preprint; 2020</p>	<p>Patients with mild to critical COVID-19. 49 assigned to zinc 220 mg twice a day and 56 assigned to standard of care</p>	<p>Mean age 45.9 ± 17.5, male 58.2%, hypertension 10.4%, diabetes 11.2%, coronary heart disease 3%,</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
<p>Abd-Elsalam et al;⁴⁷⁵ peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%</p>	<p>Hydroxychloroquine 100%,</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation is probably inappropriate.</p>	<p>Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○</p> <p>Adverse events: No information</p> <p>Hospitalization: Very</p>

Abdelmaksoud et al , ⁴⁷⁶ Peer reviewed; 2020	Patients with mild to critical COVID-19. 49 assigned to Zinc 220 mg twice a day and 56 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	low certainty ⊕○○○
COVIDAtoZ-Zinc trial , ⁴⁶⁴ 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 , ⁴⁷⁷ 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 , ¹⁹⁴ 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.	
Reszinate trial , ³⁸⁶ Kaplan et al; preprint; 2021	Patients with mild COVID-19 infection. 14 assigned to resveratrol + Zinc 4000/150 mg once a day for five days and 16 assigned to SOC	Mean age 42.4, male 40%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes:	

α -lipoic acid

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

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

Zhong et al , ⁴⁷⁸ 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 \pm 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 $\oplus\circ\circ\circ$ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Standard of care	Steroids		
Mortality 28 days	Relative risk: 0.9 (CI 95% 0.8 - 1.02) Based on data from 8000 patients in 12 studies	160 per 1000	144 per 1000	Moderate Due to serious imprecision ¹	Steroids probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 5942 patients in 6 studies Follow up 28	172 per 1000	150 per 1000	Moderate Due to serious imprecision ²	Steroids probably decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.27 (CI 95% 0.98 - 1.65) Based on data from 646 patients in 5 studies	606 per 1000	770 per 1000	Moderate Due to serious risk of bias ³	Steroids probably increases symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.89 (CI 95% 0.68 - 1.17) Based on data from 833 patients in 6 studies	102 per 1000	91 per 1000	Low Due to serious risk of bias, Due to serious imprecision ⁴	Steroids may have little or no difference on severe adverse events
Mortality (High vs standard dose) 28 to 90 days	Relative risk: 0.84 (CI 95% 0.67 - 1.04) Based on data from 1166 patients in 3 studies	160 per 1000	134 per 1000	Moderate Due to serious imprecision ⁵	High dose steroids (i.e dexamethasone 12mg a day) probably decreases mortality in comparison to standard dose steroids (i.e dexamethasone 6mg a day)
Severe adverse events (High vs. standard dose) 28 days	Relative risk: 0.85 (CI 95% 0.61 - 1.19) Based on data from 982 patients in 1 study	102 per 1000	87 per 1000	Low Due to very serious imprecision ⁶	High dose steroids (i.e dexamethasone 12mg a day) may not increase severe adverse events in comparison to standard dose steroids (i.e dexamethasone 6mg a day)

1. **Imprecision: serious.** 95%CI includes no mortality reduction;
2. **Imprecision: serious.** 95%CI include no IVM reduction;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;
5. **Imprecision: serious.** 95%CI includes no mortality decrease;
6. **Imprecision: very serious.** Low number of patients, Wide confidence intervals;

Summary of findings Table 2.

Population: Patients with COVID-19 infection

Intervention: Remdesivir

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Remdesivir		
Mortality 28 days	Relative risk: 0.97 (CI 95% 0.85 - 1.1) Based on data from 7708 patients in 7 studies Follow up Median 28 days	160 per 1000	155 per 1000	Low Due to serious imprecision, Due to serious risk of bias ¹	Remdesivir may not decrease mortality
Mechanical ventilation 28 days	Relative risk: 0.79 (CI 95% 0.51 - 1.23) Based on data from 6820 patients in 6 studies Follow up Median 28 days	173 per 1000	137 per 1000	Low Due to serious risk of bias, Due to serious imprecision ²	Remdesivir may decrease mechanical ventilation requirements
Symptom resolution or improvement 28 days	Relative risk: 1.1 (CI 95% 0.96 - 1.28) Based on data from 1981 patients in 4 studies Follow up 28 days	606 per 1000	667 per 1000	Low Due to serious risk of bias, Due to serious imprecision ³	Remdesivir may improve symptom resolution or improvement
Severe adverse events	Relative risk: 0.8 (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
Mortality 28 days	Relative risk: 0.72 (CI 95% 0.44 - 1.19) Based on data from 7600 patients in 6 studies Follow up Median 28 days	160 per 1000	115 per 1000	Low Due to serious imprecision, Due to serious risk of bias ⁵	Remdesivir may decrease mortality slightly

- 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;
- 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;
- 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 ;
- Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95%ci included significant severe adverse events increase;

5. **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;

Summary of findings Table 3.

Population: Patients with COVID-19 infection or exposed to COVID-19

Intervention: Hydroxychloroquine (HCQ)

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	HCQ		
Mortality 15 days	Relative risk: 1.07 (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
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
Symptom resolution or improvement 28 days	Relative risk: 1.01 (CI 95% 0.93 - 1.1) Based on data from 6601 patients in 10 studies Follow up 28 days	606 per 1000	612 per 1000	Moderate Due to serious inconsistency ³	Hcq probably has little or no difference on symptom resolution or improvement
COVID-19 infection (in exposed individuals) (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)
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
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

- Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
- Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
- Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious.** 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

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

Hospitalization	Relative risk: 1.24 (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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	CP		
Mortality (Low RoB studies) 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	Convalescent plasma has little or no difference on mortality
Mechanical ventilation (Low RoB studies) 28 days	Relative risk: 1.05 (CI 95% 0.94 - 1.16) Based on data from 11079 patients in 8 studies Follow up Median 28 days	173 per 1000	182 per 1000	High	Convalescent plasma has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.95 - 1.04) Based on data from 14103 patients in 10 studies Follow up 28 days	606 per 1000	600 per 1000	Moderate Due to serious inconsistency ¹	Cp probably has little or no difference on symptom resolution or improvement
Hospitalizations	Relative risk: 0.89 (CI 95% 0.68 - 1.16) Based on data from 1293 patients in 2 studies	74 per 1000	66 per 1000	Low Due to very serious imprecision ²	CP may not reduce hospitalizations
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 ³	Convalescent plasma probably increases severe adverse events

1. **Inconsistency: serious.** Point estimates vary widely;
2. **Imprecision: very serious.** Wide confidence intervals;
3. **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		Certainty of the evidence (quality of evidence)	Plain language summary
		SOC	TCZ		
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
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
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
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

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 & comparator: Anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day); Anticoagulants in full dose (i.e., enoxaparin 1 m/kg twice a day); Anticoagulants in prophylactic dose (i.e., enoxaparin 40 mg a day); No anticoagulants

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	ACO		
Mortality (full or intermediate dose vs. prophylactic dose in hospitalized patients) (excluding high risk of bias studies)	Relative risk: 0.97 (CI 95% 0.79 - 1.2) Based on data from 5415 patients in 8 studies	160 per 1000	155 per 1000	Low Due to very serious imprecision ¹	Anticoagulants in intermediate or full dose may have little or no difference on mortality in comparison with prophylactic dose
Venous thromboembolic events (intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.82 (CI 95% 0.33 - 2.0) Based on data from 921 patients in 3 studies	70 per 1000	57 per 1000	Low Due to very serious imprecision ²	Anticoagulants in intermediate dose may slightly reduce venous thromboembolic events
Venous thromboembolic events (full dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.56 (CI 95% 0.44 - 0.72) Based on data from 4739 patients in 6 studies	70 per 1000	39 per 1000	High	Anticoagulants in intermediate or full dose probably decreases venous thromboembolic events (full dose)
Major bleeding (full or intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 1.76 (CI 95% 1.19 - 2.62) Based on data from 5780 patients in 8 studies	19 per 1000	33 per 1000	Moderate Due to serious imprecision ³	Anticoagulants in intermediate or full dose probably increases major bleeding
Symptom resolution or improvement (prophylactic dose vs. no anticoagulants in	Relative risk: 1.08 (CI 95% 0.92 - 1.27) Based on data from 444 patients in 1 studies	606 per 1000	654 per 1000	Moderate Due to serious imprecision ⁴	Anticoagulants in prophylactic dose probably do not improve time to symptom resolution

mild ambulatory patients)					
Clinically important bleeding (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 2.5 (CI 95% 0.49 - 12.8) Based on data from 444 patients in 1 study	9 per 1000	23 per 1000	Very low Due to very serious imprecision ⁵	It is uncertain if anticoagulants in prophylactic dose increase or decrease clinically important bleeding
Hospitalization (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 0.42 (CI 95% 0.11 - 1.64) Based on data from 444 patients in 1 study	74 per 1000	31 per 1000	Very low Due to very serious imprecision ⁶	It is uncertain if anticoagulants in prophylactic increase or decrease hospitalization

1. **Imprecision: very serious.** 95%CI includes small benefits and harms;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: serious.** 95%CI includes harms and absence of harms;
4. **Imprecision: serious.** 95%CI includes harms and absence of harms;
5. **Imprecision: very serious.** 95%CI includes harms and absence of harms;
6. **Imprecision: very 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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	IFN		
Mortality 28 days	Relative risk: 1.07 (CI 95% 0.91 - 1.26) Based on data from 5210 patients in 4 studies Follow up Median 28 days	160 per 1000	171 per 1000	Moderate Due to serious imprecision ¹	IFN probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.97 (CI 95% 0.83 - 1.14) Based on data from 4881 patients in 4 studies Follow up 28 days	173 per 1000	168 per 1000	Moderate Due to serious imprecision ²	IFN probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 0.96 (CI 95% 0.92 - 0.99) Based on data from 969 patients in 1 study Follow up 28 days	606 per 1000	582 per 1000	Moderate Due to serious imprecision ³	Ifn probably has little or no difference on symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.94 (CI 95% 0.65 - 1.37) Based on data from 877 patients in 1 study Follow up 28 days	102 per 1000	96 per 1000	Low Due to very serious imprecision ⁴	Ifn may have little or no difference on severe adverse events
Symptom resolution or improvement (inhaled) ⁵ 30 days	Hazard Ratio: 2.19 (CI 95% 1.03 - 4.69) Based on data from 81 patients in 1 study Follow up 28 days	606 per 1000	870 per 1000	Low Due to very serious imprecision ⁶	IFN (inhaled) may increase symptom resolution or improvement

1. **Imprecision: serious.** 95%CI includes significant mortality reduction and increase;
2. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** 95% included significant mechanical ventilation requirement reduction and increase;
3. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits ;
4. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits ;
5. Nebulizations
6. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits ;

Summary of findings Table 10.

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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Favipiravir		
Mortality 28 days	Relative risk: 1.17 (CI 95% 0.82 - 1.67) Based on data from 1779 patients in 7 studies Follow up Median 28 days	160 per 1000	187 per 1000	Low Due to very serious imprecision ¹	Favipiravir may increase mortality
Mechanical ventilation 28 days	Relative risk: 1.27 (CI 95% 0.91 - 1.76) Based on data from 1632 patients in 6 studies Follow up Median 28 days	173 per 1000	220 per 1000	Low Due to very serious imprecision ²	Favipiravir may increase mechanical ventilation
Symptom resolution or improvement (Low RoB studies) 28 days	Relative risk: 1.02 (CI 95% 0.94 - 1.1) Based on data from 842 patients in 3 studies Follow up 28 days	606 per 1000	618 per 1000	Moderate Due to serious imprecision ³	Favipiravir probably has little or no difference on symptom resolution or improvement
Hospitalization (in patients with non-severe disease)	Relative risk: 0.45 (CI 95% 0.1 - 2.13) Based on data from 284 patients in 2 studies Follow up 28 days	606 per 1000	273 per 1000	Very low Due to serious risk of bias, Due to very serious imprecision ⁴	We are uncertain whether favipiravir increases or decreases hospitalization (in patients with non- severe disease)
Severe adverse events ⁵ 30 days	Relative risk: 0.83 (CI 95% 0.42 - 1.65) Based on data from 983 patients in 5 studies Follow up 28 days	606 per 1000	503 per 1000	Very low Due to very serious imprecision, Due to serious risk of bias ⁶	We are uncertain whether favipiravir increases or decreases severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant mortality reduction and increase;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits ;
4. **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 ;
5. Nebulizations
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
Imprecision: very serious. 95%CI includes significant benefits and absence of benefits ;

Summary of findings Table 12.

Population: Patients with COVID-19 infection

Intervention: Ivermectin

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Ivermectin		
Mortality (Low risk of bias studies) 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
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
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
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
Severe adverse events	Relative risk: 1.29 (CI 95% 0.44 - 3.85) Based on data from 917 patients in 5 studies Follow up 28 days	102 per 1000	132 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
Hospitalization (in non-severe patients)	Relative risk: 0.67 (CI 95% 0.39 - 1.14) Based on data from 1179 patients in 5 studies Follow up 28 days	74 per 1000	50 per 1000	Low Due to very serious imprecision ⁸	Ivermectin may decrease 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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Baricitinib		
Mortality	Relative risk: 0.64 (CI 95% 0.51 - 0.8) Based on data from 2659 patients in 3 studies	160 per 1000	102 per 1000	Moderate Due to serious risk of bias ¹	Baricitinib probably decreases mortality
Invasive mechanical ventilation	Relative risk: 0.66 (CI 95% 0.46 - 0.93) Based on data from 922 patients in 1 studies 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
Symptom resolution or improvement	Relative risk: 1.27 (CI 95% 1.13 - 1.42) Based on data from 2659 patients in 3 studies Follow up 30 days	606 per 1000	770 per 1000	Moderate Due to serious risk of bias ³	Baricitinib probably improves symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.64 - 0.95) Based on data from 2659 patients in 3 studies Follow up 30 days	102 per 1000	80 per 1000	Moderate Due to serious risk of bias ⁴	Baricitinib probably has little or no difference on severe adverse events

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;

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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Colchicine		
Mortality	Relative risk: 1.0 (CI 95% 0.93 - 1.07) Based on data from 16397 patients in 6 studies	160 per 1000	160 per 1000	Moderate Due to serious imprecision ¹	Colchicine probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 1.02 (CI 95% 0.92 - 1.13) Based on data from 15507 patients in 4 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
Symptom resolution or improvement	Relative risk: 1.0 (CI 95% 0.97 - 1.02) Based on data from 11719 patients in 3 studies Follow up 30 days	173 per 1000	173 per 1000	High	Colchicine has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 0.99) Based on data from 4880 patients in 3 studies Follow up 30 days	102 per 1000	80 per 1000	High	Colchicine has little or no difference on severe adverse events
Pulmonary embolism	Relative risk: 5.55 (CI 95% 1.23 - 25.0) Based on data from 4399 patients in 1 study Follow up 30 days	0.9 per 1000	5.0 per 1000	Low Due to very serious imprecision ³	Colchicine may have little or no difference on pulmonary embolism
Hospitalization (in patients with non-severe disease)	Relative risk: 0.81 (CI 95% 0.63 - 1.04) Based on data from 4777 patients in 2 studies Follow up 30 days	74 per 1000	60 per 1000	Low Due to very serious imprecision ⁴	Colchicine may decrease 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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir		
Mortality (Low RoB studies)	Relative risk: 1.14 (CI 95% 0.83 - 1.56) Based on data from 1163 patients in 2 studies	160 per 1000	182 per 1000	Low Due to very serious imprecision ¹	Sofosbuvir alone or in combination may have little or no difference on mortality
Invasive mechanical ventilation (Low RoB studies)	Relative risk: 1.02 (CI 95% 0.59 - 1.76) Based on data from 1163 patients in 2 studies Follow up 30 days	173 per 1000	176 per 1000	Low Due to very serious imprecision ²	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir may have little or no difference on invasive mechanical ventilation
Symptom resolution or improvement (Low RoB studies)	Relative risk: 1.01 (CI 95% 0.95 - 1.08) Based on data from 1163 patients in 2 studies Follow up 7 days	606 per 1000	612 per 1000	Moderate Due to serious imprecision ³	Sofosbuvir alone or in combination probably has little or no difference on symptom resolution or improvement

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 Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	REGEN-COV (casirivimab and imdevimab)		
Mortality	Relative risk: 0.83 (CI 95% 0.64 - 1.04) Based on data from 16667 patients in 4 studies	160 per 1000	133 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹	Regen-cov (casirivimab and imdevimab) may decrease mortality
Mortality (seronegative)	Relative risk: 0.8 (CI 95% 0.71 - 0.89) Based on data from 3673 patients in 2 studies	160 per 1000	128 per 1000	Moderate Due to serious indirectness ²	Regen-cov (casirivimab and imdevimab) probably decreases mortality in seronegative patients
Invasive mechanical ventilation	Relative risk: 0.79 (CI 95% 0.54 - 1.14) Based on data from 14575 patients in 3 studies Follow up 30 days	173 per 1000	137 per 1000	Low Due to very serious imprecision ³	Regen-cov (casirivimab and imdevimab) may decrease invasive mechanical ventilation
Invasive mechanical ventilation (seronegative)	Relative risk: 0.82 (CI 95% 0.74 - 0.9) Based on data from 3603 patients in 2 studies	173 per 1000	142 per 1000	Moderate Due to serious indirectness, Due to serious imprecision ⁴	Regen-cov (casirivimab and imdevimab) probably decreases invasive mechanical ventilation in seronegative patients
Symptom resolution or improvement	Relative risk: 1.06 (CI 95% 1.0 - 1.12) Based on data from 14746 patients in 3 studies	606 per 1000	642 per 1000	Low Due to serious imprecision, Due to serious inconsistency ⁵	Regen-cov (casirivimab and imdevimab) may increase symptom resolution or improvement
Symptom resolution or improvement (seronegative)	Relative risk: 1.12 (CI 95% 1.05 - 1.18) Based on data from 6277 patients in 3 studies Follow up 30 days	606 per 1000	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: 0.3 (CI 95% 0.2 - 0.46) Based on data from 5049 patients in 3 studies Follow up 30 days	74 per 1000	22 per 1000	Moderate Due to serious imprecision ⁷	Regen-cov (casirivimab and imdevimab) probably reduces hospitalization in patients with recent

				onset non-severe disease
Symptomatic infection (in exposed individuals)	Relative risk: 0.43 (CI 95% 0.31 - 0.59) Based on data from 2678 patients in 3 studies Follow up 30 days	174 per 1000	75 per 1000	High
		Difference: 99 fewer per 1000 (CI 95% 120 fewer - 71 fewer)		Regen-cov (casirivimab and imdevimab) decreases symptomatic infection in exposed individuals
Severe adverse events	Relative risk: 0.54 (CI 95% 0.27 - 1.07) Based on data from 9697 patients in 6 studies	102 per 1000	55 per 1000	Moderate Due to serious imprecision ⁸
		Difference: 47 fewer per 1000 (CI 95% 74 fewer - 7 more)		Regen-cov (casirivimab and imdevimab) probably has little or no difference on severe adverse events

- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.; **Imprecision: serious.** Wide confidence intervals;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis; **Imprecision: very serious.**
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: very serious.** Wide confidence intervals;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis;
- Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.; **Imprecision: serious.** Wide confidence intervals;
- Indirectness: serious.** Subgroup analysis;
- Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: serious.** Low number of events;
- Imprecision: serious.** Wide confidence intervals;

Summary of findings Table 18.

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Inhaled corticosteroids		
Mortality	Relative risk: 0.85 (CI 95% 0.64 - 1.12)	160 per 1000	136 per 1000	Very low	We are uncertain whether inhaled

	Based on data from 1856 patients in 1 study	Difference: 24 fewer per 1000 (CI 95% 58 fewer - 19 more)	Due to serious risk of bias, Due to very serious imprecision ¹	corticosteroids increases or decreases mortality
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 Difference: 10 fewer per 1000 (CI 95% 97 fewer - 170 more)	Very low Due to serious risk of bias, Due to very serious imprecision ²	We are uncertain whether inhaled corticosteroids increase or decrease invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.16 (CI 95% 1.08 - 1.24) Based on data from 2390 patients in 5 studies	606 per 1000 703 per 1000 Difference: 97 more per 1000 (CI 95% 48 more - 145 more)	Moderate Due to serious risk of bias ³	Inhaled corticosteroids probably increase symptom resolution or improvement
Hospitalizations	Relative risk: 0.85 (CI 95% 0.58 - 1.26) Based on data from 2459 patients in 3 studies	74 per 1000 63 per 1000 Difference: 11 fewer per 1000 (CI 95% 31 fewer - 19 more)	Very low Due to serious risk of bias, Due to very serious imprecision ⁴	We are uncertain whether inhaled corticosteroids increase or decrease hospitalizations

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. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
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 , Wide confidence intervals;

Summary of findings Table 19.

Patients with COVID-19 infection

Intervention: Fluvoxamine

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOC	Fluvoxamine		
Mortality	Relative risk: 0.69 (CI 95% 0.36 - 1.27) Based on data from 1497 patients in 1 study	160 per 1000	110 per 1000	Very low Due to very serious imprecision ¹	There were too few who experienced the mortality, to determine whether fluvoxamine made a difference
Mechanical ventilation	Relative risk: 0.77 (CI 95% 0.45 - 1.3) Based on data from 1497 patients in 1 study	160 per 1000	123 per 1000	Very low Due to very serious imprecision ²	There were too few who experienced the mortality, to determine whether fluvoxamine made a difference
Hospitalizations	Relative risk: 0.77 (CI 95% 0.58 - 1.02) Based on data from 1649 patients in 2 studies	74 per 1000	57 per 1000	Moderate Due to serious imprecision ³	Fluvoxamine probably reduces hospitalizations
Severe adverse events ⁴	Relative risk: 0.81 (CI 95% 0.54 - 1.22) Based on data from 1649 patients in 2 studies	102 per 1000	83 per 1000	Low Due to very serious imprecision ⁵	Fluvoxamine may not increase severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
4. Symptomatic infection in persons at risk or exposed to SARS-COV2
5. **Imprecision: very serious.** Wide confidence intervals;

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