

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

Summary of Evidence
Rapid Review, 22 June 2021



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Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence. Rapid Review, 22 June 2021

PAHO/IMS/EIH/COVID-19/21-018

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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.

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Executive summary

Background

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

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

Summary of evidence

Tables 1 and 2, which divide the total group of identified studies into randomized (Table 1) and non-randomized (Table 2) designs, indicate the primary outcome measures used for each investigation and the level of certainty. Table 3, below, summarizes the status of evidence for the 122 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=331)

Intervention	Overall number of studies including the intervention, n=331	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Hydroxychloroquine or Chloroquine	NEW	36	10	9	7	4 (*)	10
Ivermectin	NEW	32	5 (*)	4	3 (*)	4	4
Convalescent plasma	NEW	15	6 (*)	9	7	6	3
Glucocorticoids		15	12	8	5	6	
Favipiravir		14	5	3	1 (*)	1	1
Lopinavir-Ritonavir	NEW	14	3	4	2	2	1
Tocilizumab		13	11	9	5	11	
Sofosbuvir +/- Daclatasvir, ledipasvir or velpatasvir	NEW	11	2 (*)	2 (*)	2 (*)		
ACEIs or ARBs	NEW	8	7	7	2		1
Azithromycin		8	4	3	3	1	
Mouthwash		6	2	1	1		
Remdesivir		6	5 (#)	5	3	3	
Zinc		6	2	1	2	1	
Anticoagulants (Intermediate or full dose)	NEW	6	3			5 (*)	
Cochicine		4	4 (**)	3 (**)	1 (**)	1	1
IVIg		5	7	7		0	
Umifenovir		5					
Bamlanivimab	NEW	4	2		2	1	4
Bromhexine Hydrochloride		4	2	1	2	1	1
Interferon beta-1a		4	3	3	1		
Mesenchymal cell transplantation	NEW	4	3		1		2
Niloxonide		4	1	1	1		2
Vitamin C		3	3	4	2		
Vitamin D		4	2	1			1
N-acetylcysteine	NEW	3	2	2			1
Molnupiravir	NEW	3					3
REGEN-COV (casirivimab and imdevimab)	NEW	3	1 (#)	1 (#)	2 (#)	0	2
Santiumab		3	3	1	2		3
Anakinra		2	2	1	2		2
Aspirin		2	2	2	0		
Baricitinib		2	2	1	2		2
Dutasteride		2			1		
Iota-Carrageenan		2	1				2
Leflunomide		2					
Nitric oxide		2	1	1	1		2
Omega-3 fatty acids		2	1				
Ozone		2	2		1		1
Proxalutide		2	1	1	1		1
Steroids (inhaled)		2		1	2		1
99mTc-MDP		1					
Ammonium chloride		1	1	1			
Aprepitant		1					
Artemisinin		1			1		1
Auxora		1	1	1			
Aviptadil		1	1		1		1
Azvodine		1					
Baloxavir		1			1		
Bamlanivimab + etesevimab		1	1		1		1
BCG		1	1				
Bioven		1	1				1
Camostat mesilate		1	1	1	1		1
CERC-002		1	1				1
Chloroquine nasal drops		1					
Clarithromycin		1					
CIGB-325		1			1		1
Cofactors		1			1		1
Darunavir-Cobicistat		1					
Electrolyzed saline		1	1		1		1
Enisamium		1			1		
Famotidine		1					
Febuxostat		1					1
Finasteride		1	1				
Fluvoxamine		1	1	1			1
Helium (inhaled)		1					
Honey + Nigella sativa		1			1		
Hyperbaric oxygen		1	1	1	1		

Hyperimmune anti-COVID-19 IVIG	NEW	1	1			1			1
Icatibant		1							
IC1e/K		1							
IFN alpha2b + IFN-gamma		1							
IFX-1		1							1
Infliximab	NEW	1				1			1
INM005 (equine antibodies)		1		1		1			1
Interferon beta-1b		1		1		1			
Interferon beta-1a (inhaled)		1		1		1			1
Interferon gamma		1							
Interferon kappa + TFF2		1		1					1
Itolizumab		1		1					1
KB109		1				1			1
Lactococcus Lactis (intranasal)		1				1			1
Lenzilumab		1		1					1
Levamisole		1				1			
Lincomycin		1							1
Low-dose radiation therapy		1							
Mavrilimumab		1		1		1			1
Melatonin		1				1			
Mefisoprinol		1							
Methylene blue		1							
Mycobacterium w		1							
Namilumab	NEW	1				1			1
Nasal hypertonic saline		1				1			
Neem (Azadirachta indica A. Juss)		1						1	
Novaferon		1							
Otilimab		1							1
Peg-IFN alfa		1				1			
Peg-IFN lambda		1							1
PNB001 (CCK-A antagonist)		1				1			
Polymerized type I collagen (PT1C)		1							1
Povidone iodine		1							1
Progesterone		1		1					1
Prolectin-M		1		1					1
Propolis		1		1					
Pyridostigmine		1		1		1			1
Quercetin		1				1			
Ramipril		1						1	
Recombinant Super-Compound IFN		1				1			
Regdanvimab		1				1			1
Ribavirin		1							
Ribavirin + Interferon beta-1b		1							
Ruxolitinib		1				1			
rhG-CSF		1							1
Short-wave diathermy		1				1			1
Sofosbuvir/ledipasvir		1		1		1			1
Sotrovimab		1		1		1			1
Statins		1		1					
Stem cell reburization	NEW	1				1			1
Sulodexide		1		1					1
TD-0903 (inhaled JAK-inhibitor)		1							1
Thalidomide		1		1					1
Triazavirin		1				1			1
Tofacitinib	NEW	1				1			1
XAV-19 (swine polyclonal antibodies)		1							1
o-Lipoic acid		1							1

(*) Based on low risk of bias subgroup of studies; (#) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-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.



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

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

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

Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=122), as at 22 June 2021

	Intervention	Summary of findings
1	99mTc-MDP	Uncertainty in potential benefits and harms. Further research is needed.
2	Ammonium chloride	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	Anakinra	It is uncertain if anakinra affects mortality, mechanical ventilation requirements, symptom resolution or increases severe adverse events. Further research is needed.
5	Anticoagulants	There are specific recommendations on the use of antithrombotic agents ⁸ for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) probably does not decrease mortality in comparison with prophylactic dose (i.e., enoxaparin 40 mg a day). Anticoagulants in intermediate or full dose may decrease venous thromboembolic events but increase major bleeding in comparison with prophylactic dose.
6	Aprepitant	Uncertainty in potential benefits and harms. Further research is needed.
7	Artemisinin	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
8	Aspirin	Aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement.
9	Auxora	Uncertainty in potential benefits and harms. Further research is needed.
10	Aviptadil	Uncertainty in potential benefits and harms. Further research is needed.
11	Azithromycin	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
12	Azvudine	Uncertainty in potential benefits and harms. Further research is needed.
13	Baricitinib	Baricitinib probably reduces mortality and time to symptom resolution. Certainty of the evidence was moderate because of risk of bias.
14	Baloxavir	Uncertainty in potential benefits and harms. Further research is needed.
15	Bamlanivimab (monoclonal antibody)	Bamlanivimab probably does not significantly improve time to symptom resolution but it probably reduces symptomatic infections in exposed individuals. It is uncertain if it affects mortality or mechanical ventilation requirements. Further research is needed.
16	Bamlanivimab + etesevimab (monoclonal antibodies)	Bamlanivimab + etesevimab probably does not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. Further research is needed.
17	BCG	Uncertainty in potential benefits and harms. Further research is needed.
18	Bioven	Uncertainty in potential benefits and harms. Further research is needed.
19	Bromhexine hydrochloride	Uncertainty in potential benefits and harms. Further research is needed.
20	Camostat mesilate	Uncertainty in potential benefits and harms. Further research is needed.
21	CERC-002	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
22	Chloroquine nasal drops	Uncertainty in potential benefits and harms. Further research is needed.
23	CIGB-325	Uncertainty in potential benefits and harms. Further research is needed.
24	Clarithromycin	Uncertainty in potential benefits and harms. Further research is needed.
25	Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)	Uncertainty in potential benefits and harms. Further research is needed.
26	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.
27	Convalescent plasma	Convalescent plasma probably does not reduce mortality nor significantly reduces mechanical ventilation requirements or improves time to symptom resolution with moderate certainty of the evidence. Convalescent plasma may increase severe adverse events but infusion related severe adverse events are probably exceptional.
28	Darunavir-cobicistat	Uncertainty in potential benefits and harms. Further research is needed.
29	Dutasteride	Uncertainty in potential benefits and harms. Further research is needed.
30	Electrolyzed saline	Uncertainty in potential benefits and harms. Further research is needed.
31	Enisamium	Uncertainty in potential benefits and harms. Further research is needed.
32	Famotidine	Uncertainty in potential benefits and harms. Further research is needed.
33	Favipiravir	Favipiravir may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution.

	Intervention	Summary of findings
34	Febuxostat	Uncertainty in potential benefits and harms. Further research is needed.
35	Finasteride	Uncertainty in potential benefits and harms. Further research is needed.
36	Fluvoxamine	Uncertainty in potential benefits and harms. Further research is needed.
37	Helium (inhaled)	Uncertainty in potential benefits and harms. Further research is needed.
38	Honey + <i>Nigella Sativa</i>	Uncertainty in potential benefits and harms. Further research is needed.
39	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 not significantly reduce the risk of infection. However, certainty of the evidence is low because of risk of bias and imprecision. HCQ/CQ may also be associated with a small increase in severe adverse events.
40	Hyperbaric oxygen	Uncertainty in potential benefits and harms. Further research is needed.
41	Hyperimmune anti-COVID-19 Intravenous Immunoglobulin (C-IVIG)	Uncertainty in potential benefits and harms. Further research is needed.
42	Icatibant/iC1e/K	Uncertainty in potential benefits and harms. Further research is needed.
43	IFX-1	Uncertainty in potential benefits and harms. Further research is needed.
44	Infliximab	Uncertainty in potential benefits and harms. Further research is needed.
45	INM005 (polyclonal fragments of equine antibodies)	Uncertainty in potential benefits and harms. Further research is needed.
46	Interferon alpha-2b and Interferon gamma	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
47	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.
48	Interferon beta-1b	Uncertainty in potential benefits and harms. Further research is needed.
49	Interferon gamma	Uncertainty in potential benefits and harms. Further research is needed.
50	Interferon kappa and TFF2	Uncertainty in potential benefits and harms. Further research is needed.
51	Iota-Carrageenan	Uncertainty in potential benefits and harms. Further research is needed.
52	Itolizumab	Uncertainty in potential benefits and harms. Further research is needed.
53	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 only six RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality and probably does not improve time to symptom resolution. Further research is needed to confirm or discard those findings.
54	Intravenous immunoglobulin	Uncertainty in potential benefits and harms. Further research is needed.
55	KB109	Uncertainty in potential benefits and harms. Further research is needed.
56	<i>Lactococcus Lactis</i> (intranasal)	Uncertainty in potential benefits and harms. Further research is needed.
57	Leflunomide	Uncertainty in potential benefits and harms. Further research is needed.
58	Lenzilumab	Lenzilumab may reduce mortality and mechanical ventilation requirements in severe patients. However certainty of the evidence is low because of imprecision. Further research is needed.
59	Levamisole	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
60	Lincomycin	Uncertainty in potential benefits and harms. Further research is needed.
61	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.
62	Low dose radiation therapy	Uncertainty in potential benefits and harms. Further research is needed.
63	Mavrilimumab	Uncertainty in potential benefits and harms. Further research is needed.
64	Melatonin	Uncertainty in potential benefits and harms. Further research is needed.
65	Mesenchymal stem-cell transplantation	Mesenchymal stem-cell transplantation may reduce mortality. However the certainty of the evidence is low. Further research is needed.
66	Methylene blue	Uncertainty in potential benefits and harms. Further research is needed.
67	Molnupiravir	Uncertainty in potential benefits and harms. Further research is needed.
68	Mouthwash	Uncertainty in potential benefits and harms. Further research is needed.
69	Mycobacterium w	Uncertainty in potential benefits and harms. Further research is needed.
70	N-acetylcysteine	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
71	Namilumab	Uncertainty in potential benefits and harms. Further research is needed.
72	Nasal hypertonic saline	Uncertainty in potential benefits and harms. Further research is needed.
73	Neem (Azadirachta Indica A. Juss)	Uncertainty in potential benefits and harms. Further research is needed.
74	Nitazoxanide	Uncertainty in potential benefits and harms. Further research is needed.
75	Nitric oxide	Uncertainty in potential benefits and harms. Further research is needed.
76	Novaferon	Uncertainty in potential benefits and harms. Further research is needed.
77	Non-steroidal anti-inflammatory drugs (NSAIDs)	Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However, certainty of the evidence is very low because of risk of bias. Further research is needed.
78	Omega-3 fatty acids	Uncertainty in potential benefits and harms. Further research is needed
79	Otilimab	Uncertainty in potential benefits and harms. Further research is needed
80	Ozone	Uncertainty in potential benefits and harms. Further research is needed.
81	Peg-interferon alfa	Uncertainty in potential benefits and harms. Further research is needed.
82	Peg-interferon lamda	Uncertainty in potential benefits and harms. Further research is needed.
83	Pentoxifylline	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
84	PNB001 (CCK-A antagonist)	Uncertainty in potential benefits and harms. Further research is needed.
85	Polymerized type I collagen (PT1C)	Uncertainty in potential benefits and harms. Further research is needed.
86	Povidone iodine (nasal spray)	Uncertainty in potential benefits and harms. Further research is needed.
87	Progesterone	Uncertainty in potential benefits and harms. Further research is needed
88	Prolectin-M	Uncertainty in potential benefits and harms. Further research is needed
89	Propolis	Uncertainty in potential benefits and harms. Further research is needed
90	Proxalutide	Proxalutide may improve time to symptom resolution. However certainty of the evidence is low because of risk of bias. Further research is needed.
91	Pyridostigmine	Uncertainty in potential benefits and harms. Further research is needed
92	Quercetin	Uncertainty in potential benefits and harms. Further research is needed
93	Ramipril	Uncertainty in potential benefits and harms. Further research is needed.
94	Recombinant super-compound Interferon	Uncertainty in potential benefits and harms. Further research is needed.
95	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 exposed individuals REGEN-COV may reduce symptomatic infections. The certainty of the evidence was low to moderate because of imprecision and indirectness.

	Intervention	Summary of findings
96	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.
97	Remdesivir	Remdesivir may slightly reduce mortality and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.
98	rhG-CSF (in patients with lymphopenia)	Uncertainty in potential benefits and harms. Further research is needed.
99	Ribavirin	Uncertainty in potential benefits and harms. Further research is needed.
100	Ribavirin + Interferon beta-1b	Uncertainty in potential benefits and harms. Further research is needed.
101	Ruxolitinib	Uncertainty in potential benefits and harms. Further research is needed.
102	Sarilumab	Sarilumab may reduce mortality and mechanical ventilation requirements without increasing severe adverse events. However, the certainty is low because of imprecision and inconsistency.
103	Short-wave diathermy	Uncertainty in potential benefits and harms. Further research is needed.
104	Sofosbuvir +/- daclatasvir or ledipasvir	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.
105	Sotrobimab	Sotrobimab probably reduces hospitalizations in patients with recent onset mild COVID-19.
106	Statins	Uncertainty in potential benefits and harms. Further research is needed.
107	Stem cell nebulization	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
108	Steroids	Steroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Steroids may not significantly increase the risk of severe adverse events.
109	Steroids (inhaled)	Inhaled steroids may improve time to symptom resolution and may decrease hospitalizations. Further research is needed.
110	Sulodexide	Uncertainty in potential benefits and harms. Further research is needed.
111	TD-0903 (inhaled JAK-inhibitor)	Uncertainty in potential benefits and harms. Further research is needed.
112	Telmisartan	Uncertainty in potential benefits and harms. Further research is needed.
113	Thalidomide	Uncertainty in potential benefits and harms. Further research is needed.
114	Tocilizumab	Tocilizumab probably reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
115	Tofacitinib	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low, further research is needed.
116	Triazavirin	Uncertainty in potential benefits and harms. Further research is needed.
117	Umifenovir	Uncertainty in potential benefits and harms. Further research is needed.
118	Vitamin C	Uncertainty in potential benefits and harms. Further research is needed.
119	Vitamin D	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
120	XAV-19 (swine glyco-humanized polyclonal antibodies)	Uncertainty in potential benefits and harms. Further research is needed.
121	Zinc	Uncertainty in potential benefits and harms. Further research is needed.
122	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 122 therapeutic options.
- **Steroids:** The body of evidence on steroids, which includes fifteen 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 steroids or placebo/no steroids.
- **Remdesivir:** In the WHO SOLIDARITY trial, remdesivir resulted in little or no effect on overall mortality, initiation of ventilation and duration of hospital stay among hospitalized patients. When combining those findings with those from four other RCTs, remdesivir may slightly reduce mortality and invasive mechanical ventilation requirements and may improve time to symptom resolution. However, overall certainty of the evidence is low and further research is needed to confirm these findings.
- **Hydroxychloroquine, lopinavir–ritonavir and interferon beta-1a:** The body of evidence on hydroxychloroquine, lopinavir-ritonavir and interferon beta-1a, including anticipated findings from the RECOVERY and SOLIDARITY trials, showed no benefit in terms of mortality reduction, invasive mechanical ventilation requirements or time to clinical improvement. Furthermore, the analysis showed probable mortality increment in those patients treated with hydroxychloroquine. Six 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.

- **Convalescent plasma:** The results of nineteen RCTs assessing convalescent plasma in COVID-19, including the RECOVERY trial with 11558 hospitalized patients, showed no mortality reduction, significant mechanical ventilation requirement reduction or time to symptom resolution improvement with moderate certainty of the evidence. Infusion related severe adverse events were exceptional. No significant differences were observed between patients treated early (<4 days since symptom onset) or with more advanced disease.
- **Tocilizumab:** The results of thirteen RCTs assessing tocilizumab show that, in patients with severe or critical disease, tocilizumab probably reduces mortality and mechanical ventilation requirements without significantly increasing severe adverse events.
- **Sarilumab:** The results of three RCTs assessing sarilumab show that, in patients with severe or critical disease, sarilumab may reduce mortality and mechanical ventilation requirements without significantly increasing severe adverse events. However certainty of the evidence was low and further research is needed to confirm these findings.
- **Anakinra:** The results of two RCTs assessing anakinra in hospitalized patients with non-severe disease, show inconsistent results on mortality and symptom resolution. Certainty of the evidence was very low and further research is needed.
- **Tofacitinib:** The results of one RCT assessing tofacitinib in hospitalized patients with moderate to severe disease, suggest possible increase in symptom resolution or improvement and possible increase in severe adverse events with tofacitinib. Certainty of the evidence was low and further research is needed.
- **Colchicine:** The results of five RCTs assessing colchicine, including the COLCORONA study that recruited 4488 patients with recent COVID-19 diagnosis and risk factors for severe diseases and the RECOVERY trial that recruited 11340 hospitalized patients show that colchicine probably does not reduce mortality, mechanical ventilation requirements or improve time to symptom resolution. These findings are mainly driven by the RECOVERY study. The COLCORONA study that included outpatients with mild early COVID-19 suggest possible reduction in hospitalizations, mechanical ventilation requirements and mortality in this subgroup. However certainty of the evidence was low because of very severe imprecision as the number of events was low.
- **Ivermectin:** Although 29 RCTs assessed ivermectin in patients with COVID-19, only thirteen 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 only six RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality or mechanical ventilation requirements, and probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

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

- **Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir:** Eleven RCT assessed sofosbuvir with or without daclatasvir, ledipasvir or velpatasvir against standard of care or other interventions. Subgroup analysis showed significant differences between low risk of bias and high risk of bias studies. The results of the two studies classified as low risk of bias suggest that sofosbuvir alone or in combination may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

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

- **REGEN-COV (casirivimab and imdevimab):** The results of three RCT show that, in patients with severe to critical disease, overall REGEN-COV does not significantly reduce mortality, mechanical ventilation or increase symptom resolution or improvement. However subgroup analysis suggests a differential effect on seronegative patients in which REGEN-COV probably reduces mortality and 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 individuals REGEN-COV may reduce symptomatic infections. The certainty of the evidence was low to moderate because of indirectness and imprecision.

- **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 one RCT show that, in patients with mild to moderate disease, regdanvimab may improve time to symptom resolution. However the certainty of the evidence was low because of imprecision. It's effects on other important outcomes are uncertain. Further research is needed to confirm or discard these findings.

- **Proxalutide:** The results of two RCT show that, in patients with mild to moderate, proxalutide may reduce time to symptom resolution. However the certainty of the evidence was low because of risk of bias. Further research is needed to confirm or discard these findings.

- **Mesenchymal stem cell transplantation:** The results of four RCT 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.
- **Bamlinivimab:** The results of four RCTs suggest that bamlinivimab probably does not significantly improve time to symptom resolution in patients with COVID-19 but probably decreases symptomatic infection in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed.
- **Inhaled steroids:** The results of two RCTs suggest that inhaled steroids may improve time to symptom resolution and may reduce hospitalizations. However the certainty of the evidence was low and its effects on other relevant outcomes are uncertain. 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. Further research is needed.
- **Famotidine:** Currently, there is very low certainty about the effects of famotidine on clinically important outcomes. Further research is needed.
- **Anticoagulants:** Thromboembolic complications in patients infected with COVID-19 are relatively frequent. As for hospitalized patients with severe medical conditions current guidelines recommend thromboprophylactic measures to be adopted for inpatients with COVID-19 infection. Regarding the best thromboprophylactic scheme, the results of six RCTs that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day) showed no differences in mortality with moderate certainty. Results of two RCT inform that aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement.
- **NSAIDs:** No association between NSAID exposure and increased mortality was observed. However, certainty of the evidence is very low and further research is needed to confirm these findings.
- **ACEIs or ARBs:** The results of four 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

- **Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir:** New evidence included without significant changes.
- **Ivermectin:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Anticoagulants:** New evidence included without significant changes.
- **Bamlanivimab:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Short-wave diathermy:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Aspirin:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Sotrovimab:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Mesenchymal stem cell transplantation:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Stem cell nebulization:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Hydroxychloroquine:** New evidence included without significant changes.
- **Lopinavir-Ritonavir:** New evidence included without significant changes.
- **Namilumab:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Infliximab:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **ACEI/ARB:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Hyperimmune anti-COVID-19 Intravenous Immunoglobulin:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

- **REGEN-COV:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **N-Acetylcysteine:** New evidence included without significant changes.
- **Molnupiravir:** New evidence included without significant changes.
- **Convalescent plasma:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.
- **Tofacitinib** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

Concluding remarks

- The Pan American Health Organization (PAHO) is continually monitoring ongoing research on any possible therapeutic options. As evidence emerges, then WHO/PAHO will immediately assess and update its position, particularly as it applies to any special subgroup populations such as children, expectant mothers, and those with immune conditions.
- PAHO is also mindful of the emerging differential impact of COVID-19 on ethnic and minority groups and is continuously seeking data that could help in mitigating excess risk of severe illness or death in minority sub-groups. These groups are plagued by social and structural inequities that bring to bear a disproportionate burden of COVID illness.
- The safety of the patient suffering from COVID-19 is a key priority to improve the quality of care in the provision of health services.
- There remains an urgent need for additional high-quality randomized controlled trials that include patients with COVID-19 before most therapeutic options can be administered with any confidence. Adequately designed and reported clinical trials are crucial for the practice of evidence-based medicine. Most of the research to date on COVID-19 has very poor methodology that is hidden and very difficult to validate. Greater transparency and better designed studies are urgently needed.

Hallazgos clave

Opciones terapéuticas: Según el portal de búsqueda de la Plataforma Internacional de Registro de Ensayos Clínicos (ICTRP) de la OMS, se están investigando cientos de posibles tratamientos o sus combinaciones en más de 10.000 ensayos clínicos y estudios observacionales. En esta revisión, examinamos 122 opciones terapéuticas potenciales.

- **Esteroides:** El conjunto de evidencia sobre los esteroides incluye quince ensayos clínicos controlados aleatorizados (ECCA) y muestra que la administración de dosis bajas y moderadas (la dosis utilizada en el estudio RECOVERY fue dexametasona 6 mg diarios por vía oral o intravenosa durante 10 días) probablemente reducen la mortalidad en pacientes con infección grave por COVID-19. Los resultados se mantuvieron uniformes tras agregar al análisis estudios en los que pacientes con SDRA de otras etiologías recibieron corticosteroides o manejo estándar de forma aleatoria.
- **Remdesivir:** En el estudio SOLIDARITY de la OMS, el remdesivir no tuvo un efecto clínicamente relevante sobre la mortalidad global, la necesidad de ventilación mecánica invasiva o el tiempo de estadía hospitalaria. Tras combinar dichos resultados con otros cuatro ECCA, se observó que el remdesivir podría reducir la mortalidad, la necesidad de ventilación mecánica invasiva y mejorar el tiempo hasta la resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estos hallazgos.
- **Hidroxicloroquina, interferón beta 1-a y lopinavir-ritonavir:** El conjunto de evidencia sobre hidroxicloroquina, interferón beta 1-a y lopinavir-ritonavir, incluidos los resultados preliminares de los estudios RECOVERY y SOLIDARITY, no muestra beneficios en la reducción de la mortalidad, necesidad de ventilación mecánica invasiva o el plazo necesario para la mejoría clínica. Incluso la evidencia sobre hidroxicloroquina sugiere que su utilización probablemente genere un incremento en la mortalidad. Seis estudios que evaluaron la hidroxicloroquina en personas expuestas a la COVID-19 mostraron una tendencia hacia una reducción en el riesgo de infección, pero esta no resulta estadísticamente significativa. Se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estos hallazgos.
- **Plasma de convalecientes:** Los resultados de trece ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19, incluido el estudio RECOVERY que reclutó 11.558 pacientes, mostraron ausencia de reducción de la mortalidad, ausencia de reducción significativa en los requerimientos de ventilación mecánica invasiva y ausencia de mejoría en el tiempo a la resolución de síntomas con moderada certeza. Los eventos adversos graves relacionados con la

infusión fueron excepcionales. Además, 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 trece ECCA muestran que tocilizumab probablemente reduce la mortalidad y los requerimientos de ventilación invasiva sin un incremento importante en efectos adversos graves en pacientes con enfermedad grave o crítica.

- **Sarilumab:** Los resultados de tres ECCA muestran que sarilumab podría reducir la mortalidad y los requerimientos de ventilación invasiva sin un incremento importante en efectos adversos graves en pacientes con enfermedad grave o crítica. Sin embargo la certeza en la evidencia resultó baja y se necesita más información para confirmar dichos hallazgos.

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

- **Tofacitinib:** Los resultados de un ECCA que evaluó tofacitinib en pacientes hospitalizados con enfermedad moderada a grave muestran sugieren posible mejora en resolución de síntomas, pero posible aumento en eventos adversos severos. La certeza en la evidencia resultó baja y se necesita más información.

- **Colchicina:** Los resultados de cinco ECCA, incluyendo al estudio COLCORONA que incluyó 4488 pacientes con diagnóstico reciente de COVID-19 y factores de riesgo para enfermedad grave y el estudio RECOVERY que reclutó 11.340 pacientes hospitalizados muestran que colchicina probablemente no reduce la mortalidad, los requerimientos 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 sugiere una posible reducción en las hospitalizaciones, los requerimientos de ventilación mecánica y la mortalidad en este subgrupo. Sin embargo la certeza en la evidencia resultó baja por imprecisión muy grave, ya que el número de eventos fue bajo.

- **Ivermectina:** A pesar de que 29 ECCA evaluaron ivermectina en pacientes con COVID-19, solo trece de estos estudios reportaron sobre desenlaces clínicamente importantes. Los resultados combinados de estos estudios sugieren una reducción en la mortalidad con ivermectina, sin embargo la certeza en la evidencia resultó muy baja por limitaciones metodológicas y un número pequeño de eventos. Considerando la información aportada por los únicos seis estudios con bajo riesgo de sesgo, la ivermectina podría no reducir significativamente la mortalidad ni los requerimientos de ventilación mecánica, y probablemente no se asocie a una mejoría en la velocidad de resolución de los síntomas. Se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

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

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

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

- **REGEN-COV (casirivimab e imdevimab):** Los resultados de tres ECCA muestran que, en pacientes con enfermedad severa o crítica, REGEN-COV probablemente no reduzca la mortalidad, los requerimientos de ventilación invasiva o mejore la resolución de síntomas. Sin embargo, un análisis de subgrupo mostró un efecto diferencial en pacientes con anticuerpos negativos. En este subgrupo REGEN-COV probablemente reduzca la mortalidad, los requerimientos e incremente la resolución de síntomas. En paciente con enfermedad leve de reciente comienzo, REGEN-COV probablemente reduce las hospitalizaciones y mejora el tiempo a resolución de los síntomas sin aumentar el riesgo de eventos adversos graves, y en personas expuestas a SARS-COV2 REGEN-COV podría reducir las infecciones sintomáticas. La certeza en la evidencia resultó moderada por información indirecta e imprecisión.

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

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

- **Proxalutide:** Los resultados de dos ECCA muestran que, en pacientes con enfermedad leve a moderada, proxalutide podría mejorar el tiempo a resolución de los síntomas. Sin embargo la certeza en la evidencia resultó baja por riesgo de sesgo. Se necesita más información para confirmar o descartar estas conclusiones.
- **Trasplante de células madre mesenquimatosas:** Los resultados de cuatro ECCA sugieren que, en pacientes con enfermedad grave a crítica, el trasplante de células madre mesenquimatosas podría reducir la mortalidad. Sin embargo la certeza en la evidencia resultó baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.
- **Bamlinivimab:** Los resultados de cuatro ECCA sugieren que bamlinivimab probablemente no mejore significativamente el tiempo a resolución de los síntomas pero probablemente disminuya las infecciones sintomáticas en personas expuestas. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información para confirmar o descartar estas conclusiones.
- **Esteroides inhalados:** Los resultados de dos ECCA sugieren que los esteroides inhalados podrían mejorar el tiempo a resolución de los síntomas y podrían reducir las hospitalizaciones. Sin embargo la certeza en la evidencia resultó baja y sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información para confirmar o descartar estas conclusiones.
- **Lenzilumab:** Los resultados de un ECCA sugieren que lenzilumab podría reducir la mortalidad y los requerimientos de ventilación invasiva en pacientes graves. Sin embargo la certeza en la evidencia resultó baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.
- **INM005 (fragmentos policlonales de anticuerpos equinos):** Hasta el momento, la evidencia sobre los efectos de INM005 en desenlaces críticos es de muy baja certeza. Se necesita más información procedente de estudios con un diseño adecuado para evaluar su eficacia.
- **Famotidina:** Hasta el momento, la evidencia sobre los efectos de la famotidina es de muy baja certeza. Se necesita más información procedente de estudios con un diseño adecuado para evaluar su eficacia y seguridad.
- **Complicaciones tromboembólicas:** Las complicaciones tromboembólicas en pacientes con COVID-19 son frecuentes. Al igual que en pacientes hospitalizados por afecciones médicas graves, las directrices de práctica clínica vigentes indican que los pacientes hospitalizados por COVID-19 sean tratados con medidas tromboprolifácticas. En relación con el esquema tromboprolifáctico, los resultados de seis estudios aleatorizados y controlados que compararon dosis intermedias (p. ej., enoxaparina 1 mg/kg/día) o dosis completas (p. ej., enoxaparina 1 mg/kg/día cada 12 h) frente a dosis profilácticas (p. ej., enoxaparina 40 mg/día) mostraron ausencia de diferencias en mortalidad con moderada certeza. Los resultados de dos estudios aleatorizados informaron que la indicación de aspirina probablemente tampoco se asocia a

reducción en la mortalidad, la ventilación mecánica o a mejoría en la velocidad de resolución de los síntomas.

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

- **IECA y ARB:** Los resultados de cuatro ECCA con bajo riesgo de sesgo sugieren que el inicio o continuación de IECA/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 procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

Cambios respecto a la versión anterior

- **Sofosbuvir con o sin daclatasvir, ledipasvir o velpatasvir:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

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

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

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

- **Diatermia por onda corta:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

- **Trasplante de células madre mesenquimales:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

- **Nebulizaciones con células madre:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

- **Hidroxicloroquina:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Lopinavir-Ritonavir:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Namilumab:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Infliximab:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **IECA/ARB:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Suero hiperinmune anti-COVID-19:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **REGEN-COV:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **N-Acetilcisteína:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Molnupiravir:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.
- **Plasma de convalecientes:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.
- **Tofacitinib:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

Conclusiones

- La Organización Panamericana de la Salud (OPS) hace seguimiento en todo momento de la evidencia en relación con cualquier posible intervención terapéutica. A medida que se disponga de evidencia nueva, la OPS la incorporará con rapidez y actualizará sus recomendaciones, especialmente si dicha evidencia se refiere a grupos en situación de vulnerabilidad como los niños, las mujeres embarazadas, adultos 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 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 June 22, 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 RCT and non-RCT 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 December 18, 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 December 18, 2020. For venous thromboembolic events and major bleeding baseline risk we used the mean risk in the control groups from included RCTs until March 25, 2021. For hospitalization baseline risk we used the mean risk in the control groups from included RCTs until April 14, 2021. 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.

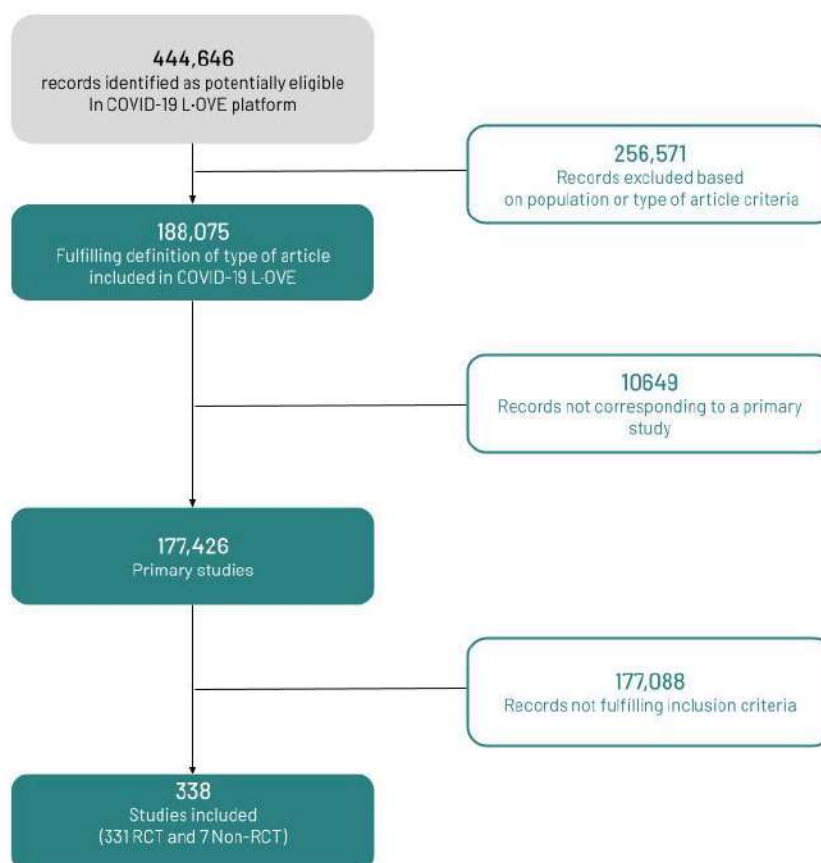
We used MAGIC authoring and publication platform (<https://app.magicapp.org/>) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in figure 1. A total of 339 studies were selected for inclusion, 331 RCT and 7 non-RCT. 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 sub-optimal. 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
Cavaicanti 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
ELACCI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CONCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
GLUCOCVID	High	Some Concerns	Low	Low	Low	High	High
ClaroCOVID19	Low	Low	Low	Some Concerns	Low	Low	Low
Devoort-Modafed et al	High	Some Concerns	Low	Low	Low	High	High
Chen et al	High	Some Concerns	Low	Low	Low	High	High
Devoort 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 FC 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
Vibar AFU et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Guzvenmez 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
Ran Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mohboob 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
Metocovid	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
Abu-Elwaleh S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sekhavali 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
CoriPias-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
Mohammed ATMM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLACID	Low	Some Concerns	Low	Some Concerns	Low	High	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
Balcalle 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
Dai 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
Dai 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	High	High
TEACH	High	Low	Low	Some Concerns	Low	High	High
Nigami et al (Iran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PEP_COVID	Low	Low	Low	Low	Low	Low	Low
de Alencar 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
Anasari K (Tabriz University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
WHO SOLIDARITY - HQQ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
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
Yehindra 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
Chaderkhani 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
Heahm HA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ILBS-COVID-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PROBIOCOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Pidmanachan U et al (Medical Education and Drugs Department)	High	Low	Low	Low	Low	High	High
Ajani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khame F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BLAZE-1	High	Low	Low	Low	Low	High	High
PETAL	Low	Low	Low	Low	Low	Low	Low
Lanzoni G et al	High	Low	Low	Low	Low	High	High
Ruzhentsova T et al (R-Pharm)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Lanza 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 (Pharso Corporata)	High	Some Concerns	Low	Some Concerns	Low	High	High
Ghandshian S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HAHPS	Low	High	Low	Some Concerns	Low	High	High
Eigazzar et al (mild)	High	Some Concerns	Low	Some Concerns	Low	High	High
Eigazzar et al (severe)	High	Some Concerns	Low	Some Concerns	Low	High	High
Eigazzar et al (prophylaxis)	High	Some Concerns	Low	Some Concerns	Low	High	High
Tabarsi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAVUS2020 (Promomed, LLC)	High	Some Concerns	Low	Some Concerns	Low	High	High
Murali H et al (University of Sao Paulo)	Low	Low	Low	Low	Low	Low	Low
Ulwadia ZF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-TOCI 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EMPACTA	Low	Low	Low	Low	Low	Low	Low
HYCOVID	Low	Low	Low	Low	Low	Low	Low
Krolewiski et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ILJAD	Low	Low	Low	Low	Low	Low	Low
AS-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
Fundacion INFANT-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
Aid-Elsalam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Prolectin-M	High	Some Concerns	Low	Some Concerns	Low	High	High
Maldonado V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
GARGLES	High	Some Concerns	Low	Some Concerns	Low	High	High
ERSul	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
Chaccour et al	Low	Low	Low	Low	Low	Low	Low
ACTT-2	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
RECOVERY	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
EIDD-2801-1001	Low	Low	Low	Low	Low	Low	Low
Weinreich	Low	Low	Low	Low	Low	Low	Low
Roozbeh F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTIV-3/TICO	Low	Low	Some Concerns	Low	Low	Low	High
Chachar et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Belykova 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
Alidmalkoud AA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kirk et al	Low	Low	Low	Low	Low	Low	Low
Kuman P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FRFAV00A-CoV/2020	High	Low	Low	Low	Low	High	High
Charla 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	Low
AS-DRUG-SARS-004 (Cadogan FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
JamaliMoghdamSiahkali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedghizyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Roostaci 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
Shohbazznejad et al	Low	Low	Low	Low	Low	Low	Low
Spoorthi et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sarrafah 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	High	Low	Low
Dabbous HM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATTRACT	Low	Some Concerns	Low	Low	Low	Low	Low
Ranjbar K et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
EAT-DUTA AndroCoV	Low	Low	High	Low	Low	High	High
Farooq G et al	Some Concerns	Some Concerns	High	Some Concerns	Low	High	High
Khalil H et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Bakhtouchev 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
Sati S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
NITFQM0320R	High	Some Concerns	Low	Some Concerns	Low	High	High
SJU-MED-CHT019-420360	High	Some Concerns	Low	Some Concerns	Low	High	High
STQIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Borges M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY-TC2	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDabZ - Zinc	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDabZ - 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
EFC16944	Low	Some Concerns	Low	Low	Low	Low	Low
ARTI-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Purabi	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-HCO	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	High	Some Concerns	Low	Some Concerns	Low	High	High
Nouri-Jaskeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopez-Medina et al	Low	Low	Low	Low	Low	Low	Low
Lakshroody M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Siva	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High
Bernaldo Galan et al	Low	Low	Low	Low	Low	Low	Low
Poti-Junior et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mikheylov	Low	Some Concerns	Low	Some Concerns	Low	Low	High
2GAMMACOVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
AAA59524	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Tolouian et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EZeh R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PEGI 20.002	High	Some Concerns	Low	Some Concerns	Low	High	High
MASH-COVID	Low	Some Concerns	Low	Low	Low	Low	Low
INSPIRATION	Low	Some Concerns	Low	Low	Low	Low	Low
Zarychanski	Low	Some Concerns	Low	Low	Low	Low	Low
Santoe 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
SURC-2020-23683	Low	Some Concerns	Low	Low	Low	Low	Low
Alavi-Moghaddam M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CT-PS9 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
Gayntdinova 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
Dosei 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
Rbakov AR et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kashona N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CERC-002-COVID-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
HDOTCOVID19	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
Soet	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
Yarguard	Low	Some Concerns	Low	Low	Low	Low	Low
Sarmaghani HR et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CansoCO-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
Sami 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
PneToVid	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
Handy Salman O et al	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-RT-01	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-ARB	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pereira U et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zarynsanski-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 - Colecladine	High	Some Concerns	Low	Some Concerns	Low	High	High
Silvia Mendez-Flores S et al	Low	Some Concerns	Low	Low	Low	Low	Low
SAVE-MORE	Low	Some Concerns	Low	Low	Low	Low	Low
Winchester S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Egohary 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
Mehmud et al	High	Low	Low	Low	Low	High	High
Abd-Elaslam 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	High	High
BLAZE-2	Low	Low	Some Concerns	Low	Low	Low	Low
ProPAC-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Tian F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY - ASA	Low	Some Concerns	Low	Low	Low	Low	Low
HONEST	Low	Low	Low	Low	Low	Low	Low
COMET-ICE	Low	Low	Low	Low	Low	Low	Low
ISIMMSCOVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
SENTAD-COVID	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
SEV-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CATALYST	Low	Low	Low	Low	Low	Low	Low
All 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

Main findings

Corticosteroids

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

We identified fifteen RCTs including 8264 participants in which systemic steroids (dexamethasone, methylprednisolone or hydrocortisone) were compared against standard of care or other treatments. Ten of these trials provided information on relevant outcomes. The RECOVERY trial was the biggest with 2,104 patients assigned to dexamethasone and 4,321 to standard of care. All ten 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:

- Steroids probably reduce mortality, RR 0.90 (95%CI 0.80 to 1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕○ (Figure 2)
- Steroids probably reduce invasive mechanical ventilation requirement, RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕○
- Steroids may improve time-to-symptom resolution, RR 1.27 (95%CI 0.98 to 1.65); RD 16.3% (95%CI -1.2% to 39.4%); Low certainty ⊕⊕○○
- Steroids 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 steroids were used to treat non COVID-19 patients with ARDS. No significant differences between subgroups of studies using different steroids were observed. (Figures 3 and 4)

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

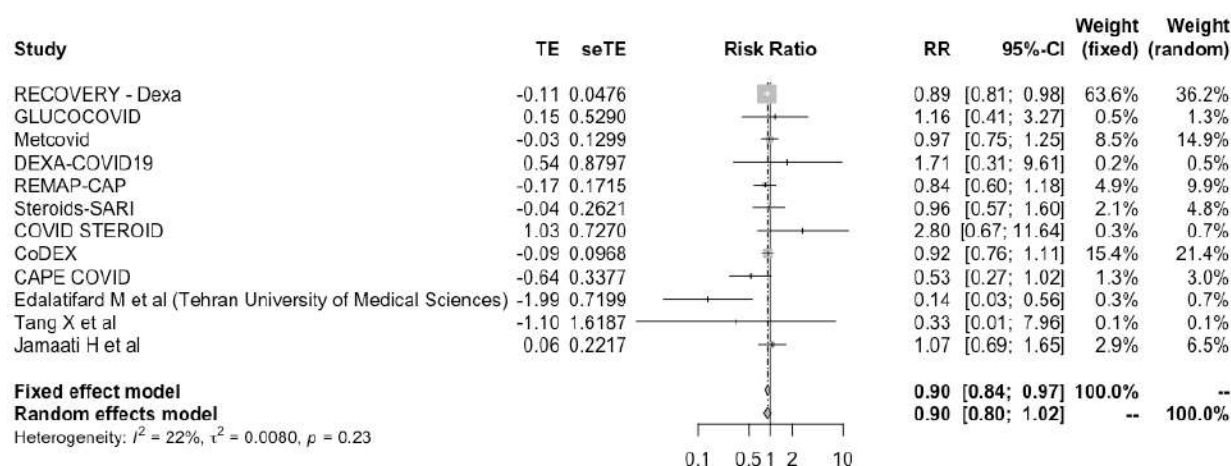


Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

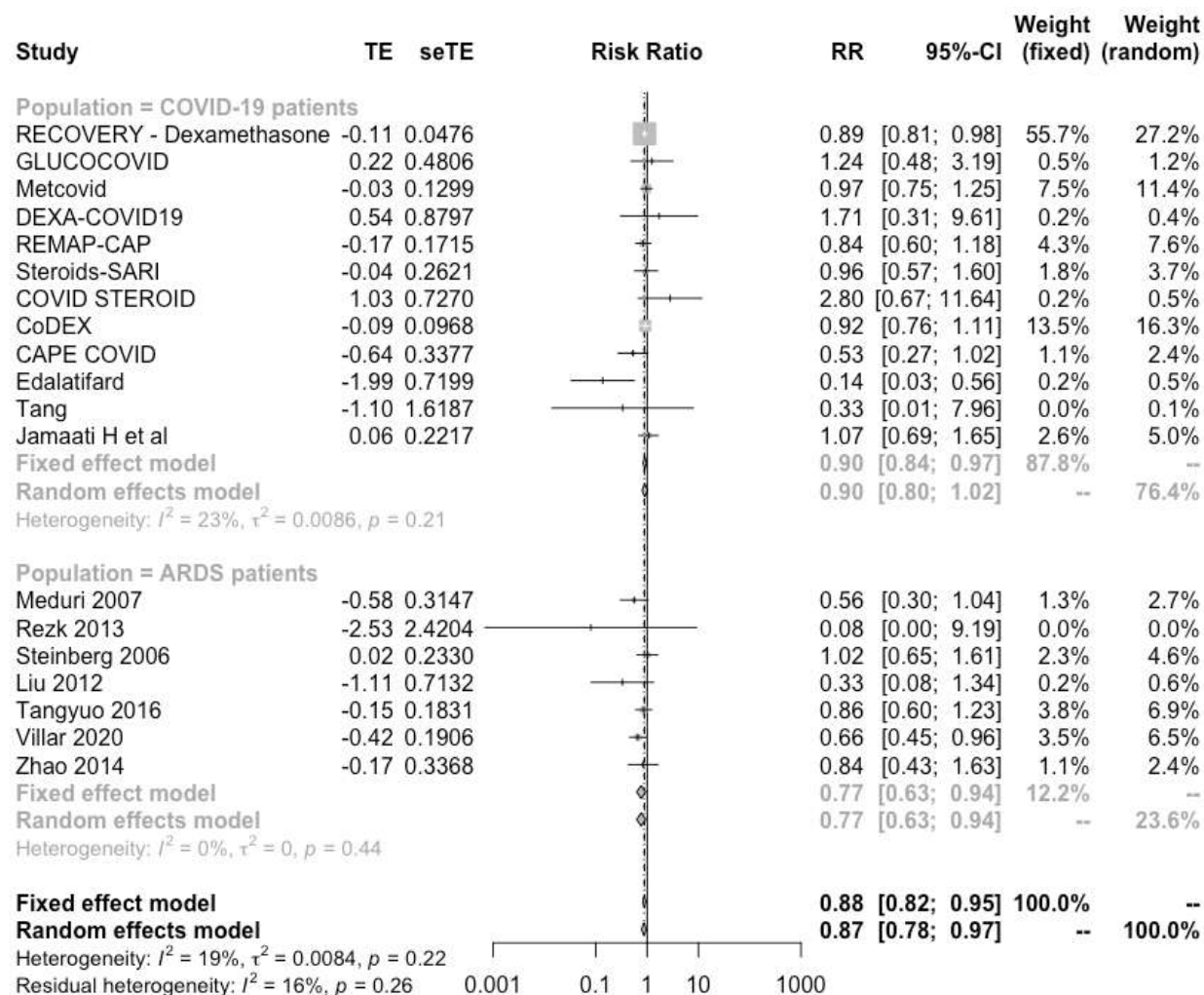
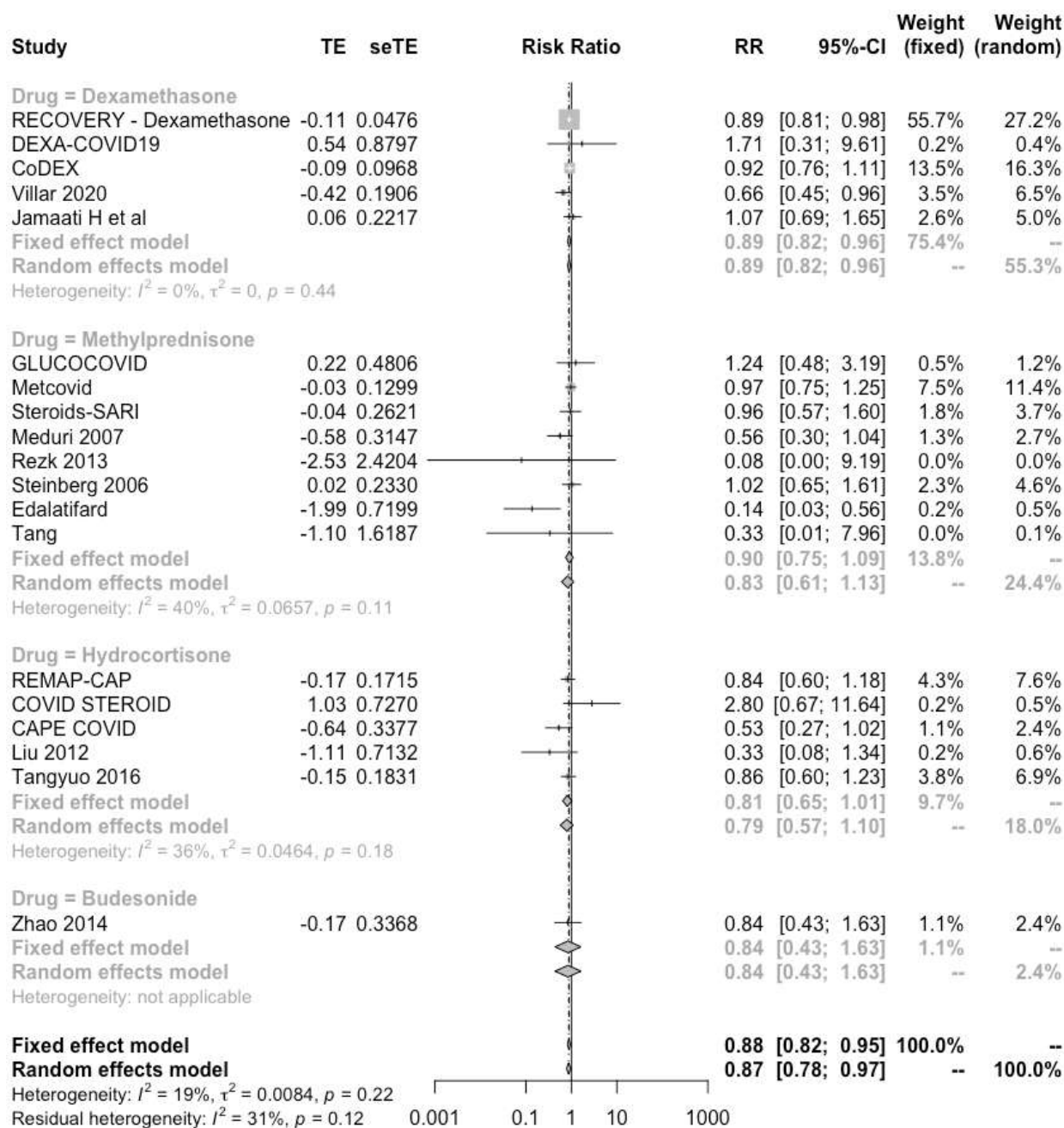


Figure 4. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19



Remdesivir

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

We identified five RCTs including 7400 patients in which remdesivir was compared against standard of care or other treatments. In addition, we identified one study that compared different remdesivir dosage schemes. The WHO SOLIDARITY trial was the biggest with 2,734 patients assigned to remdesivir and 2,708 to standard of care. Five studies included patients with severe disease as shown by the fact that mortality in the control groups ranged from 8.3% to 12.6%, and one study included non-severe patients with 2% mortality in the control arm. Our results showed:

- Remdesivir may slightly reduce mortality, RR 0.95 (95%CI 0.83 to 1.08); RD -0.8% (95%CI -2.7% to 1.3%); Low certainty ⊕⊕○○ (Figure 5)
- Remdesivir may reduce invasive mechanical ventilation requirement, RR 0.71 (95%CI 0.43 to 1.18); RD -5% (95%CI -9.9% to 3.1%); Low certainty ⊕⊕○○ (Figure 6)
- Remdesivir may improve time to symptom resolution, RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⊕⊕○○ (Figure 7)
- 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 5. All-cause mortality with remdesivir use vs. standard of care in randomized control trials including COVID-19 patients

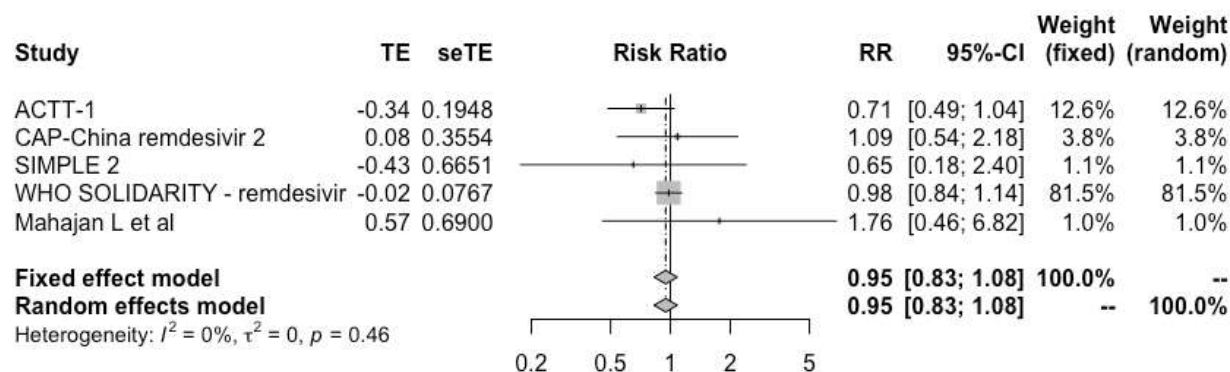


Figure 6. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

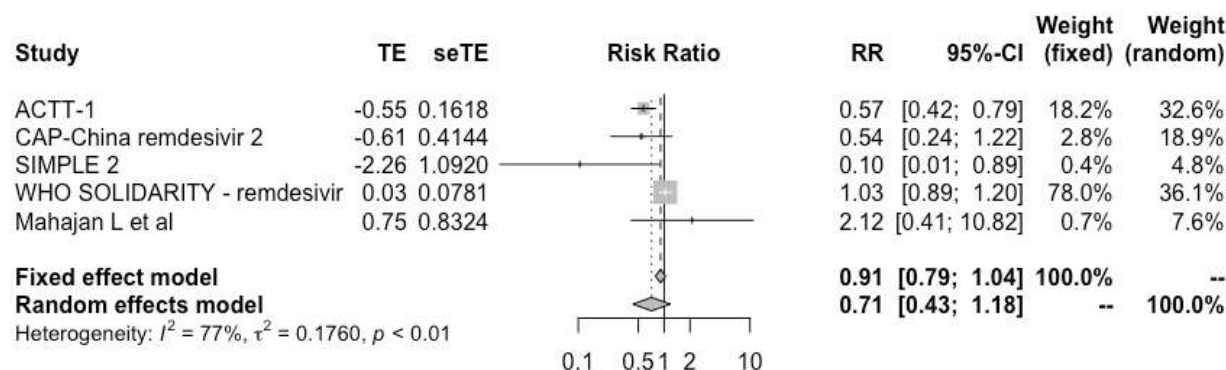
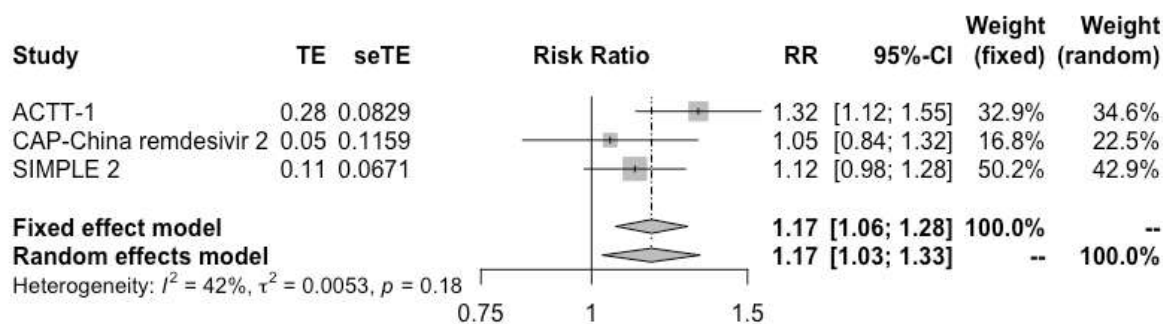


Figure 7. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

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

We identified 46 RCTs including 20,268 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 six 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 8)
- 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 1.05 (95%CI 0.95 to 1.16); RD 3% (95%CI -3% to 9.7%); Moderate certainty ⊕⊕⊕○
- Hydroxychloroquine or chloroquine may not significantly reduce COVID-19 symptomatic infection in exposed individuals, RR 0.97 (95%CI 0.65 to 1.45); RD -0.5% (95%CI -6.1% to 7.8%); Low certainty ⊕⊕○○ (Figure 9) (based on low risk of bias studies)
- Hydroxychloroquine or chloroquine may not significantly increase the risk of severe adverse events, RR 0.89 (95%CI 0.6 to 1.32); RD -1.1% (95%CI -4.0% to 3.2%); Low certainty ⊕⊕○○
- It is uncertain if hydroxychloroquine or chloroquine affects hospitalizations in patients with mild COVID-19, RR 0.82 (95%CI 0.49 to 1.36); RD -1.3% (95%CI -3.8% to 2.7%); Very low certainty ⊕○○○

Figure 8. All-cause mortality in RCTs comparing hydroxychloroquine or chloroquine with standard of care in patients with COVID-19

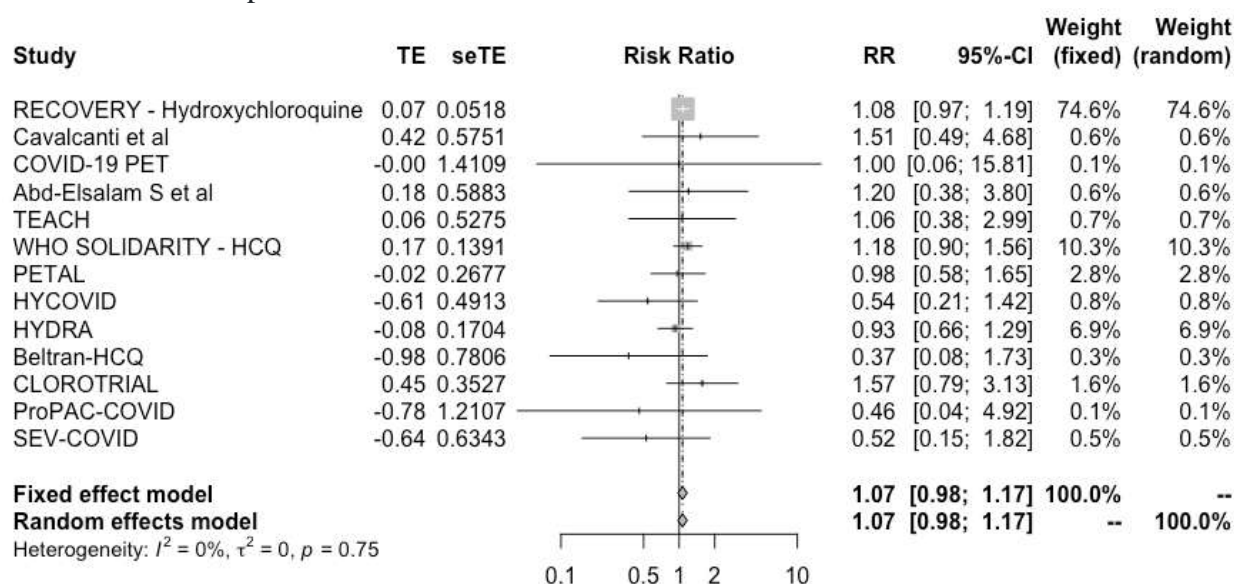
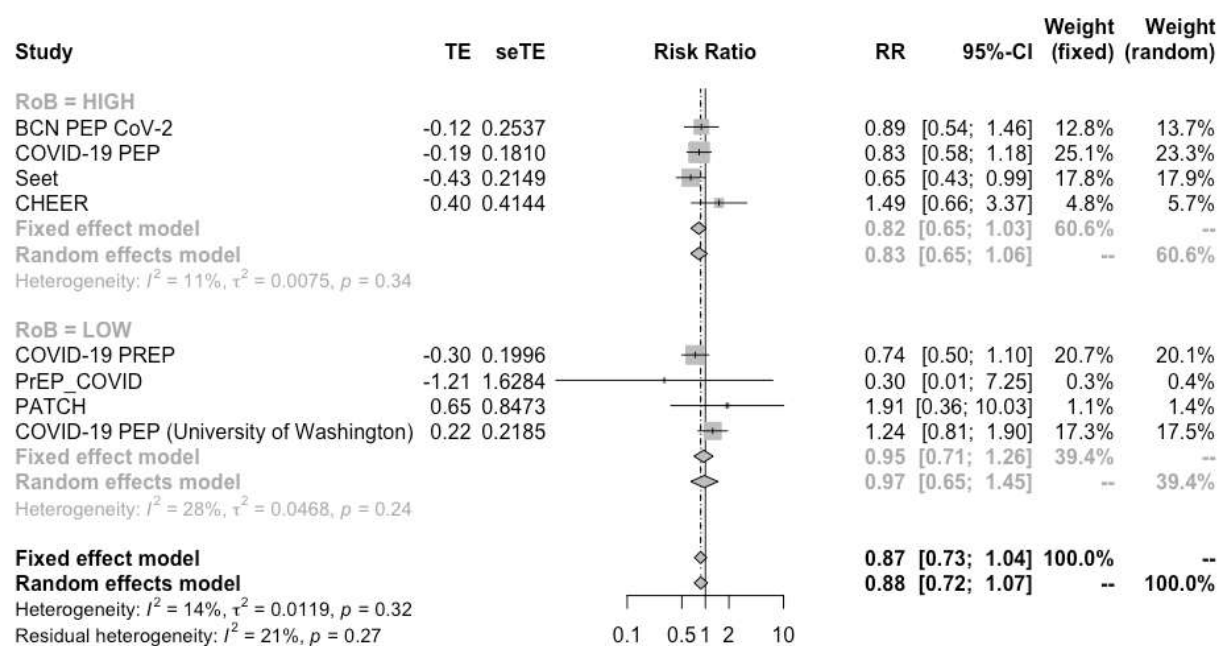


Figure 9. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



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

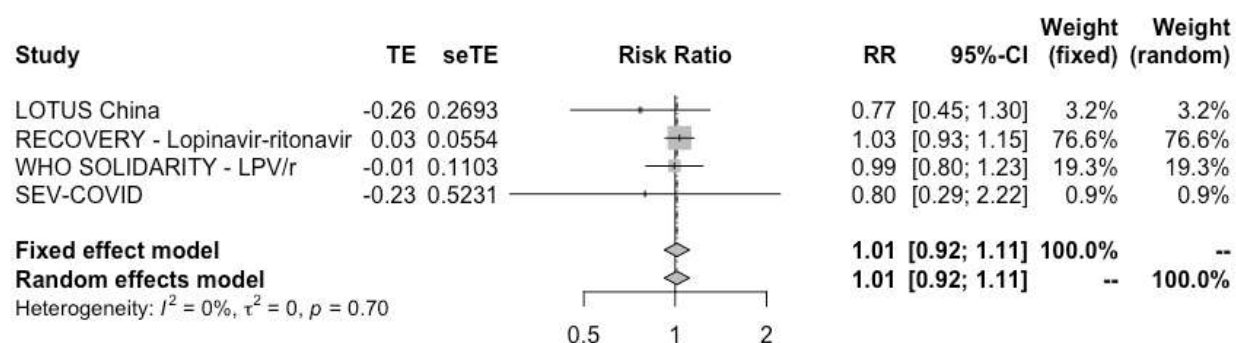
[See Summary of findings Table 4, Appendix 1](#)

We identified fourteen RCTs including 9,464 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 10)
- 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 hospitalizations, RR 1.24 (95% CI 0.6 to 2.56); RD 1.8% (95% CI -3% to -11.6%); Very low certainty ⊕○○○

Figure 10. All-cause mortality in RCTs comparing lopinavir–ritonavir with standard of care for treatment of patients with COVID-19



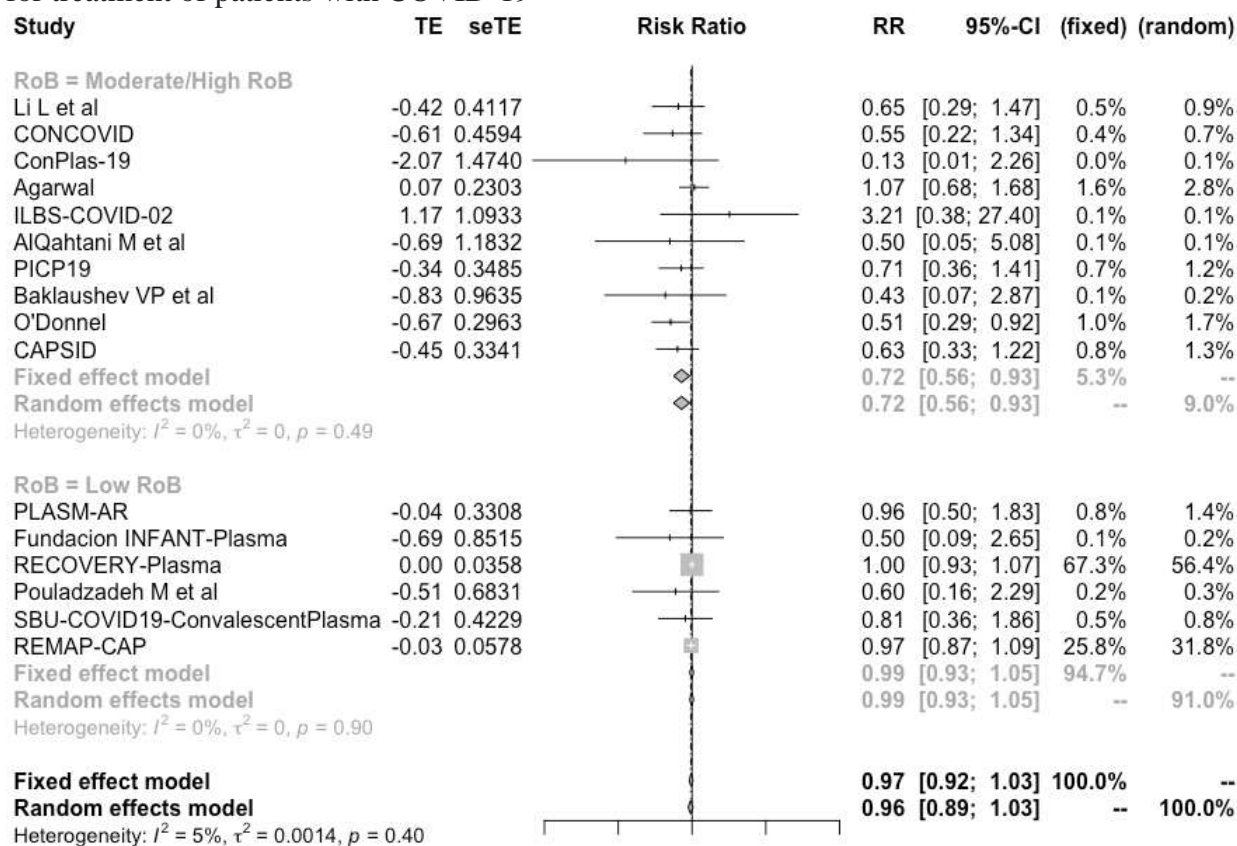
Convalescent plasma

[See summary of findings table 5 in appendix 1](#)

We identified nineteen RCT including 15719 patients in which convalescent plasma was compared against standard of care or other treatments. RECOVERY was the biggest study including 11588 patients. Most studies (16/18) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 10% to 53%. The remaining studies included patients with recent onset symptoms and reported a control-arm mortality rate of 5% and 6.6%. Convalescent plasma was administered in one or two infusions to symptomatic patients in all cases. Our results showed:

- Convalescent plasma probably does not reduce mortality, RR 0.99 (95% CI 0.93 to 1.05); RD -0.1% (95% CI -1.1% to 0.8%); Moderate certainty ⊕⊕⊕○ (Figure 11) (based on low risk of bias studies)
- Convalescent plasma does not significantly reduce invasive mechanical ventilation requirements, RR 0.98 (95% CI 0.86 to 1.12); RD -0.3% (95% CI -2.4% to 2.1%); Moderate certainty ⊕⊕⊕○.
- Convalescent plasma probably does not improve symptom resolution or improvement, RR 1.02 (95% CI 0.93 to 1.13); RD 1.2% (95% CI -4.2% to 7.9%); Moderate certainty ⊕⊕⊕○
- Convalescent plasma may increase severe adverse events, RR 1.1 (95% CI 0.76 to 1.58); RD 1% (95% CI -2.5% to 5.9%); Low certainty ⊕⊕○○
- Specific adverse events related to convalescent plasma infusion are possibly rare: transfusion-related circulatory overload 0.18%; transfusion-related lung injury 0.10%; Severe allergic transfusion reaction 0.10%. However, we are uncertain if convalescent plasma increases severe adverse events as certainty of the evidence is very low.

Figure 11. All-cause mortality 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 $\oplus\oplus\oplus\oplus$ 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 thirteen RCTs including 7395 patients in which tocilizumab was compared against standard of care or other interventions. Eight studies reported on mortality outcome, including the RECOVERY study that recruited 4116 patients. All studies included severe patients but some

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

- Tocilizumab probably reduces mortality, RR 0.88 (95%CI 0.77 to 1); RD -1.9% (95%CI -3.7% to 0%); Moderate certainty ⊕⊕⊕○ (Figure 12)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.82 (95%CI 0.76 to 0.89); RD -3.1% (95%CI -4.2% to -1.9%); High certainty ⊕⊕⊕⊕ (Figure 13)
- Tocilizumab may improve time to symptom resolution, RR 1.10 (95%CI 0.99 to 1.22); RD 6% (95%CI -0.6% to 13.3%); Low certainty ⊕⊕○○
- Tocilizumab probably does not significantly increase severe adverse events at 28-30 days, RR 0.90 (95%CI 0.76 to 1.05); RD -1% (95%CI -2.5% to 0.5%); Moderate certainty ⊕⊕⊕○

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

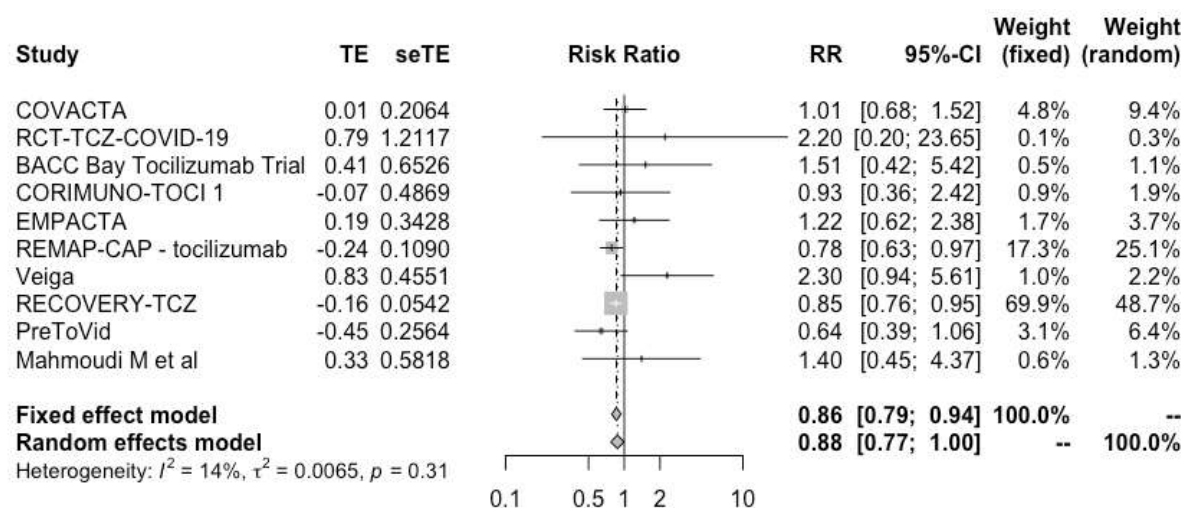
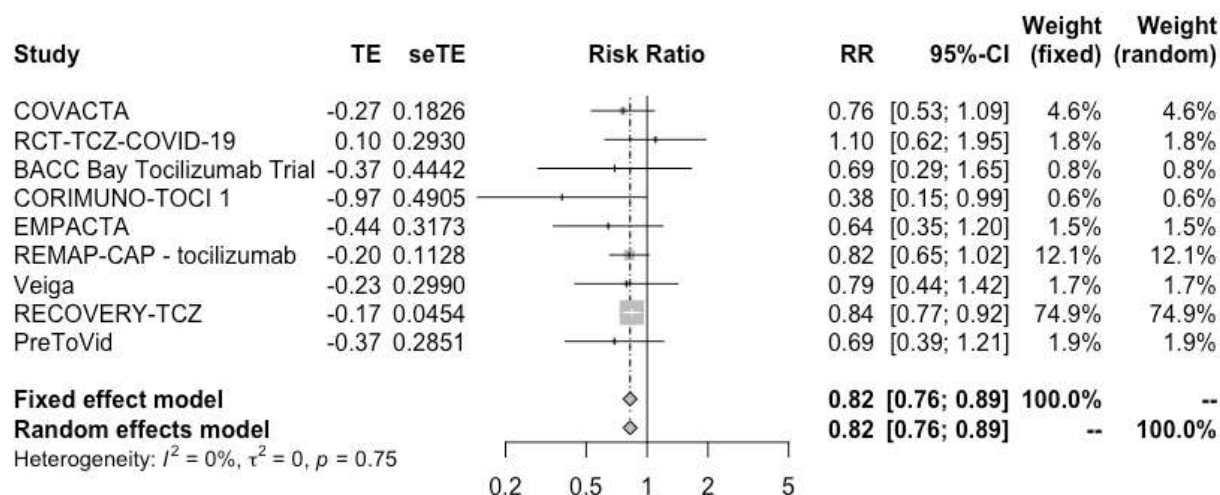


Figure 13. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



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

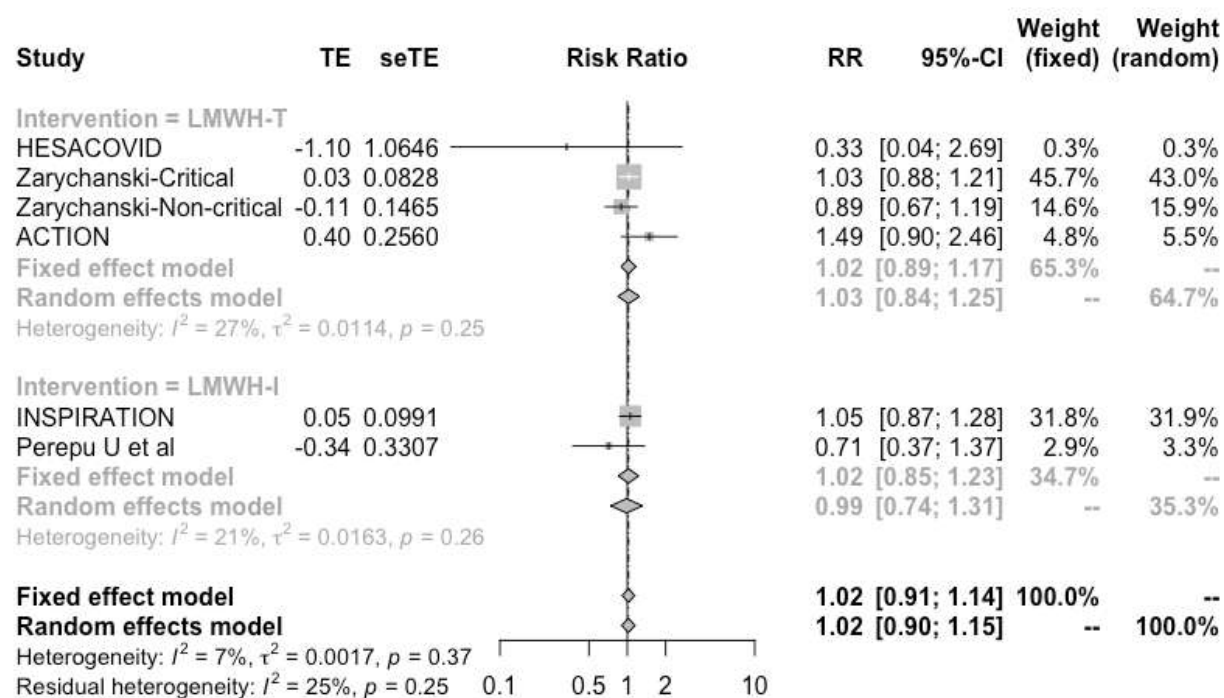
[See Summary of findings Table 7, Appendix 1](#)

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 six RCTs including 4663 patients that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day). All studies included hospitalized patients with COVID-19. Our results showed:

- Anticoagulants in intermediate dose or full dose probably does not reduce mortality in comparison with prophylactic dose, RR 1.02 (95%CI 0.90 to 1.15); RD 0% (95%CI -1.6% to 2.4%); Moderate certainty ⊕⊕⊕○ (Figure 14)
- Anticoagulants in intermediate dose may not reduce venous thromboembolic events in comparison with prophylactic dose, RR 1.02 (95%CI 0.53 to 1.96); RD 0.1% (95%CI -3.3% to 6.7%); Low certainty ⊕⊕○○
- Anticoagulants in full dose probably reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.61 (95%CI 0.45 to 0.82); RD -2.7% (95%CI -3.8% to -1.3%); Moderate certainty ⊕⊕⊕○

- Anticoagulants in intermediate dose or full dose probably increase major bleeding in comparison with prophylactic dose, RR 1.74 (95% CI 1.12 to 2.7); RD 1.4% (95% CI 0.2% to 3.2%); Moderate certainty ⊕⊕⊕○

Figure 14. 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 non-critical 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.

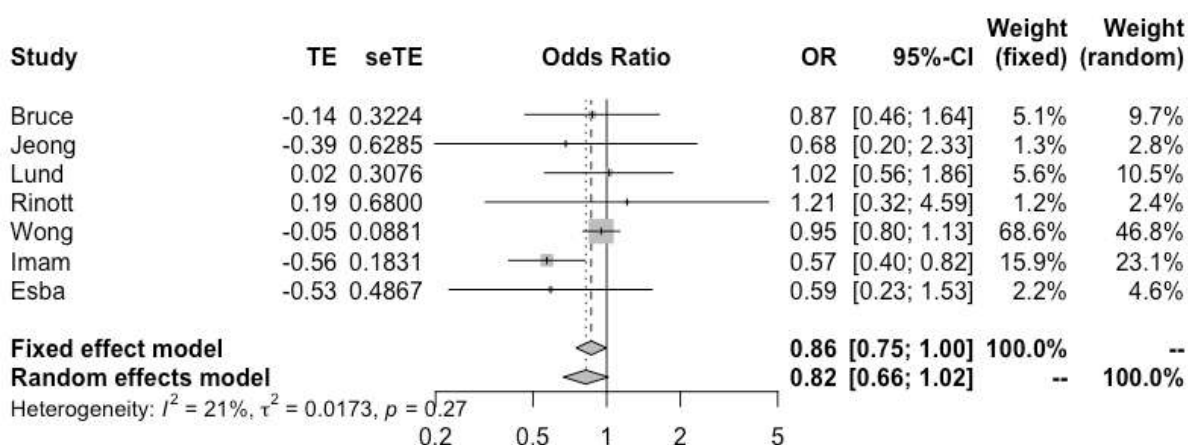
NSAIDs

[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 included 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 15)

Figure 15. All-cause mortality in non-RCTs comparing exposure to NSAIDs with no exposure in individuals exposed to or infected with COVID-19



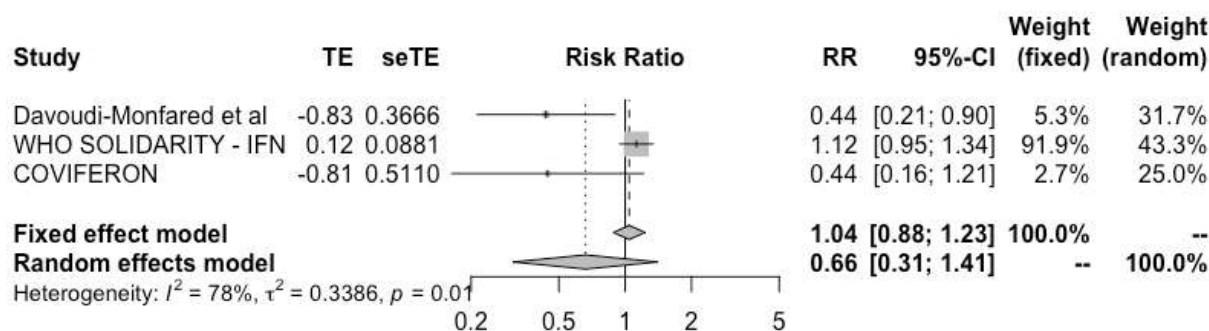
Interferon Beta-1a

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

We identified five RCT including 4487 patients in which interferon beta-1a was compared against standard of care or other treatments and informed on mortality outcome. The WHO SOLIDARITY trial was the biggest, with 2,050 patients assigned to intervention and 2,050 to control. The studies included severe patients, as shown by the fact that mortality in the control arms ranged from 10.5% to 45%. Our results showed:

- Interferon beta-1a (subcutaneous) probably does not reduce mortality, RR 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to 3.7%); Moderate certainty ⊕⊕⊕○ (Figure 16)
- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕○
- It is uncertain if interferon beta-1a (subcutaneous) affects symptom resolution or improvement; HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕○○○
- Interferon beta-1a (inhaled) may increase symptom resolution or improvement, HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕○○

Figure 16. All-cause mortality with IFN beta-1a vs. standard of care in randomized studies including COVID-19 patients



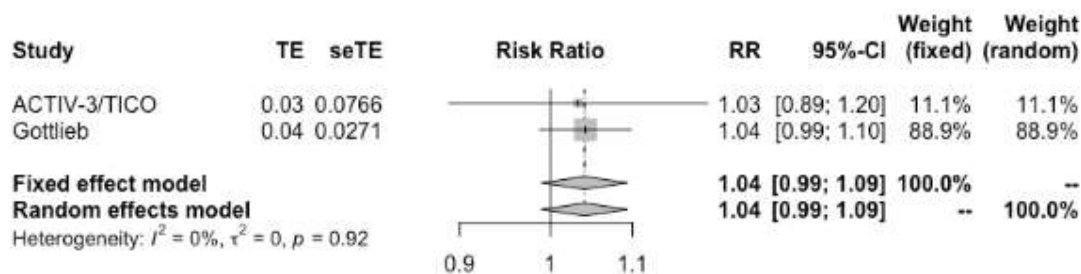
Bamlanivimab (monoclonal antibody)

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

We identified four RCT including 2153 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 1.22 (95%CI 0.55 to 2.69); RD 3.5% (95%CI -0.7% to 27%); Very low certainty ⊕○○○
- Bamlanivimab probably does not significantly improve time to symptom resolution, RR 1.04 (95%CI 0.99 to 1.09); RD 2.4% (95%CI -0.6% to 5.4%); Moderate certainty ⊕⊕⊕○ (Figure 17)
- 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 ⊕⊕⊕○
- It is uncertain if bamlanivimab increases the risk of severe adverse events; RR 0.56 (95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Very low certainty ⊕○○○
- It is uncertain if bamlanivimab affects hospitalizations in patients with non-severe disease; Very low certainty ⊕○○○

Figure 17. Symptom resolution or improvement with bamanivimab vs. standard of care in randomized studies including COVID-19 patients



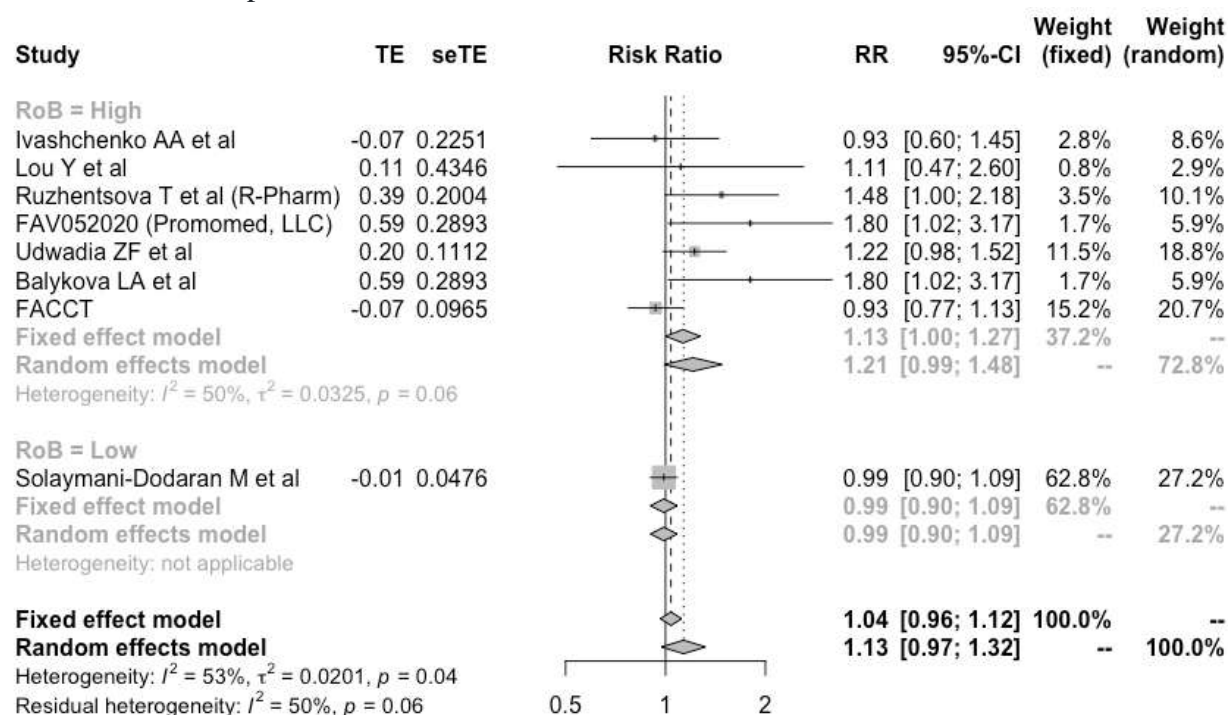
Favipiravir

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

We identified fourteen RCTs including 2028 patients in which favipiravir was compared against standard of care or other treatments. Seven studies reported on favipiravir with or without HCQ versus standard of care, two studies reported on favipiravir vs HCQ or CQ, one study reported on favipiravir vs lopinavir ritonavir and the remaining studies compared favipiravir against other active interventions. As there is moderate to high certainty that HCQ and lopinavir-ritonavir are not related to significant benefits, we assumed those interventions as equivalent to standard of care. Our results showed:

- Favipiravir may not reduce mortality; RR 1.09 (95%CI 0.72 to 1.64); RD 1.4% (95%CI -4.5% to 10.2%); Low certainty ⊕⊕○○
- Favipiravir may not reduce mechanical ventilation requirements; RR 1.24 (95%CI 0.72 to 2.12); RD 4.2% (95%CI -4.8% to 19.5%); Low certainty ⊕⊕○○
- Favipiravir probably does not increase symptom resolution or improvement, RR 0.99 (95%CI 0.9 to 1.09); RD -0.6% (95%CI -6% to 5.6%); Moderate certainty ⊕⊕⊕○ (Figure 18) (based on low risk of bias studies)
- It is uncertain if favipiravir increases the risk of severe adverse events; Very low certainty ⊕○○○
- It is uncertain if favipiravir affects hospitalizations in patients with non-severe disease; Very low certainty ⊕○○○

Figure 18. 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 twenty-nine RCT including 10382 patients in which ivermectin was compared against standard of care or other treatments. Studies included patients with mild to severe disease, as shown by the mortality rates in the control arms, which ranged from 0% to 21.7%. Most studies did not report on clinical important outcomes and most of the ones that did have important methodological limitations including inappropriate randomization process and lack or unclear report of allocation concealment. Our results showed:

- Ivermectin may not significantly reduce mortality, RR 0.92 (95%CI 0.54 to 1.57); RD - 1.3% (95%CI -7.4% to 9.1%); Low certainty ⊕⊕○○ (Figure 19) (based on low risk of bias studies)
- Ivermectin may not significantly reduce mechanical ventilation requirements, RR 1.01 (95%CI 0.6 to 1.72); RD 0.2% (95%CI -6.9% 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 20) (based on low risk of bias studies)

- It is uncertain if ivermectin affects symptomatic infection, RR 0.22 (95%CI 0.09 to 0.53); RD -13.6% (95%CI -15.8% to -8.2%); Very low certainty ⊕○○○
- It is uncertain if ivermectin affects severe adverse events, RR 1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.3%); Very low certainty ⊕○○○
- It is uncertain if ivermectin affects hospitalizations in non-severe patients, RR 0.51 (95%CI 0.18 to 1.43); RD -0.5% (95%CI -8.4% to 4.4%); Very low certainty ⊕○○○

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

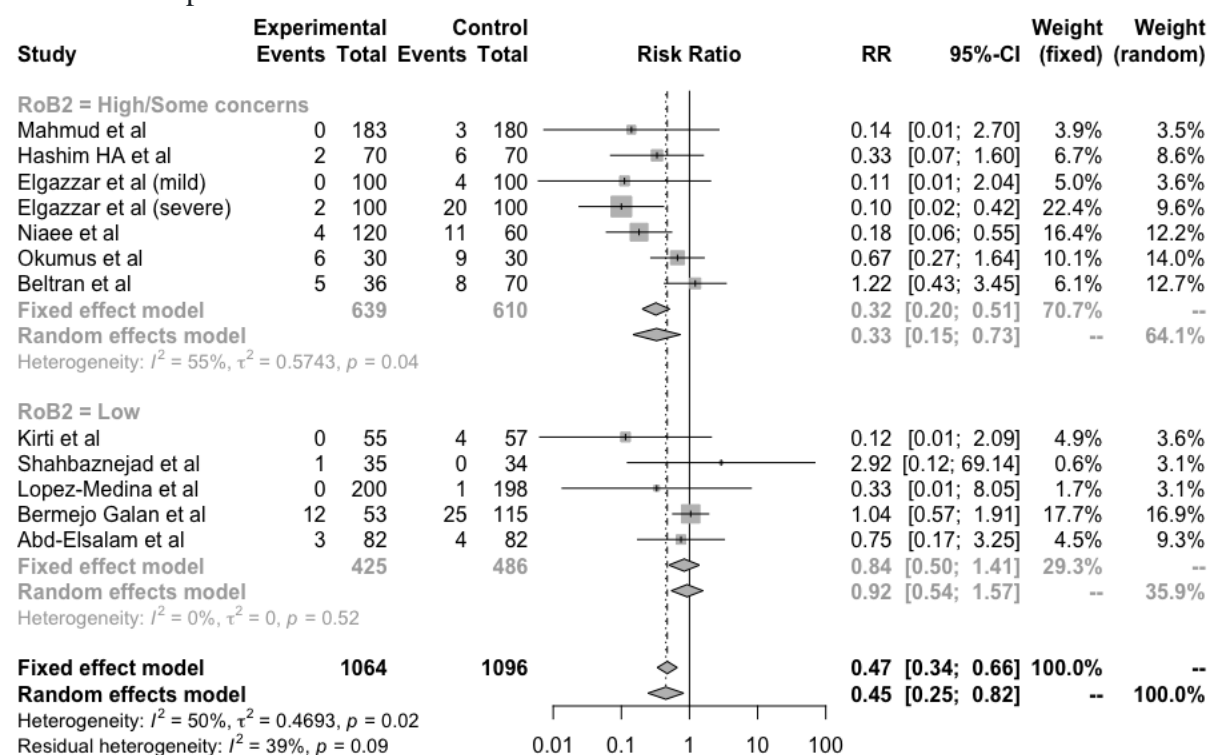
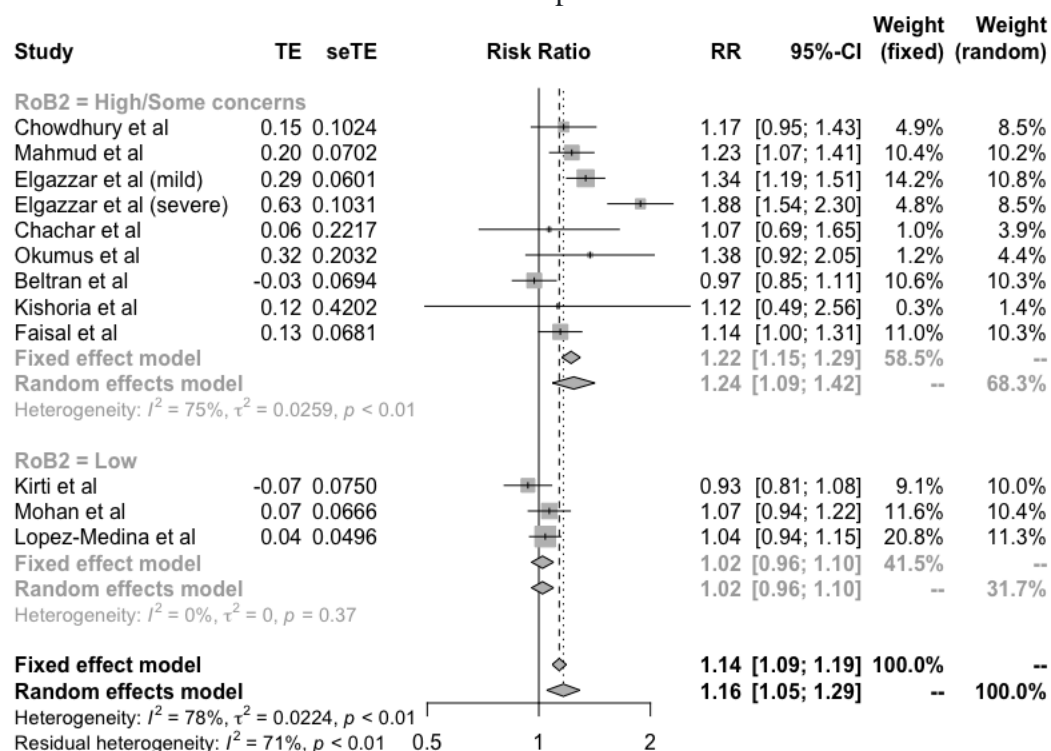


Figure 20. Symptom resolution or improvement in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



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

Baricitinib

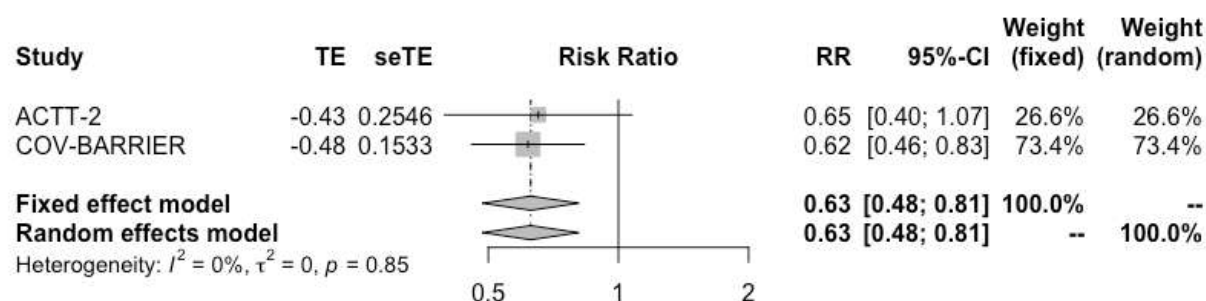
See Summary of findings Table 13, Appendix 1

We identified two RCT including 2558 patients in which baricitinib was compared against standard of care. Both studies included moderate to severe hospitalized patients. Critical patients were excluded. Our results showed:

- Baricitinib may reduce mortality, RR 0.63 (95%CI 0.48 to 0.81); RD -5.9% (95%CI -8.3% to -3%); Moderate certainty ⊕⊕⊕○ (Figure 21)
- 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 may improve time to symptom resolution, RR 1.25 (95%CI 1.11 to 1.41); RD 15.1% (95%CI 6.6% to 24.8%); Moderate certainty ⊕⊕⊕○

- Baricitinib may not increase severe adverse events, RR 0.77 (95%CI 0.63 to 0.95); RD -2.3% (95%CI -3.7% to -0.5%); Low certainty ⊕⊕○○

Figure 21. Mortality in randomized studies comparing baricitinib with standard of care in patients with COVID-19



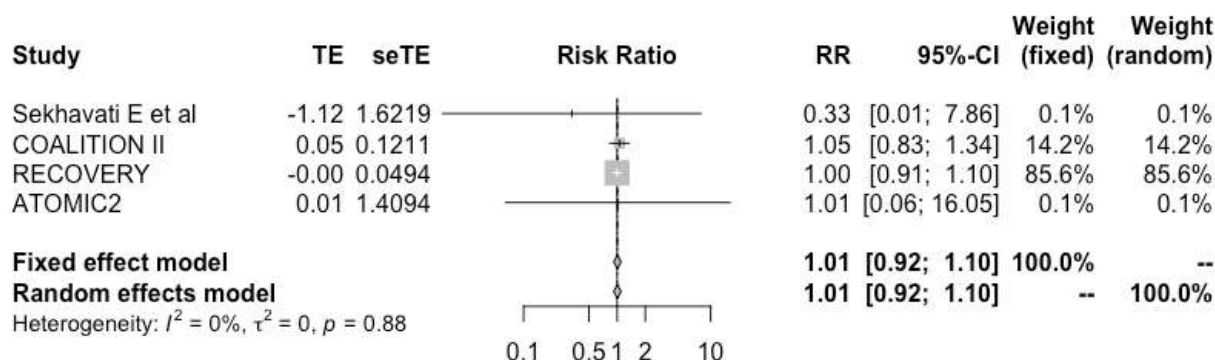
Azithromycin

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

We identified seven RCT including 9716 patients in which azithromycin was compared against standard of care or other treatments. RECOVERY trial was the biggest study including 7762 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 22)
- 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 ⊕○○○
- It is uncertain if azithromycin reduces hospitalizations, RR 0.89 (95%CI 0.46 to 1.72); RD -0.8% (95%CI -4% to 5.4%); Very low certainty ⊕○○○

Figure 22. Mortality in randomized studies comparing azithromycin with standard of care in patients with COVID-19

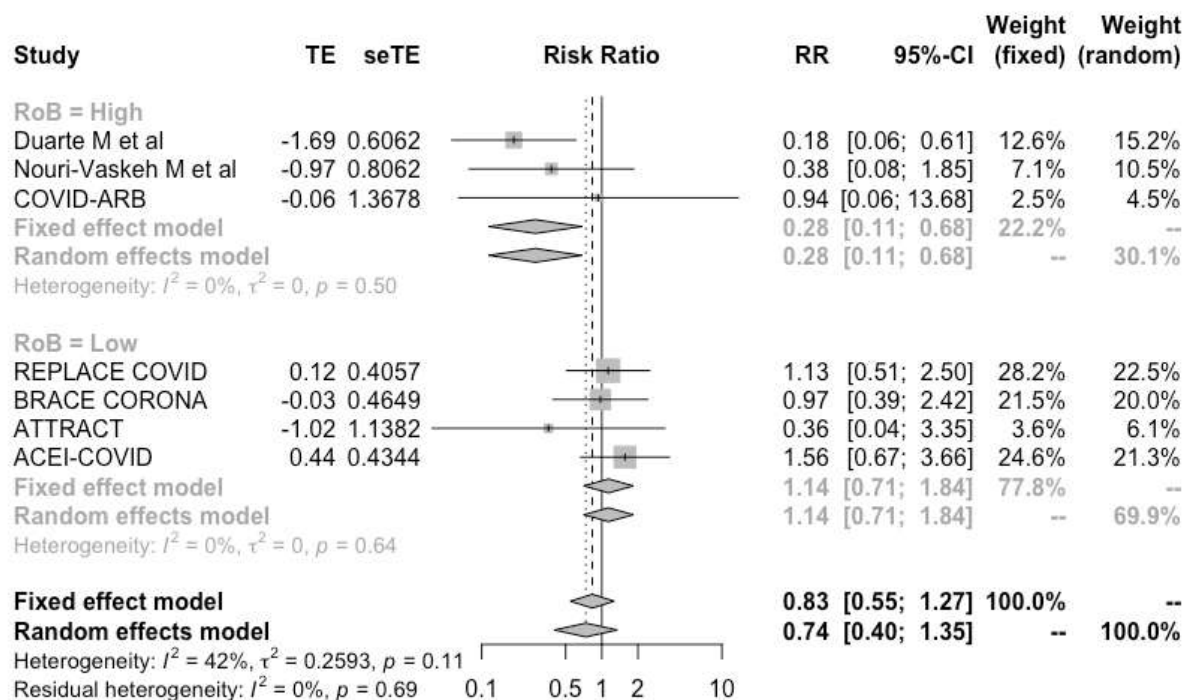


ACEI/ARB initiation or continuation

We identified seven RCT including 1490 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 1.14 (95%CI 0.71 to 1.84); RD 2.2% (95%CI -4.6% to 13.4%); Low certainty $\oplus\oplus\circ\circ$ (Figure 23) (based on low risk of bias studies)
- ACEI/ARB discontinuation may reduce mechanical ventilation requirements, RR 0.90 (95%CI 0.65 to 1.23); RD -1.7% (95%CI -6.1% to 4%); Low certainty $\oplus\oplus\circ\circ$

Figure 23. 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 five RCT including 16105 patients in which colchicine was compared against standard of care or other treatments. The COLCORONA trial was the biggest including mild ambulatory patients, with 2,235 patients assigned to intervention and 2,253 to control, and the RECOVERY trial was the biggest including moderate to critical hospitalized patients, with 5,610 patients assigned to intervention and 5,730 assigned to control. Our results showed:

- Colchicine probably does not reduce mortality, RR 1 (95%CI 0.93 to 1.08); RD 0% (95%CI -1.1% to 1.3%); Moderate certainty ⊕⊕⊕○ (Figure 24)
- 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 25)
- Colchicine probably does not increase symptom resolution or improvement, RR 0.99 (95%CI 0.96 to 1.01); RD -0.7% (95%CI -2.1% to -0.7%); High certainty ⊕⊕⊕⊕
- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 1); RD -2.2% (95%CI -4% to 0%); High certainty ⊕⊕⊕⊕

- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕○○○
- Colchicine may reduce hospitalizations in patients with recent onset disease, RR 0.8 (95%CI 0.62 to 1.03); RD -1.5% (95%CI -2.8% to 0.2%); Low certainty ⊕○○○

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

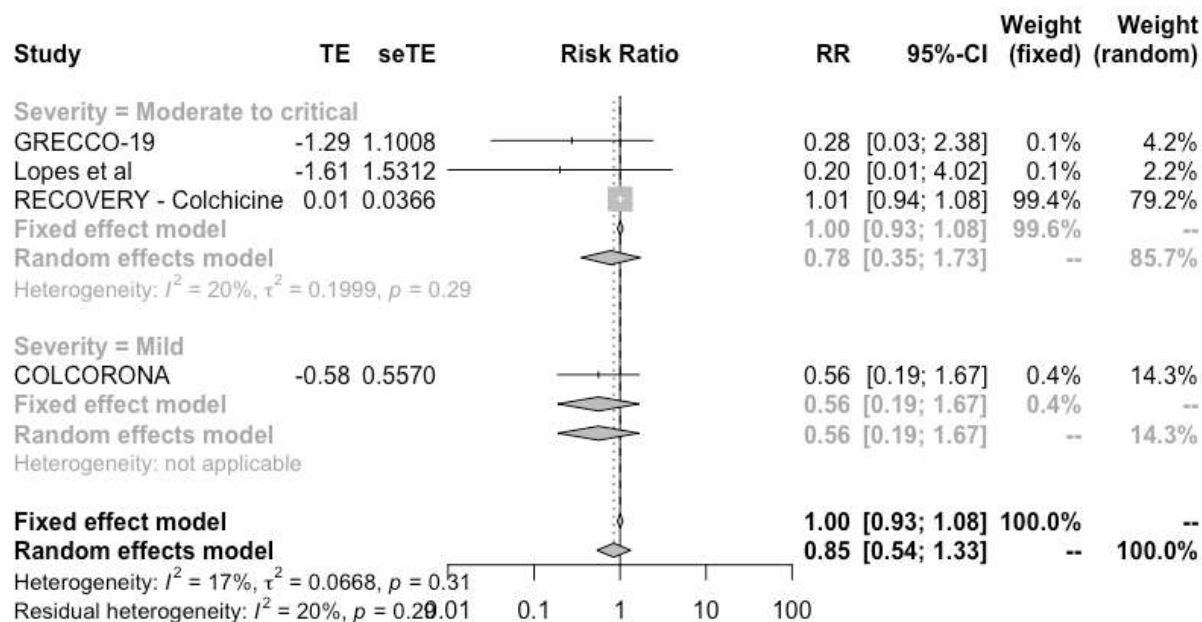
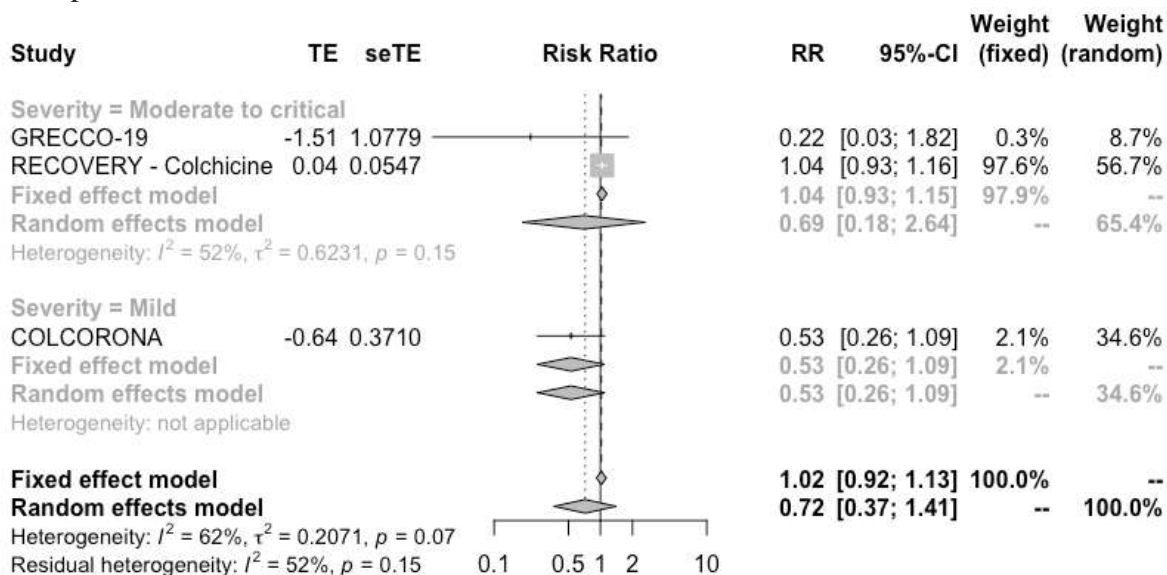


Figure 25. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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

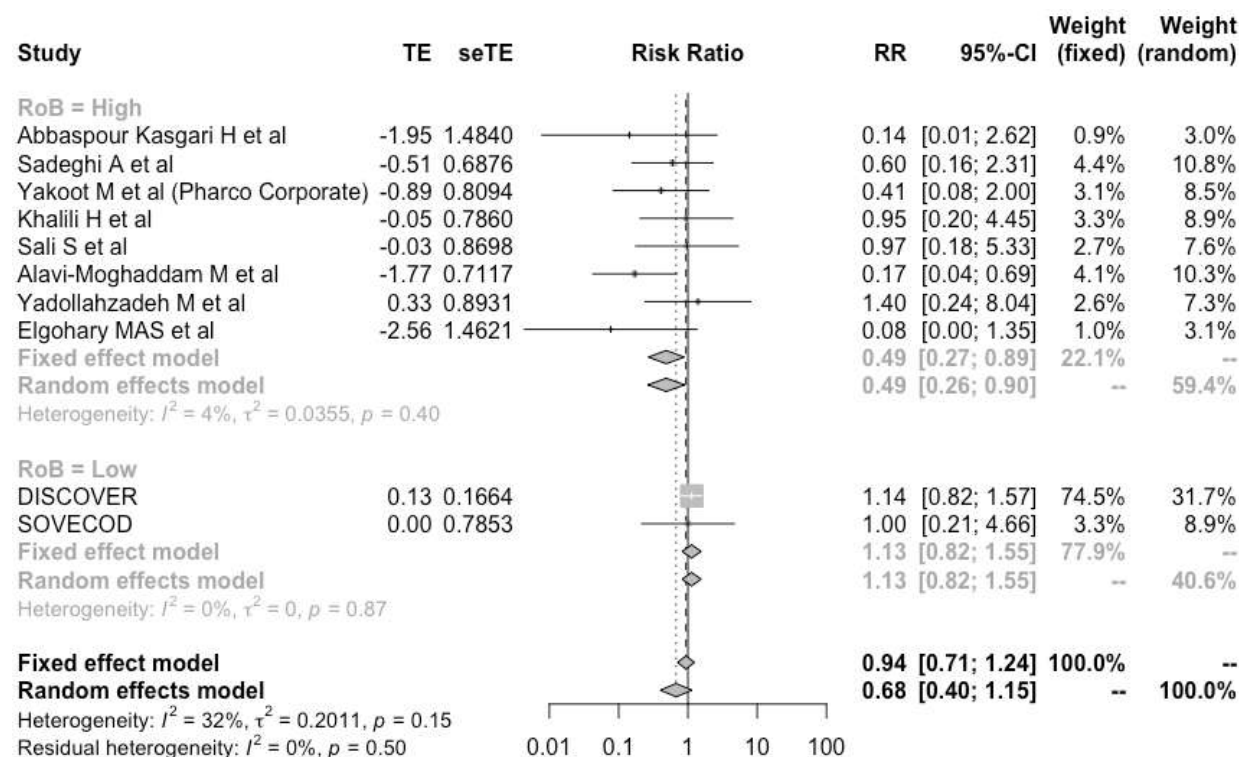
Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir

[See Summary of findings Table 16, Appendix 1](#)

We identified eleven RCT including 1976 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 alone vs. lopinavir-ritonavir, three studies compared sofosbuvir + daclatasvir vs. standard of care, two studies compared sofosbuvir + daclatasvir vs. lopinavir-ritonavir and two studies compared sofosbuvir + ledipasvir vs. standard of care. As there is moderate to high certainty that lopinavir-ritonavir is not related to significant benefits, we assumed that intervention as equivalent to standard of care. The DISCOVER trial was the biggest, with 1,083 patients and the only one categorized as with low risk of bias. Studies included patients with mild to severe disease. Our results showed:

- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mortality, RR 1.13 (95%CI 0.82 to 1.55); RD 2% (95%CI -2.9% to 8.8%); Low certainty ⊕⊕○○ (Figure 26) (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mechanical ventilation requirements, RR 1.04 (95%CI 0.29 to 3.7); RD 0.7% (95%CI -12.3% to 46.7%); Very low certainty ⊕○○○ (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir probably does not improve time to symptom resolution, RR 0.97 (95%CI 0.9 to 1.06); RD -1.8% (95%CI -6% to 3.6%); Moderate certainty ⊕⊕⊕○ (based on low risk of bias studies)

Figure 26. Mortality in randomized studies comparing sofosbuvir +/- daclatasvir or ledipasvir vs standard of care in patients with COVID-19



REGEN-COV (casirivimab and imdevimab)

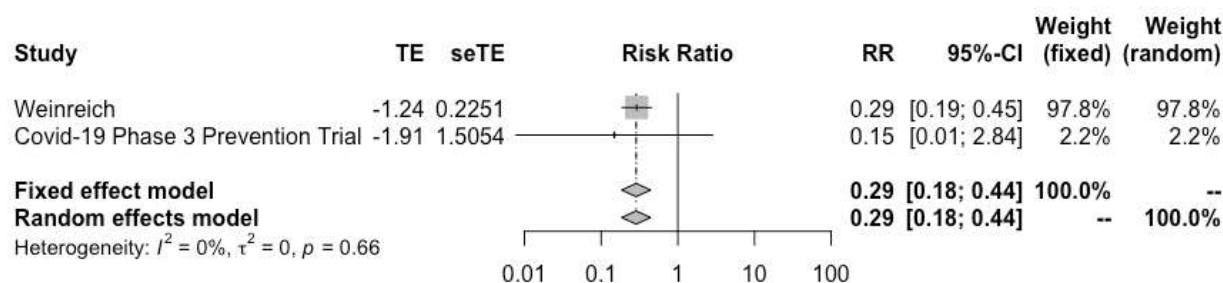
[See Summary of findings Table 17, Appendix 1](#)

We identified three RCTs including 14169 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 two studies included mild patients with recent onset disease and exposed individuals with negative PCR. Our results showed:

- Overall REGEN-COV probably does not significantly decrease mortality, RR 0.94 (95%CI 0.87 to 1.02); RD -1% (95%CI -2.1% to 0.3%); Moderate certainty ⊕⊕⊕○
- In seronegative patients REGEN-COV probably decreases mortality, RR 0.8 (95%CI 0.7 to 0.91); RD -3.2% (95%CI -4.8% to -1.4%); Moderate certainty ⊕⊕⊕○
- Overall REGEN-COV probably does not significantly decrease mechanical ventilation, RR 0.96 (95%CI 0.89 to 1.03); RD -0.7% (95%CI -1.9% to -0.5%); Moderate certainty ⊕⊕⊕○

- In seronegative patients REGEN-COV probably does not significantly decreases mechanical ventilation, RR 0.88 (95%CI 0.73 to 1.06); RD -2.1% (95%CI -4.7% to 1%); Moderate certainty ⊕⊕⊕○
- Overall REGEN-COV probably does not increase symptom resolution, RR 1.06 (95%CI 0.96 to 1.16); RD 3.6% (95%CI -2.4% to 9.7%); Moderate certainty ⊕⊕⊕○
- In seronegative patients REGEN-COV probably increases symptom resolution, RR 1.12 (95%CI 1.01 to 1.25); RD 7.2% (95%CI 0.6% to 15.1%); Moderate certainty ⊕⊕⊕○
- REGEN-COV probably decreases symptomatic infection in exposed individuals, RR 0.69 (95%CI 0.47 to 1.0); RD -5.5% (95%CI -9.2% to 0%); Low certainty ⊕⊕○○
- REGEN-COV probably does not increases severe adverse events, RR 0.63 (95%CI 0.48 to 0.81); RD -3.8% (95%CI -5.3% to -1.9%); Moderate certainty ⊕⊕⊕○
- REGEN-COV probably reduces hospitalization, RR 0.29 (95%CI 0.18 to 0.44); RD -5.3% (95%CI -6.1% to -4.1%); Moderate certainty ⊕⊕⊕○ (Figure 27)

Figure 27. Hospitalization in randomized studies comparing REGEN-COV vs standard of care in patients with COVID-19

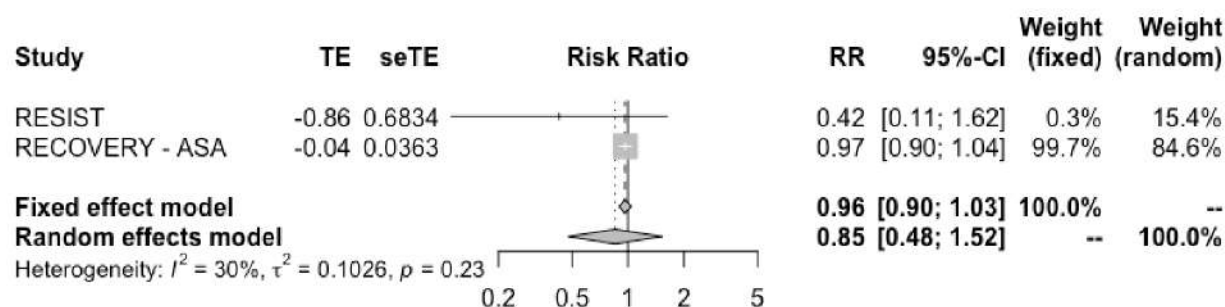


Aspirin

We identified two RCT including 15332 patients in which aspirin was compared against standard of care in patients with COVID-19. Our results showed:

- Aspirin probably does not reduce mortality, RR 0.96 (95%CI 0.90 to 1.03); RD -0.6% (95%CI -1.6% to 0.5%); Moderate certainty ⊕⊕⊕○ (Figure 28)
- Aspirin probably does not reduce mechanical ventilation, RR 0.95 (95%CI 0.87 to 1.05); RD -0.8% (95%CI -2.2% to 0.9%); Moderate certainty ⊕⊕⊕○
- Aspirin probably does not increase symptom resolution or improvement, RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕○

Figure 28. Mortality in randomized studies comparing aspirin vs standard of care in patients with COVID-19



Sotrovimab

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

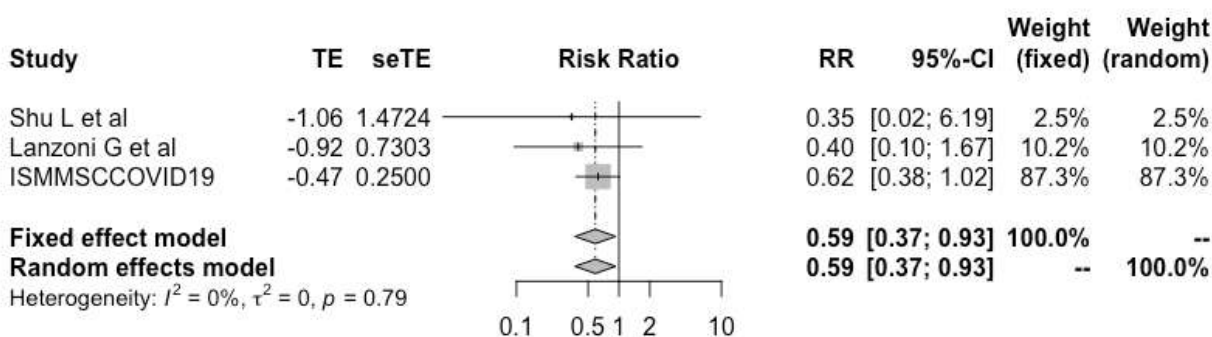
- Sotrovimab probably reduces hospitalizations, RR 0.14 (95%CI 0.04 to 0.48); RD -6.3% (95%CI -7.1% to -3.8%); Moderate certainty ⊕⊕⊕○
- Severe adverse events, RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕○○

Mesenchymal stem-cell transplantation

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

- Mesenchymal stem-cell transplantation may reduce mortality, RR 0.59 (95%CI 0.37 to 0.93); RD -6.2% (95%CI -9.8% to -1%); Low certainty ⊕⊕○○ (Figure 29)

Figure 29. Mortality in randomized studies comparing mesenchymal stem-cell transplantation 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 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

Ammonium chloride

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Siami et al. ¹⁴ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 60 assigned to ammonium chloride 125 mg and 60 assigned to SOC	NR	Steroids 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Blinding and concealment probably inappropriate	Mortality: Very low certainty ⊕⊕○○ Invasive mechanical ventilation: Very low certainty ⊕⊕○○ Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

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

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
REPLACE COVID trial ; ¹⁵ 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 1.14 (95%CI 0.71 to 1.84); RD 2.2% (95%CI -4.6% to 13.4%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 0.90 (95%CI 0.65 to 1.23); RD -1.7% (95%CI -6% to %); Low certainty ⊕⊕○○ Symptom resolution or improvement: Very low certainty ⊕○○○
BRACE CORONA trial ; ¹⁶ Lopes et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB	Median age 55.5 ± 19, male 59.6%, hypertension 100%, diabetes 31.9%, COPD %, asthma 3.9%, CHD 4.6%, CKD 1.4%, cancer 1.5%,	Steroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%	Some Concerns for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very low certainty ⊕○○○

<p>ACEI-COVID trial;¹⁷ 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;¹⁸ Tornling et al; Preprint; 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>Steroids 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;¹⁹ 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 probably inappropriate.</p>
<p>SURG-2020-28683 trial;²⁰ 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;²¹ Geriak et al; peer reviewed; 2021</p>	<p>Patients with severe COVID-19 infection. 16 assigned to losartan</p>	<p>Median age 53, male %, hypertension 38.7%, diabetes 25.8%, CHD</p>	<p>Steroids 22.6%, remdesivir 29%, hydroxychloroquine</p>	<p>High for mortality and mechanical ventilation; high for symptom</p>

	25 mg a day for 10 days and 15 assigned to SOC	3.2%, obesity 41.9%	9.7%, azithromycin 16.1%, convalescent plasma 6.5%	resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Duarte et al ; ²² peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 71 assigned to Telmisartan 80 mg twice daily and 70 assigned to SOC	Mean age 66 ± 17, male 53.2%, hypertension 44.3%, diabetes 19%, chronic lung disease 11.4%, asthma 1.3%, CHD NR%, CKD 3.2%, cerebrovascular disease 6.9%, obesity 15.2%	Steroids 50.6%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. Significant number of exclusions post randomization. Stop early for benefit in the context of multiple interim analysis.	

Anakinra

Anakinra may not improve time to symptom resolution. Further research is needed to confirm or discard these findings

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

CORIMUNO-ANA-1 trial ; ²³ Bureau et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 59 assigned to anakinra 400 mg a day for 3	Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD	Steroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and	Mortality: Very low certainty ⊕○○○ Invasive mechanical
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	days followed by 200 mg for 1 day followed by 100 mg for 1 day and 55 assigned to SOC	31.6%, cancer 9.6%,	tocilizumab 0.8%, azithromycin 24.6%,	adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○
SAVE-MORE trial ; ²⁴ 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%	Steroids 86.2%, remdesivir 71.9%, azithromycin 18.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Anticoagulants

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
HESACOVID trial ; ²⁵ Bertoldi Lemos et al; peer reviewed; 2020	Patients with critical COVID-19. Ten assigned to low molecular weight heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and ten assigned to prophylactic dose (i.e., enoxaparin 40 mg a day)	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, coronary heart disease 10%, immunosuppression 5%	Steroids 70%, hydroxychloroquine 25%, azithromycin 90%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Mortality: RR 1 (95%CI 0.90 to 1.15); RD 0% (95%CI -1.6% to 2.4%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information

REMAP-CAP, ACTIV-4a, ATTACC trial ; ²⁶ Zarychanski et al; Preprint; 2021	Patients with severe to critical COVID-19 infection. 532 assigned low molecular weight heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and 557 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%,	Steroids 79.3%, remdesivir 30.8%, tocilizumab 1.8%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes: Open-label study but outcome assessors were blinded	Symptomatic infection (prophylaxis studies): No information Venous thromboembolic events (intermediate dose): RR 1.02 (95%CI 0.53 to 1.96); RD 0.1% (95%CI -3.3% to 6.7%); Low ⊕⊕○○
INSPIRATION trial ; ²⁷ 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%	Steroids 93.2%, remdesivir 60.1%, lopinavir-ritonavir 1%, tocilizumab 13.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes: Open-label study but outcome assessors were blinded	Venous thromboembolic events (therapeutic dose): RR 0.61 (95%CI 0.45 to 0.82); RD -2.7% (95%CI -3.8% to -1.3%); Moderate ⊕⊕⊕○ Major bleeding: RR 1.74 (95%CI 1.12 to 2.7); RD 1.4% (95%CI 0.2% to 3.2%); Moderate ⊕⊕⊕○
Perepu et al ; ²⁸ Preprint; 2021	Patients with severe to critical COVID-19 infection. 87 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 86 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 64 ± 62, male 56%, hypertension 60%, diabetes 37%, COPD 23%, CHD 31%, cancer 12%, obesity 49%	Steroids 75%, remdesivir 61%, azithromycin 21%, convalescent plasma 27%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Hospitalization: No information
REMAP-CAP, ACTIV-4a, ATTACC trial ; ²⁹ Zarychanski et al;	Patients with moderate to severe COVID-19 infection. 1171 assigned to	Mean age 59 ± 14, male 58.7%, hypertension 51.8%, diabetes 29.7%, COPD 21.7%, CHD	Steroids 61.7%, remdesivir 36.4%, tocilizumab 0.6%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	

preprint; 2021	enoxaparin 1 mg/kg twice a day and 1048 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	10.6%, CKD 6.9%, immunosuppressive therapy 9.7%		adverse events Notes: Open-label study but outcome assessors were blinded	
ACTION trial ; ³⁰ 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 20mg 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%,	Steroids 83%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: Although patients and carers were aware of the intervention arm assigned, outcome assessors were blinded	

Aprepitant

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

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

Mehboob et al ; ³¹ preprint; 2020	Patients with mild to critical COVID-19 infection. 10 assigned to aprepitant 80 mg once a day for 3-5 days and 8 assigned to standard of care	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
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				study. Concealment of allocation probably inappropriate.	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 , ³² 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 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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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 , ³³ 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%	Steroids 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 , ³⁴ Horby et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 7351 assigned to aspirin 150mg 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%,	Steroids 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 Adverse events: No information Hospitalization: No information

Auxora

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

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

Miller et al. ³⁵ 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 probably inappropriate. Analysis performed on a subgroup (patients that required high-flow nasal cannula (HFNC) were excluded from primary analysis).	<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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Aviptadil

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

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

COVID-AIV trial ³⁶ Jihad et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 136 assigned to aviptadil three infusions of 50, 100	Mean age 61 ± NR, male 69%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p>
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	and 150pmol/kg/hr and 67 assigned to SOC			Notes: Blinding and concealment probably inappropriate	<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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Azithomycin

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. ³⁷ 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 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. ³⁸ peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events	<p>Symptom resolution or improvement: RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to</p>

	azithromycin 500 mg on first day followed by 250 mg a day for 5 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	2.4%); High certainty ⊕⊕⊕⊕ Symptomatic infection (prophylaxis studies): No information
COALITION II trial ; ³⁹ 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 %	Steroids 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 0.89 (95%CI 0.46 to 1.72); RD -0.8% (95%CI -4% to 5.4%); Very low certainty ⊕○○○
RECOVERY trial ⁴⁰ 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%	Steroids 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 ; ⁴¹ 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 probably inappropriate.	
PRINCIPLE trial ; ⁴²	Patients with mild to	Mean age 60.7 ± 7.8,	NR	Some Concerns for	

Butler et al; peer reviewed; 2021	severe COVID-19 infection. 500 assigned to azithromycin 500 mg a day for 3 days and 629 assigned to SOC	male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,		mortality and mechanical ventilation; 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 ; ⁴³ 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.	

Azvudine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Ren et al ; ⁴⁴ 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	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No

				Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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
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RCT

ACTT-2 trial ; ⁴⁵ 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%	Steroids 11.9%	Some Concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	Mortality: RR 0.63 (95%CI 0.48 to 0.81); RD -5.9% (95%CI -8.3% to -3%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 0.66 (95%CI 0.46 to 0.93); RD -5.9% (95%CI -9.2% to -1.2%); Low certainty ⊕⊕○○
COV-BARRIER trial ; ⁴⁶ Marconi et al; ; 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%	Steroids 79.3%, remdesivir 18.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Symptom resolution or improvement: RR 1.25 (95%CI 1.11 to 1.41); RD 15.1% (95%CI 6.6% to 24.8%); Moderate certainty ⊕⊕⊕○ Symptomatic infection

					<p>(prophylaxis studies): No information</p> <p>Adverse events: RR 0.77 (95%CI 0.63 to 0.95); RD -2.3% (95%CI -3.7% to -0.5%); Low certainty ⊕⊕○○</p> <p>Hospitalization: No information</p>
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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

<p>Lou et al;⁴⁷ preprint; 2020</p>	<p>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</p>	<p>Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%</p>	<p>Antivirals 100%, interferon 100%</p>	<p>High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation 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>
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Bamlanivimab (monoclonal antibody)

Bamlanivimab may not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases 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 (standard of care) and GRADE certainty of the evidence
RCT					
BLAZE-1 trial , ⁴⁸ 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 1.04 (95%CI 0.99 to 1.09); RD 2.4% (95%CI -0.6% to 5.4%); Moderate certainty ⊕⊕⊕○
ACTIV-3/TICO trial , ⁴⁹ 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%	Steroids 49%, remdesivir 95%	Low for mortality and adverse events; high for symptom resolution. Notes: Significant lost 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 , ⁵⁰ 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 1.01 (95%CI 0.54 to 1.90); RD 0.1% (95%CI -4.7% to -9.2%); Low certainty ⊕⊕○○
BLAZE-2 trial , ⁵¹ Cohen et al; peer reviewed; 2021	Patients exposed to SARS-COV2. 484 assigned to bamlanivimab	Median age 53	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and	Hospitalization: Very low certainty ⊕○○○

	4200 mg once and 482 assigned to SOC			adverse events	
Bamlanivimab + etesevimab (monoclonal antibodies)					
Bamlanivimab + etesevid probably does not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases 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 (standard of care) and GRADE certainty of the evidence
RCT					
Gottlieb et al. ⁵⁰ 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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: RR 1.04 (95%CI 0.98 to 1.1); RD 2.4% (95%CI -0.6% to 5.4%); Moderate certainty ⊕⊕⊕○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p>

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 , ⁵² preprint; 2020	Patients with severe COVID-19. 30 assigned to BCG 0.1 ml once and 30 assigned to standard of care	Mean age 45.2 ± 36.5, male 60%, obesity 23%	Remdesivir 6.6%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: No information</p>
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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 , ⁵³ peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 32 assigned to Bioven 0.8-1gr/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	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or</p>
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				allocation probably inappropriate.	improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

Li T et al ; ⁵⁴ 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%	Steroids 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 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 ⊕○○○
Ansarin et al ; ⁵⁵ 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 probably	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

				inappropriate.	
Mikhaylov et al. ⁵⁶ 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. ⁵⁷ 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.	

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

CamoCO-19 trial ⁵⁸ Gunst et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 137 assigned to camostat mesilate 200 mg a day for 5 days and 68 assigned to	Median age 61 ± 23, male 60%, hypertension 34%, diabetes 17%, COPD 10%, asthma 13%, CHD 19%, cancer 14%, obesity 33%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution
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	SOC				<p>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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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

<p>Perlin et al.⁵⁹ preprint; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 31 assigned to CERC-002 16 mg/kg once and 31 assigned to SOC</p>	<p>Mean age 58.5 ± 14, male 69.5%</p>	<p>Steroids 91.5%, remdesivir 68.2%</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate. Significant lost to follow-up.</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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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 ; ⁶⁰ 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 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 ; ⁶¹ 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	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	Mortality: No information Invasive mechanical ventilation: No information

	days) and 10 assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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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
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RCT

Rashad et al; ⁴¹ 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 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
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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
Hospitalization: No information					
Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
COVID-19-MCS trial ; ⁶² 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.	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

Colchicine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
GRECCO-19 trial ; ⁶³ Deftereos et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 50 assigned to colchicine 1.5 mg once followed by 0.5 mg twice daily until hospital discharge or 21 days and 55 assigned to standard of care	Median age 64 ± 11, male 58.1%, hypertension 45%, diabetes 20%, chronic lung disease 4.8%, coronary heart disease 13.3%, immunosuppression 3.75%	Hydroxychloroquine 98%, lopinavir-ritonavir 31.4%, tocilizumab 3.8%, azithromycin 92%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Mortality: RR 1 (95%CI 0.93 to 1.08); RD 0% (95%CI -1.1% to 1.3%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 1.02 (95%CI 0.92 to 1.13); RD 0.3% (95%CI -1.4% to -2.2%); Moderate certainty ⊕⊕⊕○
Lopes et al ; ⁶⁴ 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%	Steroids 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 probably inappropriate.	Symptom resolution or improvement: RR 0.99 (95%CI 0.96 to 1.01); RD -0.7% (95%CI -2.1% to -0.7%); High certainty ⊕⊕⊕⊕ Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.78 (95%CI 0.61 to 1); RD -2.2% (95%CI -4% to 0%); High certainty ⊕⊕⊕⊕
Salehzadeh et al ; ⁶⁵ preprint; 2020	Patients with moderate to critical COVID-19. 50 assigned to colchicine 1 mg a day for 6 days and 50 assigned to standard of care	Mean age 56, male 41%, hypertension 11%, diabetes 11%, chronic lung disease 4%, coronary heart disease 15%, chronic kidney disease 5%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events	Pulmonary embolism: RR 5.55 (95%CI 1.23 to 25);

				Notes: Non-blinded study. Concealment of allocation probably inappropriate.	RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕⊕○○ Hospitalization: RR 0.8 (95%CI 0.62 to 1.03); RD -1.5% (95%CI -2.8% to 0.2%); Low certainty ⊕⊕○○
Tardif et al , ⁶⁶ peer-reviewed; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe disease. 2235 assigned to colchicine 1 mg a day for 3 days followed by 0.5 mg for a total of 27 days and 2253 assigned to SOC	Mean age 54.3, male 46%, hypertension 36.3%, diabetes 19.9%, COPD 26.5%, CHD 5.4%, obesity 45.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
RECOVERY - Colchicine trial , ⁶⁷ Horby et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 5610 assigned to colchicine 500 mg twice a day for 10 days and 5730 assigned to SOC	Mean age 63.4 ± 13.8, male 69.5%, diabetes 25.5%, COPD 21.5%, asthma %, CHD 21%, CKD 3%	Steroids 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.	

Convalescent plasma

Convalescent plasma probably does not reduce mortality nor significantly reduces mechanical ventilation requirements or improves 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					
Li et al , ⁶⁸ peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 52 assigned to	Median age 70 ± 8, male 58.3%, hypertension 54.3%, diabetes 10.6%, coronary heart disease	Steroids 39.2%, antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution,	Mortality: RR 0.99 (95%CI 0.93 to 1.05); RD -0.1% (95%CI -1.1% to 0.8%);

	convalescent plasma 4 to 13 mL/kg of recipient body weight and 51 assigned to standard of care	25%, chronic kidney disease 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%		infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 0.98 (95% CI 0.86 to 1.12); RD -0.3% (95%CI -2.4% to 2.1%); Moderate certainty ⊕⊕⊕○
CONCOVID trial ; Gharbharan et al; ⁶⁹ preprint; 2020	Patients with moderate to critical COVID-19 infection. 43 assigned to convalescent plasma 300 ml once or twice and 43 assigned to standard of care	Median age 62 ± 18, male 72%, hypertension 26%, diabetes 24.4%, chronic lung disease 26.7%, coronary heart disease 23.2%, chronic kidney disease 8.1%, immunosuppression 12.8%, cancer 9.3%	NR	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Symptom resolution or improvement: RR 1.02 (95% CI 0.93 to 1.13); RD 1.2% (95%CI -4.2% to 7.9%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information
Avendaño-Solá et al ; ⁷⁰ 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%	Steroids 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 1.1 (95% CI 0.76 to 1.58); RD 1% (95%CI -2.5% to 5.9%); Low certainty ⊕⊕○○ Hospitalization: No information
PLACID trial ; ⁷¹ Agarwal et al; preprint; 2020	Patients with severe COVID-19. 235 assigned to convalescent plasma 200 ml twice in 24 hs 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	Steroids 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	

		0.9%, cancer 0.2%, obesity 7.1%		introduced bias to symptoms and adverse events outcomes results.	
PLASM-AR trial ; ⁷² 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%	Steroids 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 ; ⁷³ Bajpai et al; preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to convalescent plasma 500 ml twice and 15 assigned to standard of care	Mean age 48.2 ± 9.8, male 75.9%,	Hydroxychloroquine 100%, azithromycin 100%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
AlQahtani et al ; ⁷⁴ 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%	Steroids 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 probably inappropriate.	
Fundacion INFANT-Plasma trial ; ⁷⁵ 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	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

		3.8%, obesity 7.5%		
PICP19 trial ; ⁷⁶ 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 probably inappropriate.
RECOVERY-Plasma trial ; ⁷⁷ 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%	Steroids <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 ; ⁷⁸ 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 probably inappropriate.
O'Donnell et al ; ⁷⁹ 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%	Steroids 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 lost 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 , ⁸⁰ 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%	Steroids 82.6%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Pouladzadeh et al , ⁸¹ 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 , ⁸² 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	Steroids 60.8%, remdesivir 24.3%, hydroxychloroquine 31%, tocilizumab 21.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

		14.8%, immunosuppressive therapy 8.1%			
Salman et al; ⁸³ 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%	Steroids 76.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
CAPSID trial; ⁸⁴ 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%	Steroids 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
REMAP-CAP trial; ⁸⁵ Green et al; ; 2021	Patients with moderate to critical COVID-19 infection. 1075 assigned to CP 550-700ml 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%	Steroids 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.	
Balcells et al; ⁸⁶ 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	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	Steroids 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	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No

	when clinical deterioration was observed (43.3% received CP in this arm)	5.1%, immunosuppression 12%, cancer 7%, obesity 12%		study which might have introduced bias to symptoms and adverse events outcomes results.	information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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Non-RCT

Joyner et al , ⁸⁷ 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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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 trial , ⁸⁸ Chen et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 15 assigned to darunavir-Cobicistat 800 mg/150 mg once a day for 5 days and 15 assigned to standard of care	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, coronary heart disease 26.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
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				allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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Dutasteride

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

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

AB-DRUG-SARS-004 trial , ⁸⁹ 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 , ⁹⁰ 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 ; ⁹¹ 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%	Steroids 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 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>

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 ; ⁹² Preprint; 2020	Patients with moderate to severe COVID-19. assigned to enisamium 500 mg	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No</p>

	4 times a day for 7 days or SOC. Number of patients in each arm not reported.			adverse events Notes: Concealment of allocation probably inappropriate.	information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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Famotidine

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

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

Samimagham et al ; ⁹³ 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
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Favipiravir

Favipiravir may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Chen et al ; preprint; ⁹⁴ 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 probably inappropriate.	Mortality: RR 1.09 (95%CI 0.72 to 1.64); RD 1.4% (95%CI -4.5% to 10.2%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 1.24 (95%CI 0.72 to 2.12); RD 4.2% (95%CI -4.8% to 19.5%); Low certainty ⊕⊕○○
Ivashchenko et al ⁹⁵ 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 probably inappropriate.	Symptom resolution or improvement: RR 0.99 (95%CI 0.9 to 1.09); RD -0.6% (95%CI -6% to 5.6%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○
Lou et al ; ⁴⁷ 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	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%	Antivirals 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	Hospitalization: Very low certainty ⊕○○○ Hospitalization: No information

	care			study. Concealment of allocation probably inappropriate.
Doi et al; ⁹⁶ 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%	Steroids 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 probably inappropriate.
Dabbous et al; ⁹⁷ 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 probably inappropriate.
Zhao et al; ⁹⁸ peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to TCZ 400 mg once or twice and 5 assigned to favipiravir + TCZ	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Khamis et al; ⁹⁹ peer-	Patients with	Mean age 55 ± 14, male	Steroids 67%,	High for mortality and

reviewed; 2020	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	58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart disease 15%, chronic kidney disease 20%	tocilizumab 35%, convalescent plasma 58%	invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Ruzhentsova et al ¹⁰⁰ 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 probably inappropriate.
Udwadia et al ¹⁰¹ 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; ¹⁰² 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 probably inappropriate.
Solaymani-Dodaran et al; ¹⁰³ 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%	Steroids 27.6%, remdesivir 1.1%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events
Zhao et al; ¹⁰⁴ peer-reviewed; 2021	Patients with COVID-19 infection who were discharged from hospital. 36 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 19 assigned to SOC	Mean age 55.7 ± 13.6, male 45.5%, hypertension 30.9%, diabetes 14.5%, CHD 7.3%, cancer 7.3%	Steroids 3.6%, remdesivir 0%, hydroxychloroquine 5.5%, lopinavir-ritonavir 16.4%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
FACCT trial; ¹⁰⁵ 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%	Steroids 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.	
Febuxostat Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Davoodi et al. ¹⁰⁶ 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 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. ¹⁰⁷ peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to finasteride 5 mg a day for 7 days and 40 assigned to SOC	Mean age 72 ± 14, male 100%, hypertension 66.3%, diabetes 25%, COPD 12.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information Hospitalization: No information

Fluvoxamine

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

Study; publication status	Patients and 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. ¹⁰⁸ peer-reviewed; 2020	Patients with mild to moderate COVID-19.	Median age 45.5 ± 20.5, male 28.2%,	NR	Low for mortality and mechanical ventilation;	Mortality: Very low certainty ⊕○○○

	80 assigned to fluvoxamine incremental dose to 100 mg three times a day for 15 days and 72 assigned to standard of care	hypertension 19.7%, diabetes 11%, asthma 17.1%, obesity 56.6%		low for symptom resolution, infection and adverse events	<p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p> <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. ¹⁰⁹ peer reviewed; 2020	Patients with severe to critical COVID-19. 38 assigned to Helium 50% to 79% mixed with oxygen and 32 assigned to SOC	Mean age 53.5 ± 16, male 51.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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>
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Honey + Nigella sativa Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and 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 ; ¹¹⁰ Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + nigella sativa 1gr + 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%	Steroids 26.5%, azithromycin 73.8%, ivermectin 36.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: 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 not significantly reduce the risk of infection. However certainty of the evidence is low because of risk of bias and imprecision. HCQ/CQ may also be associated with a small increase in 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					
CloroCOVID19 trial ; ¹¹¹ Borba et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 41 assigned to chloroquine 600 mg twice a day for 10 days and 40 assigned to chloroquine 450 mg twice on day 1 followed by 450 mg once a day for 5 days	Mean age 51.1 ± 13.9, male 75.3%, hypertension 45.5%, diabetes 25.5%, chronic lung disease NR%, asthma 7.4%, coronary heart disease 17.9%, chronic kidney disease 7.4%, alcohol use disorder 27.5%, HIV 1.8%, tuberculosis 3.6%,	Azithromycin 100%, oseltamivir 89.7%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 1.07 (95%CI 0.93 to 1.24); RD 1.2% (95%CI -1.2% to 4.2%); Moderate certainty ⊕⊕⊕○
Huang et al ; ¹¹² 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 probably inappropriate.	Symptom resolution or improvement: RR 1.05 (95%CI 0.95 to 1.16); RD 3% (95%CI -3% to 9.7%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): RR 0.97 (95%CI 0.65 to 1.45); RD -0.5% (95%CI -6.1% to 7.8%); Low certainty ⊕⊕○○
RECOVERY - Hydroxychloroquine trial ; ¹¹³ 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	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	Severe Adverse events: RR 0.89 (95%CI 0.6 to 1.32); RD -1.1% (95%CI -

	assigned to standard of care			study which might have introduced bias to symptoms and adverse events outcomes results.	4.1% to 3.3%); Low certainty ⊕⊕○○ Hospitalization: Very low certainty ⊕○○○
BCN PEP CoV-2 trial ; ¹¹⁴ Mitja et al; preprint; 2020	Patients exposed to COVID-19. 1116 assigned to hydroxychloroquine 800 mg once followed by 400 mg x once a day for 6 days and 1198 assigned to standard of care	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, coronary heart disease 13.3%, Nervous system disease 4.1%	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant number of patients excluded from analysis.	
COVID-19 PEP trial ; ¹¹⁵ Boulware et al; peer-reviewed; 2020	Patients exposed to COVID-19. 414 assigned to hydroxychloroquine 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	Median age 40 ± 6.5, male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma 7.6%, comorbidities 27.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss of information that might have affected the study's results.	
Cavalcanti et al trial ; ¹¹⁶ 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	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%,	Steroids 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	

	care	obesity 15.5%		introduced bias to symptoms and adverse events outcomes results.
Kamran SM et al trial ; ¹¹⁷ Kamran et al; preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to hydroxychloroquine 400 mg twice a day once then 200 mg twice a day for 4 days and 151 assigned to standard of care	Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%	NR	High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
COVID-19 PET trial ; ¹¹⁸ 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 ; ¹¹⁹ 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; ¹²⁰ 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	Mean age 46.1 ± 14.7, male 54.7%, hypertension 6%, diabetes 14%, other comorbidities 31%	Steroids 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

	75 assigned to standard of care			introduced bias to symptoms and adverse events outcome results.
Chen et al; ¹²¹ 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 probably inappropriate.
Chen et al; ¹²² 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 probably inappropriate.
Chen et al; ¹²³ 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 probably inappropriate.
HC-nCoV trial; ¹²⁴ 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 probably inappropriate.
Abd-Elsalam et al ; ¹²⁵ 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 probably inappropriate.
COVID-19 PREP trial ; ¹²⁶ 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 ; ¹²⁷ Ulrich et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 67 assigned to hydroxychloroquine 800 mg on day 1 followed by 200 mg twice a day for 2 to 5 days and 61 assigned to standard of care	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart disease 26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%	Steroids 10.2%, remdesivir 0.8%, lopinavir-ritonavir 0.8%, azithromycin 23.4%, convalescent plasma 13.3%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.

<p>PrEP COVID trial;¹²⁸ Grau-Pujol et al; preprint; 2020</p>	<p>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</p>	<p>Median age 39 ± 20, male 26.8%, hypertension 1.8%, diabetes 0.4%, chronic lung disease 2.6%</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>PATCH trial;¹²⁹ Abella et al; peer-reviewed; 2020</p>	<p>Patients exposed to COVID-19. 64 assigned to hydroxychloroquine 600 mg a day for 8 weeks and 61 assigned to standard of care</p>	<p>Median age 33 ± 46, male 31%, hypertension 21%, diabetes 3%, asthma 17%</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events</p>	
<p>WHO SOLIDARITY trial;¹³⁰ Pan et al; preprint; 2020</p>	<p>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</p>	<p>Age < 70 years 61%, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%, chronic kidney disease %</p>	<p>Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%</p>	<p>Low for mortality and 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>Davoodi et al;¹⁰⁶ peer-reviewed; 2020</p>	<p>Patients with moderate to severe COVID-19 infection. 30 assigned to Febuxostat 80 mg per day and 30 assigned to hydroxychloroquine</p>	<p>Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%</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 probably inappropriate.</p>	

COVID-19 PEP (University of Washington) trial ; Barnabas et al; ¹³¹ 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 ; ¹³² 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%,	Steroids 18.4%, remdesivir 21.7%, azithromycin 19%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
HAHPS trial ; ¹³³ Brown et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19. 42 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 5 days and 43 assigned to azithromycin	Median age 55 ± 23, male 61%, diabetes 26%, coronary heart disease 11%, chronic kidney disease 9%, cerebrovascular disease 8%, cancer 2%	Steroids 15%, remdesivir 11%, lopinavir-ritonavir 1%, tocilizumab 24%, convalescent plasma 24%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Co-interventions were not balanced between study arms	
HYCOVID trial ; ¹³⁴ 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%	Steroids 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 ; ¹³⁵ Omrani et	Patients with mild COVID-19. 152	Mean age 41 ± 16, male 98.4%,	NR	Low for mortality and mechanical ventilation;	

al; peer-reviewed; 2020	assigned to hydroxychloroquine 600 mg daily for 7 days and 152 assigned to hydroxychloroquine + azithromycin			low for symptom resolution, infection and adverse events
Dabbous et al; ¹³⁶ 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 probably inappropriate.
HYDRA trial; ¹³⁷ 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%	Steroids 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; ¹³⁸ Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to HCQ 800 mg once followed by 400 mg a day for 10 days, 65 assigned to HCQ + AZT 500 mg once followed by 250 mg a day for 5 days and 65 assigned to SOC	Median age 37 ± , male 43.3%, hypertension 20.9%, diabetes 11.6%, COPD 9.3%, asthma 1.6%, immunosuppressive therapy 0.8%, obesity 76%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
Purwati et al; ¹³⁹ 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 probably inappropriate.
Beltran et al ; ¹⁴⁰ 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%	Steroids 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 probably inappropriate.
PATCH 1 trial ; ¹⁴¹ 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 ; ¹⁴² 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%	Steroids 98%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
Seet et al ; ¹⁴³ 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 ; ¹⁴⁴ 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 ; ¹⁴⁵ 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%	Steroids 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 probably inappropriate.	
CHEER trial ; ¹⁴⁶ 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 probably inappropriate.	
ProPAC-COVID trial ; ¹⁴⁷ Sivapalan et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 61 assigned to HCQ + AZT 400mg plus 500 to 250mg 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%	Steroids 32%, remdesivir 25%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
HONEST trial ; ¹⁴⁸	Patients with	Median age 32 ± 27,	NR	Low for mortality and	

Byakika-Kibwika et al; preprint; 2021	moderate COVID-19 infection. 55 assigned to HCQ 800mg once followed by 400mg a day for 5 days and 50 assigned to SOC	male 72%, hypertension 2.8%, diabetes 2.8%, COPD %, CHD 0.9%		mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SEV-COVID trial ; ¹⁴⁹ Singh et al; preprint; 2021	Patients with severe COVID-19 infection. 20 assigned to Ribavirin + HCQ (dosage not reported) and 21 assigned to SOC	Mean age 53.3 ± , male 77.2%, hypertension 34%, diabetes 27.2%, COPD 13.6%, asthma 2.2%, CHD 20.4%, cancer 0%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

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
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RCT

Hadanny et al ; ¹⁵⁰ preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric Oxygen two sessions a day for 4 days and 9 assigned to SOC	Median age 65.4 ± 7.8, male 60%, hypertension 72%, diabetes 60%, COPD %, asthma 8%, CHD 24%, cancer 4%, obesity 8%	Steroids 92%, tocilizumab 24%, convalescent plasma 80%	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: 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>
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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

<p>Ali et al.¹⁵¹ peer reviewed; 2021</p>	<p>Patients with severe to critical COVID-19 infection. 40 assigned to C-IVIG 0.15-0.3 gr/kg once and 10 assigned to SOC</p>	<p>Mean age 56.5 ± 13.1, male 70%, hypertension 52%, diabetes 36%, COPD 10%, CHD 8%</p>	<p>Steroids 100%, remdesivir 94%, tocilizumab 6%</p>	<p>Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: 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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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. ¹⁵² 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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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. ¹⁵³ peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1 800 mg IV with a maximum of seven doses and 15 assigned	Mean age 60 ± 9, male 73%, hypertension 30%, diabetes 27%, obesity 20%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information
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	to standard of care			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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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

<p>CATALYST trial¹⁵⁴ Fisher et al; preprint; 2021</p>	<p>Patients with moderate to critical COVID-19 infection. 29 assigned to infliximab and 34 assigned to SOC</p>	<p>Median age 64.5 ± 20, male 61.8%</p>	<p>Steroids 94.3%, remdesivir 61.8%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	<p>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
RCT					
Lopardo et al; ¹⁵⁵ peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005 4 mg/kg in two doses on days 1 and 3 and 123 assigned to SOC	Mean age 53.8 ± 12.5, male 65.1%, comorbidities 80%	Steroids 57.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: RR 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>

Interferon alpha-2b and Interferon gamma

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ESPERANZA trial ; ¹⁵⁶ Esquivel-Moynelo et al; preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to interferon alpha-2b plus interferon gamma twice a week for two weeks (standard care) and 33 assigned to interferon alpha-2b three times a week (IM)	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%, coronary heart disease 6.3%, any comorbidities 50.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, antibiotics 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Interferon beta-1a

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Davoudi-Monfared et al ; ¹⁵⁷ preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%,	Steroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	Mortality: RR 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to 3.7%); Moderate certainty ⊕⊕⊕○

	times a week and 39 assigned to standard of care	asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	30.8%	events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Invasive mechanical ventilation: RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕○
WHO SOLIDARITY ; ¹³⁰ 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%,	Steroids 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: HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
COVIFERON trial ; ¹⁵⁸ 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.	Adverse events: No information Hospitalization: No information
Darazam et al ; ¹⁵⁹ 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%	Steroids 1.1%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Monk P et al , ¹⁶⁰ 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 , ¹⁶¹ peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to Interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to standard of care	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%,	Steroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low certainty ⊕○○○</p> <p>Symptom resolution or improvement: Very low certainty ⊕○○○</p>
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		immunosuppression NR%, cancer 3%, obesity NR%		inappropriate.	Symptomatic infection (prophylaxis studies): No information
COVIFERON trial ¹⁵⁸ 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.	Adverse events: No information Hospitalization: No information

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 ¹⁶² 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 probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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Interferon kappa plus TFF2

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Fu et al ; ¹⁶³ peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2 mg once a day for six days and 40 assigned to standard of care	Mean age 35.2 ± 11.2, male 63.7%, hypertension 5%, diabetes 3.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Iota-Carrageenan

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
IVERCAR-TUC trial ; ¹⁶⁴ Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin +Iota-Carrageenan 12 mg a week + 6	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	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information

	sprays a day for 4 weeks and 117 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information Symptom resolution or improvement: No information
CARR-COV-02 trial ; ¹⁶⁵ 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
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RCT

ITOLI-C19-02-I-00 trial ; ¹⁶⁶ 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 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
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Ivermectin					
Ivermectin may not reduce mortality and mechanical ventilation requirements, and probably does not improve time to symptom resolution. It is uncertain if it affects symptomatic infection as prophylaxis, hospitalizations 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 ; ¹⁶⁷ 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 probably inappropriate.	Mortality: RR 0.92 (95%CI 0.54 to 1.57); RD -1.3% (95%CI -7.4% to 9.1%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 1.01 (95%CI 0.6 to 1.72); RD 0.2% (95%CI -6.9% to 12.5%); Very low certainty ⊕○○○
Chowdhury et al ; ¹⁶⁸ 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 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 ; ¹⁶⁹ peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 µgm/kg once and 30	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	

	assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Adverse events: RR 1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.3%); Very low certainty ⊕○○○
Hashim et al , ¹⁷⁰ 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 %	Steroids 100%, 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.	Hospitalization: , RR 0.51 (95%CI 0.18 to 1.43); RD -0.5% (95%CI -8.4% to 4.4%); Very low certainty ⊕○○○
Mahmud et al , ¹⁷¹ 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), ¹⁷² preprint; 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 probably inappropriate.	
Elgazzar et al (severe), ¹⁷² preprint; 2020	Patients with severe COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4	Mean age 58.9 ± 19.5, male 71%, hypertension 16%, diabetes 20%, COPD %, asthma 13%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and	

	days and 100 assigned to hydroxychloroquine	coronary heart disease 7.5%		adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Elgazzar et al (prophylaxis); ¹⁷² preprint; 2020	Patients exposed to COVID-19. 100 assigned to ivermectin 400 µg/kg twice (second dose after one week) and 100 assigned to standard of care	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Krolewiecki et al ; ¹⁷³ 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 ; ¹⁷⁴ 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 ; ¹⁷⁵	Patients with mild	Mean age 42 , male 46%,	NR	High for mortality and

peer-reviewed; 2020	COVID-19. 55 assigned to ivermectin 12 mg a day for 5 days +/- doxycycline and 23 assigned to standard of care			mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.
SAINT trial ; ¹⁷⁶ 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 ; ¹⁷⁷ 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 probably inappropriate.
Babalola et al ; ¹⁷⁸ 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%,	Steroids 3.2%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:
Kirti et al ; ¹⁷⁹ 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	Steroids 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 ; ¹⁶⁴ 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 probably inappropriate.
Mohan et al ; ¹⁸⁰ Preprint; 2020	Patients with mild to moderate COVID-19 infection. 80 assigned to ivermectin 12 to 24mg once and 45 assigned to SOC	Mean age 35.3 ± 10.4, male 88.8%, hypertension 11.2%, diabetes 8.8%, CHD 0.8%,	Steroids 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 ; ¹⁸¹ 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 ; ¹⁸² Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to ivermectin 0.2 mg/kg once or SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. RoB assessment from secondary sources as publication not available.

<p>Samaha et al.¹⁸³ peer-reviewed; 2020</p>	<p>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</p>	<p>Mean age 31.6 ± 7.7, male 50%, hypertension 8%, diabetes 6%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Randomization process and concealment of allocation probably inappropriate.</p>	
<p>Bukhari et al.¹⁸⁴ Preprint; 2020</p>	<p>Patients with mild to moderate COVID-19. 45 assigned to ivermectin 12 mg once and 41 assigned to SOC</p>	<p>NR</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>Okumus et al.¹⁸⁵ peer-reviewed; 2021</p>	<p>Patients with severe COVID-19. 30 assigned to ivermectin 0.2 mg/kg for 5 days and 30 assigned to SOC</p>	<p>Mean age 62 ± 12, male 66%, hypertension 21.6%, diabetes 45%, COPD 1.6%, CHD 1.6%, cancer 1.6%</p>	<p>NR</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study. Concealment of allocation probably inappropriate.</p>	
<p>Beltran et al.¹⁴⁰ Preprint; 2021</p>	<p>Patients with moderate to severe COVID-19. 36 assigned to ivermectin 12-18 mg once and 37 assigned to SOC</p>	<p>Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%</p>	<p>Steroids 9.6%, lopinavir-ritonavir 44.7%</p>	<p>High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>	

Lopez-Medina et al , ¹⁸⁶ 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%	Steroids 4.5%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events
Bermejo Galan et al , ¹⁴² 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%	Steroids 98%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events
Pott-Junior et al , ¹⁸⁷ 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%	Steroids 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 , ¹⁸⁸ 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 , ¹⁴³ peer-reviewed; 2021	Patients exposed to COVID-19 infection. 617 assigned to ivermectin 12 mg once	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and

	and 619 assigned to SOC (vitamin C)			adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Abd-Elsalam et al. ¹⁸⁹ 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. ¹⁹⁰ preprint; 2021	Patients with mild recent onset COVID-19 infection. 47 assigned to ivermectin 48 to 55 mg administered during 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. ¹⁹¹ 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 probably inappropriate.	

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. ¹⁹² preprint; 2020	Patients with severe COVID-19 infection. 16 assigned to IVIG 0.5 g/kg/day for 3 days and 17 assigned to standard of care	Mean age 54 ± NR, male 60.6%, hypertension 33.3%, diabetes 36.3%, chronic lung disease 12%, coronary heart disease 3%, chronic kidney disease 3%, immunosuppression 3%	Steroids 78.7%, remdesivir 51.5%, convalescent plasma 15.2%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○
Gharebaghi et al. ¹⁹³ preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to IVIG 5 gr 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.	Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○
Tabarsi et al. ¹⁹⁴ 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 probably inappropriate.	Hospitalization: No information

Raman et al ; ¹⁹⁵ Peer reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to IVIG 0.4/gr/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 probably inappropriate.	
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KB109 (microbiome modifcator)

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

Study; publication status	Patients 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 ; ¹⁹⁶ preprint; 2021	Patients with mild to moderate COVID-19 infection. 169 assigned to KB109 9-36 gr 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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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 ; ¹⁹⁷ Endam et al; preprint; 2021	Patients with mild recently diagnosed COVID-19 infection. 12 assigned to Lactococcus lactis (intranasal) two nasal irrigations a day and 11 assigned to SOC	Mean age 30.4 ± 9.1, male 30%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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
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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
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RCT

Hu et al ; ¹⁹⁸ peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50 mg	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,	Mortality: No information Invasive mechanical
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	every 12 hs (three doses) followed by 20 mg a day for 10 days and 5 assigned to standard of care			infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
Wang et al; ¹⁹⁹ 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%	Steroids 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 probably inappropriate.	

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; ²⁰⁰ Temesgen et al; preprint; 2021	Patients with severe COVID-19 infection. 236 assigned to lenzilumab 1800 mg once and 243 assigned to SOC	Mean age 60.5 ± 13.9, male 64.7%, diabetes 53.4%, COPD 7.3%, asthma 10.6%, CHD 13.6%, CKD 14%	Steroids 93.7%, remdesivir 72.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: RR 0.7 (95%CI 0.42 to 1.15); RD -4.8% (95%CI -9.3% to 2.4%); Low certainty ⊕⊕⊕○ Invasive mechanical ventilation: RR 0.71 (95%CI 0.48 to 1.04); RD -5% (95%CI -9% to 0.7%); Low certainty ⊕⊕⊕○ Symptom resolution or improvement: No
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					<p>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>
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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
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RCT

<p>Roostaei et al.²⁰¹ Preprint; 2020</p>	<p>Patients with mild to moderate COVID-19. 25 assigned to levamisole 150 mg a day for 3 days and 25 assigned to SOC</p>	<p>Mean age 36.6 ± 13.7, male 60%,</p>	<p>Hydroxychloroquine 100%,</p>	<p>High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events</p> <p>Notes: Concealment of allocation probably inappropriate.</p>	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: Mortality: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: No information</p> <p>Hospitalization: Very low certainty</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

Guvenmez et al. ³⁸ peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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
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RCT

LOTUS China	Patients with severe to	Median age 58 ± 9.5,	Steroids 33.7%,	Low for mortality and	Mortality: RR 1.01
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trial ; ²⁰² Cao et al; peer-reviewed; 2020	critical COVID-19 infection. 99 assigned to lopinavir-ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	remdesivir NR%, IFN 11.1%, ATB 95%	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.	(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 ; ²⁰³ 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%	Steroids 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): No information 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 ; ²⁰⁴ Horby et al; other; 2020	Patients with mild to critical COVID-19 infection. 1616 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days and 3424 assigned to standard of care	Mean age 66.2 ± 15.9, male 60.5%, diabetes 27.5%, chronic lung disease 23.5%, coronary heart disease 26%	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Hospitalization: Very low certainty ⊕○○○
Huang et al ; peer-reviewed; ¹¹² 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500 mg twice a day for 10	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	

	days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Zheng et al; preprint; ²⁰⁵ 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Chen et al; preprint; ²⁰⁶ 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2gr IV loading dose followed by orally 400-600 mg every 8 hours for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
WHO SOLIDARITY-trial; ¹³⁰ 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%	Steroids 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 ; ²⁰⁷ 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 probably inappropriate.	
Purwati et al ; ²⁰⁸ 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 probably inappropriate.	
Kasgari et al ; ²⁰⁹ 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 probably inappropriate.	
Yadollahzadeh et al ; ²¹⁰ Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/daclatasvir	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	400/60 mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100 mg twice a day for 7 days	CKD 6.2%, immunosuppression 3.6%, cancer 10.7%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
TOGETHER trial ; ¹⁴⁴ Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 244 assigned to lopinavir-ritonavir 1600 mg/400 mg once followed by 800 mg/200 mg a day for 9 days and 227 assigned to SOC	Mean age 53 ± 76, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
SEV-COVID trial ; ¹⁴⁹ Singh et al; preprint; 2021	Patients with severe COVID-19 infection. 20 assigned to Ribavirin + Lopinavir-Ritonavir (dosage not reported) and 21 assigned to SOC	Mean age 53.3 ±, male 77.2%, hypertension 34%, diabetes 27.2%, COPD 13.6%, asthma 2.2%, CHD 20.4%, cancer 0%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Low-dose radiation therapy

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COVID-RT-01 trial ; ²¹¹ 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%,	Steroids 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

					<p>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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Mavrilimumab

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

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

<p>MASH-COVID trial;²¹² 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>
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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. ²¹³ Preprint; 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 probably inappropriate. Significant loss to follow-up.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Mesenchymal stem cell transplantation

Mesenchymal stem cell transplantation may reduce mortality.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Shu et al. ²¹⁴ peer-reviewed; 2020	Patients with severe COVID-19 infection. 12 assigned to mesenchymal stem cell 2×10^6 cells/kg one	Median age 61 ± 10, male 58.5%, hypertension 22%, diabetes 19.5%	Steroids 100%, antibiotics 87.8%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	Mortality: RR 0.59 (95%CI 0.37 to 0.93); RD -6.2% (95%CI -9.8% to -1%); Low certainty ⊕⊕○○

	infusion and 29 assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
Shi et al. , ²¹⁵ 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%	Steroids 22%	Low for mortality and mechanical ventilation	Symptomatic infection (prophylaxis studies): No information Adverse events: No information
Lanzoni et al. , ²¹⁶ 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%	Steroids 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. , ²¹⁷ peer reviewed; 2021	Patients with critical COVID-19 infection. 20 assigned to mesenchymal stem cell one 100 ml infusion and 20 assigned to SOC	age >60 45%, male 75%, hypertension 42.5%, diabetes 50%, CHD 25%, CKD 17.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Methylene blue

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

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

Hamidi-Alamdari et al. ²¹⁸ peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to methylene blue 1 mg/kg every 12 to 8hs for 14 days and 40 assigned to SOC	Mean age 54 ± 13, male 52.5%, hypertension 17.5%, diabetes 10%	Steroids 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 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. ²¹⁹ peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to metisoprinol 1500 mg/kg/day for 14 days and 30 assigned to	Mean age 33.2 ± 16, male 53.3%, COPD 10%, CKD 16.6%, cancer 3.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p>
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	SOC			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: No information</p> <p>Hospitalization: No information</p>
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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
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RCT

Painter et al; ²²⁰ Preprint; 2020	Patients with mild to moderate COVID-19. 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	<p>Mortality: No information</p> <p>Invasive mechanical ventilation: No information</p>
AGILE trial; ²²¹ 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	<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>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p>
Fischer et al; ²²² peer reviewed; 2021	Patients with mild to moderate COVID-19	Age >65 6%± , male 48.6%	NR	Low for mortality and mechanical ventilation;	Hospitalization: No information

	infection. 140 assigned to molnupiravir 200 to 800mg twice a day for 5 days and 62 assigned to SOC			low for symptom resolution, infection and adverse events	
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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
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RCT

Mukhtar et al; ²²³ 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%	Steroids 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 probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○
GARGLES trial; ²²⁴ 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 probably inappropriate.	Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
KILLER trial; ²²⁵ 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	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	Adverse events: No information

	to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Elzein et al; ²²⁶ 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 probably inappropriate.	
Santos et al; ²²⁷ 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; ²²⁸ 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; ²²⁹ peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 66 assigned to mouthwash chlorhexidine 0.12% 15 ml twice a day for 4 days and 55 assigned to SOC	Median age 62 ± 66, male 58%	Steroids 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.	
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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
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RCT

ARMY-1 trial , ²³⁰ 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%	Steroids 100%, hydroxychloroquine 26.2%, tocilizumab 12%, convalescent plasma 7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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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 , ²³¹ peer-reviewed; 2020	Patients with severe COVID-19. 68 assigned to NAC 21 gr once and 67 assigned	Mean age 58.5 ± 22.5, male 59.2%, hypertension 46.6%, diabetes 37.7%, cancer	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution,	Mortality: Very low certainty ⊕○○○ Invasive mechanical
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	to standard of care	12.6%,		infection and adverse events	ventilation: Very low certainty ⊕○○○
Gaynitdinova et al. ; ²³² 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 probably inappropriate.	Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○
Taber et al. ; ²³³ peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 47 assigned to NAC 40 mg/kg a day for 3 days and 45 assigned to SOC	Mean age 57.6 ± 18.7, male 58.7%, diabetes 23.9%, COPD 15.2%, asthma %, CHD 28.2%,	Steroids 69.6%, hydroxychloroquine 90.2%, azithromycin 51.1%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	Hospitalization: No information

Namilumab

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

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

CATALYST trial ; ¹⁵⁴ 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%	Steroids 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 probably	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
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				inappropriate.	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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

<p>Kimura et al.²³⁴ peer-reviewed; 2020</p>	<p>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</p>	<p>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%,</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 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>
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Neem (Azadirachta Indica A. Juss)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Nesari et al. , ²³⁵ 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 probably inappropriate. Significant lost to follow-up.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: No information Hospitalization: No information

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 , ²³⁶ Rocco et al; preprint; 2020	Patients with mild COVID-19. 194 assigned to nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	Age range 18 - 77, male 47%, comorbidities 13.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement:

				introduced bias to symptoms and adverse events outcomes results. Significant lost to follow up.	Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information
Fontanesi et al , ²³⁷ 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 , ²³⁸ preprint; 2021	Patients with mild to moderate COVID-19 infection. 23 assigned to nitazoxanide 2-3 gr 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 probably inappropriate.	
Vanguard trial , ²³⁹ Rossignol et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 184 assigned to nitazoxanide 600 mg a day for 5 days and 195 assigned to SOC	Mean age 40.3 ± 15.4, male 43.5%, comorbidities 34%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	

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. , ²⁴⁰ 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. , ²⁴¹ 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 probably inappropriate.	Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Novaferon

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zheng et al. , ²⁰⁵ preprint; 2020	Patients with moderate to severe	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical	Mortality: No information

	COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir			ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information
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Non-steroidal anti-inflammatory drugs (NSAID)

Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However certainty of the evidence is very low 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 and GRADE certainty of the evidence
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Non-RCT

Eilidh et al; ²⁴² peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 54 received NSAID and 1168 received alternative treatment schemes	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%, coronary heart disease 22.3%, chronic kidney disease 38.7%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function)	Mortality: OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕○○○
Jeong et al; ²⁴³ preprint; 2020	Patients with moderate to severe	Age >65 36%, male 41%, hypertension 20%,	NR	High for mortality and invasive mechanical	

	COVID-19 infection. 354 received NSAID and 1470 received alternative treatment schemes	diabetes 12%, chronic lung disease 16%, asthma 6%, chronic kidney disease 2%, cancer 6%		ventilation Notes: Non-randomized study with retrospective design. Propensity score and IPTW were implemented to adjust for potential confounders (age, sex, health insurance type, hypertension, hyperlipidemia, diabetes mellitus, malignancy, asthma, chronic obstructive pulmonary disease, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal, conditions, and use of co-medications)	
Lund et al , ²⁴⁴ peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 224 received NSAID and 896 received alternative treatment schemes	Median age 54 ± 23, male 41.5%, chronic lung disease 3.9%, asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%	Steroids 7.1%	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and matching were implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, and phase of the outbreak)	
Kinott et al , ²⁴⁵ peer-reviewed; 2020	Patients with moderate to critical	Median age 45 ± 37, male 54.6%, diabetes	NR	High for mortality and invasive mechanical	

	COVID-19 infection. 87 received NSAID and 316 received alternative treatment schemes	9.4%, coronary heart disease 12.9%,		ventilation Notes: Non-randomized study with retrospective design. No adjustment for potential confounders.
Wong et al. , ²⁴⁶ 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%,	Steroids 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. , ²⁴⁷ 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. , ²⁴⁸ 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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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
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RCT

Sedighyan et al ; ²⁴⁹ 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 probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information
Doaei et al ; ²⁵⁰ 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 probably inappropriate. Significant lost to follow up.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Otilimab

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

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

OSCAR trial ; ²⁵¹ 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%	Steroids 83%, remdesivir 34%, tocilizumab 1.2%, convalescent plasma 6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: No information</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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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

PROBIOZOVID trial ; ²⁵² Araimo et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 14 assigned to ozone 250 ml ozonized blood and	Mean age 61.7 ± 13.2, male 50%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No</p>
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	14 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information Symptom resolution or improvement: Very low certainty ⊕○○○
SEOT trial ; ²⁵³ Shah et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to ozone 150 ml rectal insufflation plus 5 ml with venous blood once a day for 10 days and 30 assigned to SOC	Mean age 43.8 ± 9, male 80%, diabetes 10%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Peg-interferon (IFN) alfa

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

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

PEGL20.002 trial ; ²⁵⁴ 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 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
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					Hospitalization: No information
Peg-interferon (IFN) lamda Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ILLAD trial ; ²⁵⁵ 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 Notes:	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: Very low certainty ⊕○○○
COVID-Lambda trial ; ²⁵⁶ Jagannathan et al; preprint; 2020	Patients with mild COVID-19. 60 assigned to Peg-IFN lambda 180 mcg subcutaneous injection once and 60 assigned to standard of care	Median age 36 ± 53, male 68.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○

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
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RCT

Maldonado et al. ²⁵⁷ 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 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
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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
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RCT

BCR-PNB-001 trial ²⁵⁸ 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	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information
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				study. Concealment of allocation probably inappropriate.	<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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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
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RCT

Mendez-Flores et al. , ²⁵⁹ 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%	Steroids 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>
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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
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RCT

Seet et al ; ¹⁴³ 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 ⊕○○○
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Progesterone

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

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

Ghandehari et al ; ²⁶⁰	Patients with severe	Mean age 55.3 ± 16.4,	Steroids 60%,	High for mortality and	Mortality: Very low
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preprint; 2020	COVID-19. 18 assigned to progesterone 100 mg twice a day for 5 days and 22 assigned to standard of care	male 100%, hypertension 48%, diabetes 25%, obesity 45%	remdesivir 60%, hydroxychloroquine 2.5%, tocilizumab 12.5%, azithromycin 50%, convalescent plasma 5%	mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	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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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
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RCT

Prolectin-M trial ; ²⁶¹ Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 gr 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 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
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					information Hospitalization: No information
Propolis Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Bee-Covid trial ; ²⁶² 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%	Steroids 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

Proxalutide

Proxalutide may improve time to symptom resolution and reduce hospitalizations. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cadegiani et al. , ²⁶³ Preprint; 2020	Patients with mild COVID-19. 114 assigned to proxalutide 200 mg a day for 15 days and 100 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Randomization and concealment methods probably not appropriate	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: RR 3.34 (95%CI 2.17 to 5.15); RD 57.1% (95%CI -28.5% to 76%); Low certainty ⊕○○○
AB-DRUG-SARS-004 trial , ²⁶⁴ Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 171 assigned to proxalutide 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.	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: RR 0.02 (95%CI 0.001 to 0.26); RD -7.3% (95%CI -7.4% to -5.5%); Low certainty ⊕⊕○○

Pyridostigmine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PISCO trial ; ²⁵⁵ 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%	Steroids 74.5%, tocilizumab 5.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○ Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information

Quercetin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Onal et al ; ²⁶⁶ Preprint; 2020	Patients with moderate to severe COVID-19. 52 assigned to Quercetin	Age > 50 65.7%, male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No

	1000 mg and 395 assigned to SOC	13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%		adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study	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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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
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RCT

RASTAVI trial , ²⁶⁷ 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
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Recombinant Super-compound Interferon

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

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

Li et al. , ²⁶⁸ 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%	Steroids 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 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>
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REGEN-COV (casirivimab and imdevimab)

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

Study; publication status	Patients 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

Weinreich et al. , ²⁶⁹ preprint; 2020	Patients with recent onset mild disease with risk factors COVID-	Median age 50 ± 21, male 48.7%, obesity 58%, comorbidities	NR	Low for mortality and mechanical ventilation; low for symptom	<p>Mortality: RR 0.94 (95%CI 0.87 to 1.02); RD -1% (95%CI -</p>
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	19 infection. 2091 assigned to REGEN-COV (casirivimab and imdevimab) 1.2 to 2.4 gr single infusion and 2089 assigned to SOC	100%		resolution, infection and adverse events	2.1% to 0.3%); Moderate certainty ⊕⊕⊕○ Mortality (seronegative): RR 0.8 (95%CI 0.7 to 0.91); RD -3.2% (95%CI -4.8% to -1.4%); Moderate certainty ⊕⊕⊕○
RECOVERY-REGEN-COV trial ; ²⁷⁰ Horby et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 4839 assigned to REGEN-COV (Regeneron) 8 gr once and 4946 assigned to SOC	Mean age 61.9 ± 14.4, male 63%, diabetes 26.5%, COPD %, CHD 21%, CKD 5%	Steroids 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 0.96 (95%CI 0.89 to 1.03); RD -0.7% (95%CI -1.9% to -0.5%); Moderate certainty ⊕⊕⊕○ Invasive mechanical ventilation (seronegative): RR 0.88 (95%CI 0.73 to 1.06); RD -2.1% (95%CI -4.7% to 1%); Low certainty ⊕⊕○○
O'Brien et al ; ²⁷¹ preprint; 2021	Patients exposed to COVID-19 infection. 100 assigned to REGEN-COV (Regeneron) 1.2 gr once and 104 assigned to SOC	Mean age 40.9 ± 18, male 45.4%, diabetes 7.8%, CKD 2.5%, immunosuppressive therapy 1.5%, obesity 13.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	Symptom resolution or improvement: RR 1.06 (95%CI 0.96 to 1.16); RD 3.6% (95%CI -2.4% to 9.7%); Moderate certainty ⊕⊕⊕○ Symptom resolution or improvement: RR 1.12 (95%CI 1.01 to 1.25); RD 7.2% (95%CI 0.6% to 15.1%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): RR 0.69 (95%CI 0.47

					<p>to 1.0); RD -5.5% (95%CI -9.2% to 0%); Low certainty ⊕⊕○○</p> <p>Adverse events: RR 0.63 (95%CI 0.48 to 0.81); RD -3.8% (95%CI -5.3% to -1.9%); Moderate certainty ⊕⊕⊕○</p> <p>Hospitalization: RR 0.29 (95%CI 0.18 to 0.44); RD -5.3% (95%CI -6.1% to -4.1%); Moderate certainty ⊕⊕⊕○</p>
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Regdanvimab (monoclonal antibody)

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

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

<p>Eom et al.²⁷² Preprint; 2021</p>	<p>Patients with mild to moderate COVID-19 infection. 204 assigned to regdanvimab 40-80 mg/kg once and 103 assigned to SOC</p>	<p>Mean age 51 ± 20, male 44.6%, comorbidities 73%</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: RR 0.94 (95%CI 0.82 to 1.08); RD 13.9% (95%CI 1.8% to 27.3%); Low certainty ⊕⊕○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p>
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					<p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: Very low certainty ⊕○○○</p>
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Remdesivir

Remdesivir may slightly reduce mortality, mechanical ventilation requirement and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.

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

<p>ACTT-1 trial; Beigel et al;²⁷³ peer-reviewed; 2020</p>	<p>Patients with mild to critical COVID-19 infection. 541 assigned to remdesivir intravenously 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death and 522 assigned to standard of care</p>	<p>Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: RR 0.95 (95%CI 0.83 to 1.08); RD -0.8% (95%CI -2.7% to 1.3%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: RR 0.71 (95%CI 0.43 to 1.18); RD -5% (95%CI -9.9% to 3.1%); Low certainty ⊕⊕○○</p> <p>Symptom resolution or improvement: RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⊕⊕○○</p>
<p>SIMPLE trial; Goldman et al;²⁷⁴ peer-reviewed; 2020</p>	<p>Patients with severe COVID-19 infection. 200 assigned to remdesivir (5 days) 200 mg once followed 100 mg for 5 days and 197 assigned to remdesivir (10 days)</p>	<p>Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%</p>	<p>NR</p>	<p>Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events</p> <p>Notes: Non-blinded study which might have introduced bias to</p>	<p>Symptomatic infection (prophylaxis studies): No information</p> <p>Severe Adverse events: RR 0.8</p>

				symptoms and adverse events outcomes results.	(95%CI 0.48 to 1.33); RD -2% (95%CI -5.3% to 3.4%); Low certainty ⊕⊕○○
CAP-China remdesivir 2 trial ; ²⁷⁵ 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%	Steroids 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; ²⁷⁶ 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%	Steroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	Some Concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY ; ¹³⁰ Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2743 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 2708 assigned to standard of care	age < 70 years 61%, male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Mahajan et al ; ²⁷⁷	Patients with mild to	Mean age 57.7 ± 13.1,	NR	High for mortality and	

peer reviewed; 2021	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	male 65.5%, hypertension 45.7%, diabetes 60%, asthma 1.4%, CHD 12.9%, CKD 4.3%		mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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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 ; ²⁷⁸ 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 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>Severe Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Ribavirin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Chen et al; ²⁰⁶ preprint; 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 gr 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 probably inappropriate.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Ribavirin plus Interferon beta-1b

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hung et al. ²⁷⁹ 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%	Steroids 6.2%, ATB 53.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Mortality: No information Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: No information

Ruxolitinib

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cao et al. ²⁸⁰ 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%,	Steroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	Mortality: No information Invasive mechanical ventilation: No information

					<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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Sarilumab

Sarilumab may reduce mortality and mechanical ventilation requirements. However 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
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RCT

REMAP-CAP-tocilizumab trial ; ²⁸¹ 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 %	Steroids 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.	<p>Mortality: RR 0.9 (95%CI 0.75 to 1.09); RD -1.6% (95%CI -4% to 1.4%); Low certainty ⊕⊕○○</p> <p>Invasive mechanical ventilation: RR 0.67 (95%CI 0.42 to 1.05); RD -5.6% (95%CI -10% to 0.8%); Low certainty ⊕⊕○○</p>
Lescure et al ; ²⁸² 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%	Steroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	<p>Symptom resolution or improvement: RR 0.99 (95%CI 0.92 to 1.08); RD -0.6% (95%CI -4.8% to 4.8%); Low certainty ⊕⊕○○</p>

Sarilumab-COVID19 Study trial ; ²⁸³ Sivapalasingam, et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 1136 assigned to sarilumab 200-400 mg once and 309 assigned to SOC	Critical patient population: Mean age 61 ± 20, male 68.4%, hypertension 52.1%, diabetes 18.7%, obesity 46.5%	Steroids 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 1.02 (95%CI 0.89 to 1.17); RD 0.2% (95%CI -1.1% to 1.7%); Low certainty ⊕⊕○○ Hospitalization: No information
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Short-wave diathermy

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

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

Tian et al , ²⁸⁴ 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
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Sofosbuvir +/- daclatasvir, ledipasvir 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; ²⁰⁹ 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 probably inappropriate.	Mortality: RR 1.13 (95%CI 0.82 to 1.55); RD 2% (95%CI -2.9% to 8.8%); Low certainty ⊕⊕○○ Invasive mechanical ventilation: RR 1.04 (95%CI 0.29 to 3.7); RD 0.7% (95%CI -12.3% to 46.7%); Very low certainty ⊕○○○
Sadeghi et al; ²⁸⁵ 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%	Steroids 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 probably inappropriate.	Symptom resolution or improvement: RR 0.97 (95%CI 0.9 to 1.06); RD -1.8% (95%CI -6% to 3.6%); Moderate certainty ⊕⊕⊕○ Symptomatic infection (prophylaxis studies): No information
Yakoot et al; ²⁸⁶ preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 10 days and 45 assigned to standard of	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %, asthma 1%, coronary heart disease 8%	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of	Adverse events: No information Hospitalization: Very low certainty ⊕○○○

	care			allocation probably inappropriate.
Roozbeh et al; ²⁸⁷ 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; ²⁰⁷ 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 probably inappropriate.
DISCOVER trial; ²⁸⁸ Mobarak et al; Preprint; 2021	Patients with moderate to severe COVID-19 infection. 541 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 10 days and 542 assigned to SOC	Median age 58 ± 54, male 54%, hypertension 34%, diabetes 27.6%, COPD 2.1%, asthma 4.8%, CHD 9.1%	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; ²⁸⁹ Preprint; 2021	Patients with severe to critical COVID-19 infection. 27 assigned to sofosbuvir 400 mg a day and 30 assigned to SOC	Mean age 57.2 ±, male 49.1%, hypertension 21%, diabetes 29.8%, COPD 7%, CHD 19.3%, CKD 1.7%, obesity 1.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably

				inappropriate.	
Yadollahzadeh et al. , ²¹⁰ 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 probably inappropriate.	
Khalili et al. , ²⁹⁰ 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%,	Steroids 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. , ²⁹¹ preprint; 2021	Patients with moderate COVID-19 infection. 125 assigned to sofosbuvir/ledipasvir 400/90 mg once a day for 15 days and 125 assigned to SOC	Mean age 43 ±, male 0.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
SOVECOD trial , ²⁹² Sayad et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to sofosbuvir/velpatasvir 400/100mg once a day for 10 days and 40	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	

	assigned to SOC			study which might have introduced bias to symptoms and adverse events outcomes results.	
Sotrovimab					
Sotrovimab probably reduces hospitalizations in patients with mild recent onset COVID-19 with risk factors for severe disease.					
Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COMET-ICE trial ; ²⁹³ Gupta et al; preprint; 2021	Patients with recent onset mild to moderate COVID-19 infection, with risk factors for severity progression. 291 assigned to sotrovimab 500 mg once and 292 assigned to SOC	Median age 53 ±, male 46%, diabetes 23%, COPD 4%, asthma 16%, CKD 0.7%, obesity 63%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: Stopped early for benefit	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕○○ Hospitalization: RR 0.14 (95%CI 0.04 to 0.48); RD -6.3% (95%CI -7.1% to -3.8%); Moderate certainty ⊕⊕⊕○

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
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RCT

RESIST trial , ³³ 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%	Steroids 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
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Stem cell nebulization

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

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

SENTAD-COVID trial , ²⁹⁴ 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	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	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information
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	assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	<p>Symptom resolution or improvement: Very low certainty ⊕○○○</p> <p>Symptomatic infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>
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Steroids

Steroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Steroids may not significantly increase the risk of 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

GLUCOCOVID trial ; ²⁹⁵ 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 probably inappropriate.	<p>Mortality: RR 0.90 (95%CI 0.80 to 1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕○</p> <p>Invasive mechanical ventilation: RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕○</p>
Metcovid trial ; ²⁹⁶ 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	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease 0.5%, asthma 2.5%, coronary heart disease	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	<p>Symptom resolution or improvement: RR 1.27 (95%CI 0.98 to 1.65); RD 16.4% (95%CI -1.2% to</p>

	assigned to standard of care	6.9%, alcohol use disorder 27%, liver disease 5.5%			39.4%); Low certainty ⊕⊕○○
RECOVERY-Dexamethasone trial ; ²⁹⁷ Horby et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 2104 assigned to dexamethasone 6 mg once daily for 10 days and 4321 assigned to standard of care	Mean age 66.1 ± 15.7, male 64%, diabetes 24%, chronic lung disease 21%, asthma NR%, coronary heart disease 27%, chronic kidney disease 8%, liver disease 2%, any comorbidities 56%	Steroids NA%, remdesivir 0.08%, hydroxychloroquine 1%, lopinavir-ritonavir 0.5%, tocilizumab 3%, azithromycin 25%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	Symptomatic infection (prophylaxis studies): No information Severe adverse events: RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕○○ Hospitalization: No information
DEXA-COVID19 trial ; ²⁹⁸ 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 ; ²⁹⁹ 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 ; ³⁰⁰ Arabi et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 278 assigned to	Mean age 59.9 ± 13, male 71%, diabetes 32%, chronic lung disease	NR	Low for mortality and invasive mechanical ventilation; high for	

	hydrocortisone 50 mg every 6 hours for 7 days and 99 assigned to standard of care	20.3%, coronary heart disease 7.5%, chronic kidney disease 9.2%, immunosuppression 4.9%		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 ; ²⁹⁸ 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 ; ³⁰¹ 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	
Steroids-SARI trial ; ²⁹⁸ 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 ; ³⁰² preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to methylprednisolone 1000 mg/day for three days followed by	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	

	prednisolone 1 mg/kg for 10 days, and 15 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Edalatifard et al. ³⁰³ 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 probably inappropriate.
Tang et al. ³⁰⁴ 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. ³⁰⁵ 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 probably inappropriate.
Rashad et al. ³⁰⁶ 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 probably inappropriate. Significant lost to follow-up as patients who died in the first 3 days after randomization were excluded.	
Ranjbar et al , ³⁰⁷ 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: 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

Steroids (inhaled)

Inhaled steroids may improve symptom resolution and may decrease hospitalizations. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
STOIC trial , ³⁰⁸ Ramakrishnan et al; peer reviewed ; 2020	Patients with mild to moderate COVID-19. 71 assigned to budesonide (inh) 800 µg twice a day and	Mean age 45 ± 56, male 42.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	Mortality: No information Invasive mechanical ventilation: Very low

	69 assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	certainty ⊕○○○ Symptom resolution or improvement: RR 1.10 (95%CI 1.03 to 1.17); RD 6% (95%CI 1.8% to 10.3%); Low certainty ⊕○○○
PRINCIPLE trial ; ³⁰⁹ Yu et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 751 assigned to budesonide (inh) 800 µg twice daily for 14 days and 1028 assigned to SOC	Mean age 68.2, male 46.3%, hypertension 21.9%, diabetes 20.5%, COPD 18.3%, CHD 15.4%, disease 6.2%	NR	Some Concerns for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study. Significant lost to follow-up	Symptomatic infection (prophylaxis studies): No information Hospitalization: RR 0.82 (95%CI 0.61 to 1.12); RD -1.3% (95%CI -2.8% to 0.9%); Low certainty ⊕○○○ Adverse events: 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
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RCT

ERSul trial ; ³¹⁰ 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%	Steroids 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
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					Adverse events: Very low certainty ⊕○○○ Hospitalization: Very low certainty ⊕○○○
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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
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RCT

Singh et al. ³¹¹ 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%	Steroids 92%, remdesivir 12%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information Adverse events: Very low certainty ⊕○○○ Hospitalization: No information
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Thalidomide

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Amra et al. ³¹² 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%	Steroids 100%, hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	<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>

Tocilizumab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COVACTA trial ; Rosas et al. ³¹³ peer-reviewed; 2020	Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, coronary heart	Steroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse	<p>Mortality: RR 0.88 (95%CI 0.77 to 1); RD -1.9% (95%CI -3.7% to 0%); Moderate certainty</p>

	to standard of care	disease 28%, obesity 20.5%		events	⊕⊕⊕○
Wang et al ; ³¹⁴ 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 probably inappropriate.	Invasive mechanical ventilation: RR 0.82 (95%CI 0.76 to 0.89); RD -3.1% (95%CI -4.2% to -1.9%); High certainty ⊕⊕⊕⊕ Symptom resolution or improvement: RR 1.10 (95%CI 0.99 to 1.22); RD 6% (95%CI -0.6% to 13.3%); Low certainty ⊕⊕○○
Zhao et al ; ¹⁰⁴ 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 probably inappropriate.	Symptomatic infection (prophylaxis studies): No information Adverse events: RR 0.90 (95%CI 0.76 to 1.05); RD -1% (95%CI -2.5% to 0.5%); Moderate certainty ⊕⊕⊕○ Hospitalization: No information
RCT-TCZ-COVID-19 trial ; ³¹⁵ Salvarani et al; peer-reviewed; 2020	Patients with severe COVID-19. 60 assigned to tocilizumab 8 mg/kg twice on day 1 and 66 assigned to standard of care	Median age 60 ± 19, male 61.1%, hypertension 44.4%, diabetes 15.1%, COPD 3.2%, obesity 32.2%	Hydroxychloroquine 91.3%, azithromycin 20.6%, antivirals 41.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BACC Bay Tocilizumab Trial ; ³¹⁶ Stone et al;	Patients with severe COVID-19. 161 assigned to	Median age 59.8 ± 15.1, male 58%, hypertension 49%, diabetes 31%,	Steroids 9.5%, remdesivir 33.9%, hydroxychloroquine	Low for mortality and mechanical ventilation; low for symptom	

peer-reviewed; 2020	tocilizumab 8 mg/kg once and 81 assigned to standard of care	COPD 9%, asthma 9%, coronary heart disease 10%, chronic kidney disease 17%, cancer 12%,	3.7%,	resolution, infection and adverse events
CORIMUNO-TOCI 1 trial ; ³¹⁷ 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%,	Steroids 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 ; ³¹⁸ 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%	Steroids 59.4%, remdesivir 54.6%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
REMAP-CAP-tocilizumab trial ; ²⁸¹ Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8 mg/kg once or twice, 48 assigned to sarilumab 400 mg once and 402 assigned to SOC	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%, cancer %, obesity %	Steroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Veiga et al ; ³¹⁹ peer reviewed; 2020	Patients with severe to critical COVID-19. 65 assigned to TCZ 8 mg/kg once and 64	Mean age 57.4 ± 14.6, male 68%, hypertension 49.6%, diabetes 32.6%, COPD 3%, CHD 5.5%,	Steroids 71.3%	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution,

	assigned to SOC	cancer 7%,		infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
RECOVERY-TCZ trial ; ³²⁰ 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%	Steroids 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 ; ³²¹ Rutgers et al; preprint; 2021	Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice and 180 assigned to SOC	Median age 66.5 ± 16.5, male 67%, comorbidities 74.3%	Steroids 88.4%, remdesivir 18.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Talaschian et al ; ³²² 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%	Steroids 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.

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					
<p>STOP-COVID trial;³²³ Guimaraes et al; peer reviewed; 2021</p>	<p>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</p>	<p>Mean age 56 ± 14, male 65.1%, hypertension 50.2%, diabetes 23.5%</p>	<p>Steroids 78.5%</p>	<p>Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events</p>	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: No information</p> <p>Symptom resolution or improvement: 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
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RCT

Wu et al. ³²⁴ peer-reviewed; 2020	Patients with mild to critical COVID-19. 26 assigned to triazavirin 250 mg orally three or four times a day for 7 days and 26 assigned to standard of care	Median age 58 ± 17, male 50%, hypertension 28.8%, diabetes 15.4%, chronic lung disease 5.8%, coronary heart disease 15.4%, cerebrovascular disease 7.7%	Steroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%, umifenovir 61.5%, ribavirin 28.9%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	<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
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RCT

Chen et al. ⁹⁴ preprint; 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to	Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	<p>Mortality: No information</p> <p>Invasive mechanical</p>
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	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			infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	ventilation: No information Symptom resolution or improvement: No information Symptomatic infection (prophylaxis studies): No information
ELACOI trial ; Li et al, ²⁰³ 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%	Steroids 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.	Adverse events: No information Hospitalization: No information
Nojomi et al , ³²⁵ preprint; 2020	Patients with severe COVID-19. 50 assigned to umifenovir 100 mg two twice a day for 7 to 14 days and 50 assigned to lopinavir-ritonavir 400 mg a day for 7 to 14 days	Mean age 56.4 ± 16.3, male 60%, hypertension 39%, diabetes 28%, asthma 2%, coronary heart disease 9%, chronic kidney disease 2%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Yethindra et al , ³²⁶ 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 probably inappropriate.	
Ghaderkhani S et al (Tehran University of Medical Sciences) trial ; ³²⁷ 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 probably inappropriate.	

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 ; ³²⁸ preprint; 2020	Patients with severe COVID-19 infection. 26 assigned to vitamin C 12 gr 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 probably inappropriate.	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○
Kumari et al ; ³²⁹ 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	Symptomatic infection (prophylaxis studies): No information Adverse events: No information Hospitalization: Very

				study. Concealment of allocation probably inappropriate.	low certainty ⊕○○○
Jamali Moghadam Siahkali et al , ³³⁰ Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5gr 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 probably inappropriate.	
COVIDAtoZ - Vit C trial , ³³¹ 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%	Steroids 8.4%,	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Vitamin D

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COVIDIOL trial ; Entrenas Castillo et al, ³³² 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	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, coronary heart disease	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events	Mortality: Very low certainty ⊕○○○ Invasive mechanical ventilation: Very low certainty ⊕○○○

	assigned to standard of care	3.9%, immunosuppression 9.2%, cancer %, obesity %		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>
SHADE trial ; ³³³ 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	<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>	
Murai et al ; ³³⁴ 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	<p>Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events</p>	
Lakkireddy et al ; ³³⁵ 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	<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>	

XAV-19 (swine glyco-humanized polyclonal antibodies)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
POLYCOR trial ; ³³⁶ 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%	Steroids 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 infection (prophylaxis studies): No information</p> <p>Adverse events: Very low certainty ⊕○○○</p> <p>Hospitalization: No information</p>

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
RCT					
Hassan et al ; ³³⁷ preprint; 2020	Patients with mild to critical COVID-19. 49 assigned to zinc 220 mg twice a day and 56 assigned to standard of	Mean age 45.9 ± 17.5, male 58.2%, hypertension 10.4%, diabetes 11.2%, coronary heart disease	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	<p>Mortality: Very low certainty ⊕○○○</p> <p>Invasive mechanical ventilation: Very low</p>

	care	3%,		Notes: Concealment of allocation probably inappropriate.	certainty ⊕○○○ Symptom resolution or improvement: Very low certainty ⊕○○○
Abd-Elsalam et al. ³³⁸ peer-reviewed; 2020	Patients with mild to critical COVID-19. 96 assigned to zinc 220 mg twice a day for 15 days and 95 assigned to standard of care	Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	Symptomatic infection (prophylaxis studies): Very low certainty ⊕○○○ Adverse events: No information Hospitalization: Very low certainty ⊕○○○
Abdelmaksoud et al. ³³⁹ 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 probably inappropriate.	
COVIDAtoZ-Zinc trial ³³¹ 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%	Steroids 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 ³⁴⁰ Patel et al; Peer reviewed; 2020	Patients with severe to critical COVID-19. 15 assigned to Zinc 0.24	Mean age 61.8 ± 16.9, male 63.6%, hypertension 48.4%,	Steroids 75.8%, remdesivir 30.3%,	Low for mortality and mechanical ventilation; Low for symptom	

	mg/kg a day for 7 days and 18 assigned to SOC	diabetes 18.2%, COPD 6%, CHD 21.2%,		resolution, infection and adverse events	
Seet et al ; ¹⁴³ peer reviewed; 2021	Patients exposed to COVID-19 infection. 634 assigned to zinc 80 mg and 500 mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33 , male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

α -Lipoic acid

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

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

Zhong et al ; ³⁴¹ 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.	<p>Mortality: Very low certainty $\oplus\circ\circ\circ$</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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Appendix 1. Summary of findings tables

Summary of findings table 1.

Population: Patients with severe COVID-19 disease

Intervention: Steroids

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text 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

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;

Summary of findings table 2.

Population: Patients with COVID-19 infection

Intervention: Remdesivir

Comparator: Standard of care

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text summary
		SOC	Remdesivir		
Mortality 28 days	Relative risk: 0.94 (CI 95% 0.82 - 1.08) Based on data from 7330 patients in 4 studies Follow up Median 28 days	160 per 1000	150 per 1000	Low Due to serious imprecision, Due to serious risk of bias ¹	Remdesivir may decrease mortality slightly
		Difference: 10 fewer per 1000 (CI 95% 29 fewer - 13 more)			
Mechanical ventilation 28 days	Relative risk: 0.65 (CI 95% 0.39 - 1.11) Based on data from 6551 patients in 4 studies Follow up Median 28 days	173 per 1000	112 per 1000	Low Due to serious risk of bias, Due to serious imprecision ²	Remdesivir may decrease mechanical ventilation requirements
		Difference: 61 fewer per 1000 (CI 95% 106 fewer - 19 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.17 (CI 95% 1.03 - 1.33) Based on data from 1873 patients in 3 studies Follow up 28 days	606 per 1000	709 per 1000	Low Due to serious risk of bias, Due to serious imprecision ³	Remdesivir may improve symptom resolution or improvement
		Difference: 103 more per 1000 (CI 95% 18 more - 200 more)			
Severe adverse events	Relative risk: 0.8 (CI 95% 0.48 - 1.33) Based on data from 1869 patients in 3 studies	102 per 1000	82 per 1000	Low Due to serious risk of bias, Due to serious imprecision ⁴	Remdesivir may have little or no difference on severe adverse events
		Difference: 20 fewer per 1000 (CI 95% 53 fewer - 34 more)			

- 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

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 text 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
		Difference: 11 more per 1000 (CI 95% 3 fewer - 27 more)			
Mechanical ventilation 15 days	Relative risk: 1.07 (CI 95% 0.93 - 1.24) Based on data from 7297 patients in 9 studies Follow up Median 15 days	173 per 1000	185 per 1000	Moderate Due to serious risk of bias ²	Hcq probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.05 (CI 95% 0.95 - 1.16) Based on data from 6305 patients in 7 studies Follow up 28 days	606 per 1000	636 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: 0.97 (CI 95% 0.65 - 1.45) Based on data from 2566 patients in 4 studies	174 per 1000	169 per 1000	Low Due to very serious imprecision ⁴	Hcq may have little or no difference on covid-19 infection (in exposed individuals)
Hospitalizations (in patients with non- severe disease)	Relative risk: 0.82 (CI 95% 0.49 - 1.36) Based on data from 1195 patients in 4 studies	74 per 1000	61 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: 0.89 (CI 95% 0.6 - 1.32)	102 per 1000	91 per 1000	Low	Hcq may have little or no difference on

Based on data from 6855 patients in 14 studies	Difference: 11 fewer per 1000 (CI 95% 41 fewer - 33 more)	Due to serious risk of bias, Due to serious imprecision ⁶	severe adverse events
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1. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
2. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
3. **Risk of Bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** I2 82%; **Imprecision: No serious.** Secondary to inconsistency;
4. **Imprecision: Very 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 Timeframe	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
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
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
Severe adverse events	Relative risk: 0.6 (CI 95% 0.37 - 0.98) Based on data from 199 patients in 1 studies	102 per 1000	61 per 1000	Low Due to serious risk of bias, Due to serious imprecision ³	Lpv may have little or no difference on severe adverse events
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 ⁴	We are uncertain whether LPV increases or decreases hospitalization

1. **Imprecision: Serious.** 95%CI includes significant mortality reduction and increase;
2. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: No serious.** Secondary to inconsistency;

3. **Risk of Bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients;
4. **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 text summary
		SOC	CP		
Mortality (Low RoB studies) ¹ 28 days	Relative risk: 0.99 (CI 95% 0.93 - 1.05) Based on data from 12185 patients in 5 studies Follow up Median 28 days	160 per 1000	158 per 1000	Moderate Due to serious imprecision ²	Convalescent plasma probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.98 (CI 95% 0.86 - 1.12) Based on data from 7558 patients in 4 studies Follow up Median 28 days	173 per 1000	170 per 1000	Moderate Due to serious imprecision ³	Cp probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.02 (CI 95% 0.93 - 1.13) Based on data from 12678 patients in 7 studies Follow up 28 days	606 per 1000	618 per 1000	Moderate Due to serious inconsistency ⁴	Cp probably has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.1 (CI 95% 0.76 - 1.18) Based on data from 845 patients in 5 studies	102 per 1000	112 per 1000	Low Due to serious risk of bias, Due to serious imprecision ⁵	Cp may increase severe adverse events
Specific severe adverse events	Based on data from 20000 patients in 1 study	Observed risk of severe adverse events were: TRALI 0.1%, TACO 0.1%, severe allergic reactions 0.1%		Very low Due to very serious risk of bias ⁶	We are uncertain whether lpv increases or decreases severe adverse events

1. Low risk of bias studies
2. **Inconsistency: No serious.** Point estimates vary widely; **Imprecision: Serious.** 95%CI includes significant mortality reduction and increase;
3. **Imprecision: Serious.** Wide confidence intervals;
4. **Inconsistency: Serious.** Point estimates vary widely;
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.** Low number of patients, Wide confidence intervals;

6. **Risk of Bias: Very serious.** Although adverse events were rare, we assume that some might have been missed and assumed as related to disease progression. RCT are needed to determine interventions safety. ;

Summary of findings table 6.

Population: Patients with COVID-19 infection

Intervention: Tocilizumab (TCZ)

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text summary
		SOC	TCZ		
Mortality 28 days	Relative risk: 0.88 (CI 95% 0.77 - 1.0) Based on data from 6740 patients in 10 studies Follow up Median 28 days	160 per 1000	141 per 1000	Moderate Due to serious imprecision ¹	TCZ probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.82 (CI 95% 0.76 - 0.89) Based on data from 5706 patients in 9 studies Follow up Median 28 days	173 per 1000	142 per 1000	High ²	TCZ decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.1 (CI 95% 0.99 - 1.22) Based on data from 4549 patients in 4 studies Follow up 28 days	606 per 1000	667 per 1000	Low Due to serious imprecision, Due to serious risk of bias ³	TCZ may increase symptom resolution or improvement
Severe adverse events	Relative risk: 0.9 (CI 95% 0.76 - 1.05) Based on data from 2702 patients in 10 studies	102 per 1000	92 per 1000	Moderate Due to serious risk of bias ⁴	TCZ probably has little or no difference on severe adverse events

1. **Imprecision: Serious.** 95%CI includes absence of significant mortality reduction;
2. **Imprecision: No serious.** 95% included significant and trivial reduction mechanical ventilation requirement reduction ;
3. **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 ;
4. **Risk of bias: Serious. Imprecision: No serious.** 95%ci included significant severe adverse events increase;

Summary of findings table 7.

Population: Patients with COVID-19 infection

Intervention: Anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 m/kg twice a day)

Comparator: Anticoagulants in prophylactic dose (i.e., enoxaparin 40 mg a day)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text summary
		SOC	ACO		
Mortality	Relative risk: 1.0 (CI 95% 0.9 - 1.15) Based on data from 4663 patients in 6 studies	160 per 1000	160 per 1000	Moderate Due to serious imprecision ¹	Anticoagulantes in intermediate or full dose probably has little or no difference on mortality in comparison with prophylactic dose
Venous thromboembolic events (intermediate dose)	Relative risk: 1.02 (CI 95% 0.53 - 1.96) Based on data from 737 patients in 2 studies	70 per 1000	71 per 1000	Low Due to very serious imprecision ²	Anticoagulantes in intermediate dose may slightly reduce venous thromboembolic events
Venous thromboembolic events (full dose)	Relative risk: 0.61 (CI 95% 0.45 - 0.82) Based on data from 3953 patients in 3 studies	70 per 1000	43 per 1000	Moderate Due to serious imprecision ³	Anticoagulantes in intermediate or full dose probably decreases venous thromboembolic events (full dose)
Major bleeding	Relative risk: 1.74 (CI 95% 1.12 - 2.7) Based on data from 4686 patients in 5 studies	19 per 1000	33 per 1000	Moderate Due to serious imprecision ⁴	Anticoagulantes in intermediate or full dose probably increases major bleeding

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

Summary of findings table 8.

Population: Patients with COVID-19 infection

Intervention: Non-steroids anti-inflammatory drugs (NSAID)

Comparator: Standard of care

Outcome Timeframe	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 text summary
		SOC	IFN		
Mortality 28 days	Relative risk: 1.04 (CI 95% 0.88 - 1.23) Based on data from 4242 patients in 3 studies Follow up Median 28 days	160 per 1000	166 per 1000	Moderate Due to serious imprecision ¹	IFN-B-1a probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.98 (CI 95% 0.83 - 1.16) Based on data from 3981 patients in 3 studies Follow up 28 days	173 per 1000	170 per 1000	Moderate Due to serious imprecision ²	IFN-B-1a probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Hazard Ratio: 1.1 (CI 95% 0.64 - 1.87) Based on data from 121 patients in 2 studies Follow up 28 days	606 per 1000	641 per 1000	Very low Due to serious risk of bias, Due to very serious imprecision ³	We are uncertain whether IFN-B-1a increases or decreases symptom resolution or improvement
Symptom resolution or improvement (inhaled) ⁴ 30 days	Hazard Ratio: 2.19 (CI 95% 1.03 - 4.69) Based on data from 81 patients in 1 study Follow up 28 days	606 per 1000	870 per 1000	Low Due to very serious imprecision ⁵	IFN-B-1a (inhaled) may increase symptom resolution or improvement

- Imprecision: Serious.** 95%CI includes significant mortality reduction and increase;
- 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;
- Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits;
- Nebulizations
- 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

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text summary
		SOC	Bamlanivimab		
Mortality	Relative risk: 1.22 (CI 95% 0.55 - 2.69) Based on data from 1280 patients in 2 studies	160 per 1000	195 per 1000	Very low Due to serious imprecision, Due to very serious imprecision ¹	We are uncertain whether bamlanivimab increases or decreases mortality
Symptom resolution or improvement ²	Relative risk: 1.04 (CI 95% 0.99 - 1.09) Based on data from 745 patients in 2 studies	606 per 1000	630 per 1000	Moderate Due to serious imprecision ³	Bamlanivimab probably has little or no difference on symptom resolution or improvement
Symptomatic infection	Relative risk: 0.56 (CI 95% 0.39 - 0.81) Based on data from 961 patients in 1 study Follow up 28 days	174 per 1000	97 per 1000	Moderate Due to serious imprecision ⁴	Bamlanivimab probably decreases symptomatic infection
Severe adverse events ⁵	Hazard Ratio: 1.01 (CI 95% 0.54 - 1.9) Based on data from 2309 patients in 4 studies	102 per 1000	103 per 1000	Low Due to very serious imprecision ⁶	Bamlanivimab may have little or no difference on severe adverse events
Hospitalization ⁷	Hazard Ratio: 0.25 (CI 95% 0.08 - 0.75) Based on data from 442 patients in 1 study	74 per 1000	19 per 1000	Very low Due to serious risk of bias, Due to very serious imprecision ⁸	We are uncertain whether bamlanivimab increases or decreases hospitalization

- Imprecision: Very serious.** 95%CI includes significant benefits and harms;
- Symptomatic infection in persons at risk or exposed to SARS-COV2
- Imprecision: Serious.** 95%CI includes benefits and absence of benefits;
- Imprecision: Serious.** OIS not met;
- Symptomatic infection in persons at risk or exposed to SARS-COV2
- Imprecision: Very serious.** 95%CI includes significant benefits and harms;
- Symptomatic infection in persons at risk or exposed to SARS-COV2
- Risk of Bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias;
Imprecision: Very 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 text summary
		SOC	Favipiravir		
Mechanical ventilation 28 days	Relative risk: 1.16 (CI 95% 0.25 - 5.35) Based on data from 525 patients in 3 studies Follow up Median 28 days	173 per 1000	201 per 1000	Low Due to very serious imprecision ¹	Favipiravir may have little or no difference on mechanical ventilation
Mortality 28 days	Relative risk: 1.16 (CI 95% 0.7 - 1.94) Based on data from 672 patients in 4 studies Follow up Median 28 days	160 per 1000	186 per 1000	Low Due to very serious imprecision ²	Favipiravir may have little or no difference on mortality
Severe adverse events ³ 30 days	Relative risk: 1.02 (CI 95% 0.32 - 3.23) Based on data from 163 patients in 1 study Follow up 28 days	606 per 1000	618 per 1000	Very low Due to very serious imprecision ⁴	We are uncertain whether favipiravir increases or decreases severe adverse events
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.9 - 1.09) Based on data from 373 patients in 1 study Follow up 28 days	606 per 1000	600 per 1000	Moderate Due to serious imprecision ⁵	Favipiravir probably has little or no difference on symptom resolution or improvement
Hospitalization (in patients with non- severe disease)	Relative risk: 0.75 (CI 95% 0.13 - 4.36) Based on data from 168 patients in 1 study Follow up 28 days	606 per 1000	455 per 1000	Very low Due to serious risk of bias, Due to very serious imprecision ⁶	We are uncertain whether favipiravir increases or decreases hospitalization (in patients with non- severe disease)

1. **Imprecision: Very Serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: Very Serious.** 95%CI includes significant mortality reduction and increase;
3. Nebulizations
4. **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits ;

5. **Imprecision: Serious.** 95%CI includes significant benefits and absence of benefits ;
6. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits ;

Summary of findings table 12.

Population: Patients with COVID-19 infection

Intervention: Ivermectin

Comparator: Standard of care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		SOC	Ivermectin		
Mortality (Low risk of bias studies) ¹	Relative risk: 0.92 (CI 95% 0.54 - 1.57) Based on data from 911 patients in 5 studies	160 per 1000	147 per 1000	Low Due to very serious imprecision ²	Ivermectin may have little or no difference in mortality
Mechanical ventilation	Relative risk: 1.01 (CI 95% 0.6 - 1.72) Based on data from 545 patients in 5 studies	173 per 1000	175 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: 1.04 (CI 95% 0.32 - 3.38) Based on data from 824 patients in 4 studies Follow up 28 days	102 per 1000	106 per 1000	Very low Due to very serious imprecision, Due to very serious risk of bias ⁷	We are uncertain whether ivermectin increases or decreases severe adverse events
Hospitalization (in non-severe patients)	Relative risk: 0.51 (CI 95% 0.18 - 1.43) Based on data from 587 patients in 3 studies Follow up 28 days	102 per 1000	52 per 1000	Very low Due to very serious imprecision ⁸	We are uncertain whether ivermectin increases or decreases 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: Very 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 text summary
		SOC	Baricitinib		
Mortality	Relative risk: 0.63 (CI 95% 0.48 - 0.81) Based on data from 2558 patients in 2 studies	160 per 1000	101 per 1000	Moderate Due to serious risk of bias ¹	Baricitinib probably decreases mortality
Invasive mechanical ventilation	Relative risk: 0.66 (CI 95% 0.46 - 0.93) Based on data from 922 patients in 1 study Follow up 30 days	173 per 1000	114 per 1000	Low Due to serious risk of bias, Due to serious imprecision ²	Baricitinib may decrease invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.25 (CI 95% 1.11 - 1.41) Based on data from 1797 patients in 2 studies Follow up 30 days	606 per 1000	758 per 1000	Moderate Due to serious risk of bias ³	Baricitinib probably improves symptom resolution or improvement
Severe adverse events	Relative risk: 0.77 (CI 95% 0.63 - 0.95) Based on data from 2558 patients in 2 studies Follow up 30 days	102 per 1000	79 per 1000	Low Due to serious risk of bias, Due to serious imprecision ⁴	Baricitinib may have little or no difference on severe adverse events

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

Summary of findings table 14.

Population: Patients with COVID-19 infection

Intervention: Azithromycin

Comparator: Standard of care

Outcome Timeframe	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
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
Symptom resolution or improvement ³	Relative risk: 1.02 (CI 95% 0.99 - 1.04) Based on data from 9086 patients in 3 studies	606 per 1000	618 per 1000	High	Azithromycin has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.23 (CI 95% 0.51 - 2.96) Based on data from 439 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

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;

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 text summary
		SOC	Colchicine		
Mortality	Relative risk: 1.0 (CI 95% 0.93 - 1.08) Based on data from 16005 patients in 4 studies	160 per 1000	160 per 1000	Moderate Due to serious imprecision ¹	Colchicine probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 1.02 (CI 95% 0.92 - 1.13) Based on data from 15404 patients in 3 studies Follow up 30 days	173 per 1000	176 per 1000	Moderate Due to serious imprecision ²	Colchicine probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 0.99 (CI 95% 0.96 - 1.01) Based on data from 11340 patients in 1 study Follow up 30 days	173 per 1000	171 per 1000	High	Colchicine has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 1.0) Based on data from 4488 patients in 1 study Follow up 30 days	102 per 1000	80 per 1000	High	Colchicine has little or no difference on severe adverse events
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: 0.8 (CI 95% 0.62 - 1.03) Based on data from 4488 patients in 1 study Follow up 30 days	74 per 1000	59 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 text summary
		SOC	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir		
Mortality	Relative risk: 1.13 (CI 95% 0.82 - 1.55) Based on data from 1163 patients in 2 studies	160 per 1000	181 per 1000	Low Due to very serious imprecision ¹	Sofosbuvir alone or in combination may have little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 1.04 (CI 95% 0.29 - 3.7) Based on data from 1083 patients in 1 study Follow up 30 days	173 per 1000	180 per 1000	Very low Due to very serious imprecision ²	We are uncertain whether sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir increases or decreases invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 0.97 (CI 95% 0.9 - 1.06) Based on data from 1343 patients in 5 studies Follow up 7 days	606 per 1000	588 per 1000	Moderate Due to serious imprecision ³	Sofosbuvir alone or in combination probably has little or no difference on symptom resolution or improvement

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 text summary
		SOC	REGEN-COV (casirivimab and imdevimab)		
Mortality	Relative risk: 0.94 (CI 95% 0.87 - 1.02) Based on data from 13965 patients in 2 studies	160 per 1000	150 per 1000	Moderate Due to very serious imprecision ¹	Regen-cov (casirivimab and imdevimab) probably has little or no difference on mortality
Mortality (seronegative)	Relative risk: 0.8 (CI 95% 0.7 - 0.91) Based on data from 3153 patients in 1 study	160 per 1000	128 per 1000	Moderate Due to serious indirectness ²	Regen-cov (casirivimab and imdevimab) probably decreases mortality in seronegative patients
Invasive mechanical ventilation	Relative risk: 0.96 (CI 95% 0.89 - 1.03) Based on data from 13387 patients in 2 studies Follow up 30 days	173 per 1000	166 per 1000	Moderate Due to very serious imprecision ³	Regen-cov (casirivimab and imdevimab) probably has little or no difference on invasive mechanical ventilation
Invasive mechanical ventilation (seronegative)	Relative risk: 0.88 (CI 95% 0.73 - 1.06) Based on data from 3083 patients in 1 study Follow up 30 days	173 per 1000	152 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁴	Regen-cov (casirivimab and imdevimab) may decrease invasive mechanical ventilation in seronegative patients
Symptom resolution or improvement	Relative risk: 1.06 (CI 95% 0.96 - 1.16) Based on data from 13549 patients in 2 studies Follow up 30 days	606 per 1000	642 per 1000	Moderate Due to serious imprecision ⁵	Regen-cov (casirivimab and imdevimab) probably has little or no difference on symptom resolution or improvement
Symptom resolution or	Relative risk: 1.12 (CI 95% 1.01 - 1.25)	606 per 1000	679 per 1000	Moderate Due to serious indirectness ⁶	Regen-cov (casirivimab and imdevimab) probably

improvement (seronegative)	Based on data from 5757 patients in 2 studies Follow up 30 days	Difference: 73 more per 1000 (CI 95% 6 more - 152 more)		increases symptom resolution or improvement in seronegative patients	
Hospitalization (in patients with non-severe disease)	Relative risk: 0.29 (CI 95% 0.18 - 0.44) Based on data from 4384 patients in 2 studies Follow up 30 days	74 per 1000	21 per 1000	Moderate Due to serious imprecision ⁷	Regen-cov (casirivimab and imdevimab) probably improves hospitalization in patients with recent onset non-severe disease
Symptomatic infection (in exposed individuals)	Relative risk: 0.69 (CI 95% 0.47 - 1.0) Based on data from 204 patients in 1 study Follow up 30 days	74 per 1000	51 per 1000	Low Due to serious imprecision, Due to very serious imprecision ⁸	Regen-cov (casirivimab and imdevimab) may decrease symptomatic infection in exposed individuals
Severe adverse events	Relative risk: 0.63 (CI 95% 0.48 - 0.81) Based on data from 5735 patients in 2 studies Follow up 30 days	102 per 1000	64 per 1000	Moderate Due to serious imprecision ⁹	Regen-cov (casirivimab and imdevimab) probably has little or no difference on severe adverse events

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

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