COVID-19

ONGOING LIVING UPDATE OF COVID-19 THERAPEUTIC OPTION

Summary of Evidence

Rapid Review, 6 May 2021

PAHO Pan American Health Organization World Health Organization Regional Office for the Americas

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Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence. Rapid Review, 6 May 2021

PAHO/IMS/EIH/COVID-19/21-015

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 110 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=290)

Intervention		Overall number of studies including the intervention, n=	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	41	11	8	7	4 (*)	12	4
Ivermectin	NEW	28	4 (*)	3	2 (*)	4	4	1
Convalecent plasma	NEW	16	3 (*)	8	7		4	
Glucocorticoids	NEW	15	12	6	5		6	
Favipiravir	NEW	14	5	4	1(*)		1	1
Lopinavir-Ritonavir	NEW	13	3	3	2		2	1
Tocilizumab	NEW	11	8	8	4		8	
Sofosbuvir +/- Daclatasvir or ledipasvir		9	1(*)	1(*)	5			
Azithromycin	NEW	8	4	3	3		1	
Mouthwash		6	2	1	1			
Remdesivir		6	5 (#)	5	3		3	
Zinc	NEW	6	2	1	2		1	
IVIG		5	4	2			1	
Umifenovir		5						
Bromhexine Hydrochloride		4	2	1	2	1	1	
Colchicine		4	3	2			1	1
Interferon beta-1a		4	3	3	2			
Nitazoxanide	NEW	4	1	1	1		2	2
Vitamin C		4	4	4	2			
Vitamin D		4	2	1			1	
ACEIs or ARBs (treatment)		3	3	2				1
Anticoagulants (Intermediate or full dose)		3	3				2 (^)	
Bamlanivimab		3	1		2		3	1
Mesenchimal cell tranplantation		3	1		1		1	
ACEIs or ARBs (continuation)		2	2	2				
Baricitinib	NEW	2	2	1	2		2	
Dutasteride		2			1			
Leflunomide		2						
N-acetylcysteine		2	1	1			1	
Omega-3 fatty acids		2	1					
Ozone		2	2		1		1	
Proxalutide		2	1	1	1			1
Sarilumab		2	2	1	1		1	
Steroids (inhaled)		2		1	2			1
99mTc-MDP		1						
Ammonium chloride		1	1	1				
Anakinra		1	1	1	1		1	
Aprepitant		1						
Artemisinin		1			1		1	
Aspirin		1	1	1				
Auxora		1	1	1				
Aviptadil		1	1		1		1	
Azvudine		1						
Baloxavir		1			1			
Bamlanivimab + etesevimab		1	1		1		1	
BCG		1	1					
Bioven		1	1				1	
Camostat mesilate	NEW	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	NEW	1	1					
Febuxostat		1						1
Fluvoxamine		1	1	1			1	1
Helium (inhaled)		1						
Honey + Nigella sativa	NEW	1	1		1			
Hyperbaric oxygen		1	1	1	1			
Icatibant		1	1					
iC1e/K		1	1					
IFN-alpha2b + IFN-gamma		1						

IFX-1		1	1				1	
INM005 (equine antibodies)		1	1	1	1		1	
Interferon beta-1b		1	1	1	1			
Interferon beta-1a (inhaled)		1	1	1	1		1	
Interferon gamma		1						
Interferon kappa + TFF2		1	1				1	
Iota-Carrageenan		2	1				2	1
Itolizumab		1	1	1			1	
KB109		1	1		1		1	
Lactococcus Lactis (intranasal)	NEW	1			1		1	
Lenzilumab	NEW	1	1	1			1	
Levamizole		1			1			1
Lincomecin		1						
Mavrilimumab		1	1	1	1		1	
Melatonin		1	1		1			
Metisoprinol		1						
Molnupiravir		1					1	
Nasal hypertonic saline		1			1			
Neem (Azadirachta Indica A. Juss)	NEW	1				1		
Nitric oxide	NEW	1	1	1			1	
Novaferon		1						
Otilimab	NEW	1	1				1	
Peg-IFN alfa		1			1			
Peg-IFN lambda		1					1	
PNB001 (CCK-A antagonist)	NEW	1	1		1			
Povidone iodine	NEW	1	1				1	1
Progesterone		1	1	1			1	
Prolectin-M		1	1	1			1	
Propolis		1	1	1	1			
Pyridostigmine	NEW	1	1	1	1		1	
Querceritin		1	1		1			
Ramipril		1	1			1		
Recombinant Super-Compound IFN		1	1		1			
REGN-COV2 (Regeneron)		1	1	1			1	
Regdanvimab		1			1		1	1
Ribavirin		1						
Ribavirin + Interferon beta-1b		1						
Ruxolitinib		1			1			
rhG-CSF		1	1		1		1	
Sofosbuvir/ledipasvir		1	1	1	1			1
Statins		1	1	1				
Sulodexide		1	1	1			1	1
TD-0903 (inhaled JAK-inhibitor)		1	1				1	
Telmisartan		1	1	1				
Thalidomide		1	1	1			1	
Triazavirin		1	1		1		1	
XAV-19 (swine polyclonal antibodies)	NEW	1	1				1	
α-Lipoic acid		1	1					

(*) Based on low risk of bias subgroup of studies; (#) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-statitically significant mortality reduction (RR 0.95, 95%CI 0.83 - 1.08); (^) Major bleeding

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

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

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

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

Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=110), as of 6 May 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 not increase mortality nor mechanical ventilation requirements
4	**Anakinra**	Anakinra may not improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements 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 1mg/kg a day) or full dose (i.e enoxaparin 1mg/kg twice a day) probably does not decrease mortality in comparison with prophylactic dose (i.e enoxaparin 40mg 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.

	Intervention	Summary of findings
7	**Artemisinin**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Aspirin**	Uncertainty in potential benefits and harms. Further research is needed.
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. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. 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.

	Intervention	Summary of findings
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.
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 may reduce mortality, mechanical ventilation requirements and hospitalizations in non-severe recently diagnosed patients. 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. 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.

	Intervention	Summary of findings
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.
34	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
35	**Fluvoxamine**	Uncertainty in potential benefits and harms. Further research is needed.
36	**Helium (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
37	**Honey + Nigella Sativa**	Uncertainty in potential benefits and harms. Further research is needed.
38	**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.
39	**Hyperbaric oxygen**	Uncertainty in potential benefits and harms. Further research is needed.
40	**Icatibant/iC1e/K**	Uncertainty in potential benefits and harms. Further research is needed.
41	**IFX-1**	Uncertainty in potential benefits and harms. Further research is needed.
42	**INM005 (polyclonal fragments of equine antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
43	**Interferon alpha-2b and Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
44	**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.
45	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
46	**Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
47	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.
48	**Iota-Carrageenan**	Uncertainty in potential benefits and harms. Further research is needed.
49	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
50	**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 four 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.
51	**Intravenous immunoglobulin**	Uncertainty in potential benefits and harms. Further research is needed.
52	**KB109**	Uncertainty in potential benefits and harms. Further research is needed.
53	**Lactococcus Lactis (intranasal)**	

	Intervention	Summary of findings
54	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
55	**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.
56	**Levamisole**	Uncertainty in potential benefits and harms. Further research is needed.
57	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.
58	**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.
59	**Mavrilimumab**	Uncertainty in potential benefits and harms. Further research is needed.
60	**Melatonin**	Uncertainty in potential benefits and harms. Further research is needed.
61	**Mesenchymal stem-cell transplantation**	Uncertainty in potential benefits and harms. Further research is needed.
62	**Molnupiravir**	Uncertainty in potential benefits and harms. Further research is needed.
63	**Mouthwash**	Uncertainty in potential benefits and harms. Further research is needed.
64	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
65	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
66	**Neem (Azadirachta Indica A. Juss)**	Uncertainty in potential benefits and harms. Further research is needed.
67	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.
68	**Nitric oxide**	Uncertainty in potential benefits and harms. Further research is needed.
69	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
70	**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.
71	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed
72	**Otilimab**	Uncertainty in potential benefits and harms. Further research is needed
73	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
74	**Peg-interferon alfa**	Uncertainty in potential benefits and harms. Further research is needed.
75	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
76	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
77	**PNB001 (CCK-A antagonist)**	Uncertainty in potential benefits and harms. Further research is needed.
78	**Povidone iodine (nasal spray)**	Uncertainty in potential benefits and harms. Further research is needed.
79	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed
80	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed
81	**Propolis**	Uncertainty in potential benefits and harms. Further research is needed
82	**Proxalutide**	Proxalutide may improve time to symptom resolution. However certainty of the evidence is low because of risk of bias. Further research is needed.
83	**Pyridostigmine**	Uncertainty in potential benefits and harms. Further research is needed
84	**Quercetin**	Uncertainty in potential benefits and harms. Further research is needed
85	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
86	**Recombinant super-Compound Interferon**	Uncertainty in potential benefits and harms. Further research is needed.
87	**REGN-COV2 (Regeneron)**	Uncertainty in potential benefits and harms. Further research is needed.
88	**Regdanvimab**	Regdanivimab may improve time to symptom resolution in mild to moderate patients. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.

	Intervention	Summary of findings
89	**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.
90	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.
91	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.
92	**Ribavirin + Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
93	**Ruxolitinib**	Uncertainty in potential benefits and harms. Further research is needed.
94	**Sarilumab**	Sarilumab may reduce mortality and mechanical ventilation requirements. However, the certainty is low because of imprecision and inconsistency.
95	**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.
96	**Statins**	Uncertainty in potential benefits and harms. Further research is needed.
97	**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.
98	**Steroids (inhaled)**	Inhaled steroids may improve time to symptom resolution and may decrease hospitalizations. Further research is needed.

	Intervention	Summary of findings
99	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
100	**TD-0903 (inhaled JAK-inhibitor)**	Uncertainty in potential benefits and harms. Further research is needed.
101	**Telmisartan**	Uncertainty in potential benefits and harms. Further research is needed.
102	**Thalidomide**	Uncertainty in potential benefits and harms. Further research is needed.
103	**Tocilizumab**	Tocilizumab may not reduce mortality but probably reduces mechanical ventilation requirements without possibly increasing severe adverse events.
104	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.
105	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
106	**Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
107	**Vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
108	**XAV-19 (swine glyco-humanized polyclonal antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
109	**Zinc**	Uncertainty in potential benefits and harms. Further research is needed.
110	**α-Lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** More than 200 therapeutic options or their combinations are being investigated in more than 1,700 clinical trials. In this review, we examined 110 therapeutic options.

• **Steroids:** The body of evidence on steroids, which includes twelve 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 thirteen 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 ten 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.

• **Colchicine:** The results of four RCTs assessing Colchicine, including the COLCORONA study that recruited 4488 patients with recent COVID-19 diagnosis and risk factors for severe diseases, suggest that colchicine may reduce mortality, mechanical ventilation requirements and hospitalizations. These findings are mainly driven by the COLCORONA study that included outpatients with early COVID-19. Recently a press release reported that RECOVERY trial, which included hospitalized patients with COVID-19, stopped enrolment to colchicine arm because of futility. Caution should be exerted until results of RECOVERY trial and other ongoing studies are available and subgroup analysis can be performed.

• **Ivermectin:** Although 28 RCTs assessed ivermectin in patients with COVID-19, only eleven 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 four 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 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 or ledipasvir:** Nine RCT assessed sofosbuvir with or without daclatasvir or ledipasvir against standard of care or other interventions. Their results 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.

• **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 one 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.

• **Bamlinivimab:** The results of three RCTs suggest thas bamlinivimab may not significantly improve time to symptom resolution. Its effects on other relevant 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 lenziliumab may reduce mortality and invasive mechanical ventilation requirements in severe patients. However the certainty of the evidence was low because of imprecision. Further research is needed.

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

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

• **Anticoagulants:** Thromboembolic complications in patients infected with COVID-19 are relatively frequent. As for hospitalized patients with severe medical conditions current guidelines recommend thromboprophylactic measures to be adopted for inpatients with COVID-19 infection. Regarding the best thromboprophylactic scheme, the results of three RCTs that compared anticoagulants in intermediate (i.e enoxaparin 1mg/kg a day) or full dose (i.e enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e enoxaparin 40mg a day) showed no differences in mortality with moderate certainty.

• **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:** Continuing ACEIs or ARBs in patients with COVID-19 may not increase mortality nor invasive mechanical ventilation requirements. However, certainty of the evidence is low and further research is needed to confirm these findings.

Changes since previous edition

• **Povidone iodine (nasal spray):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

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

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

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

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

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

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

• **XAV-19 (swine glyco-humanized polyclonal antibodies):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

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

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

• **PNB001 (CCK-A antagonist):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

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

• **Lactococcus Lactis (intranasal):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Neem (Azadirachta Indica A. Juss):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

• **Honey + Nigella Sativa:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

• **Systemic steroids:** New evidence included without significant changes.

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

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

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

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

• **Lenzilumab:** 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: Se están investigando más de 200 intervenciones terapéuticas o sus combinaciones en más de 1700 estudios clínicos. En esta revisión se incluyen 110 intervenciones para el manejo de pacientes con COVID-19.

• **Esteroides:** El conjunto de evidencia sobre los esteroides incluye doce 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 endovenosa 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, incluyendo el estudio RECOVERY que reclutó 11558 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 severos relacionados a la infusión fueron excepcionales. Adicionalmente, no se observó un efecto diferencial entre aquellos pacientes tratados rápidamente (<4 días de inicio de los síntomas) y aquellos con enfermedad más avanzada al iniciar dicho tratamiento.

• **Tocilizumab:** Los resultados de diez ECCA muestran que tocilizumab probablemente reduce la mortalidad y los requerimientos de ventilación invasiva sin un incremento importante en efectos adversos severos en pacientes con enfermedad severa o crítica.

• **Colchicina:** Los resultados de cuatro ECCA, incluyendo al estudio COLCORONA que incluyó 4488 pacientes con diagnóstico reciente de COVID-19 y factores de riesgo para enfermedad severa, sugieren una posible reducción de la mortalidad, de los requerimientos de ventilación mecánica invasiva y de las hospitalizaciones. Estos hallazgos reflejan fundamentalmente los resultados del estudio COLCORONA que incluyó pacientes con enfermedad precoz por COVID-19. Un reporte de prensa reciente sobre el estudio RECOVERY informa que dicho estudio dejó de reclutar pacientes hospitalizados con COVID-19 en la rama de colchicina por futilidad. Los mencionados hallazgos deben ser considerados con cuidado a la espera de los resultados definitivos del estudio RECOVERY y otros estudios en marcha que permitan realizar los análisis de subgrupos correspondientes.

• **Ivermectina:** A pesar que 28 ECCA evaluaron ivemectina en pacientes con COVID-19, solo once 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 cuatro estudios con bajo riesgo de sesgo, ivermectina podría no reducir significativamente la mortalidad 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 standard de cuidado 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 +/- daclatasvir o ledipasvir:** Nueve ECCA evaluaron sofosbuvir solo o en combinación con daclatasvir o ledipasvir en comparación con standard de cuidado u otras intervenciones. Sus resultados sugieren que sofosbuvir solo o en combinacion 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 severa, 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.

• **Regdanvimab:** Los resultados de un ECCA muestran que, en pacientes con enfermedad leve a moderada, regdanivimab 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 un 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.

• **Bamlinivimab:** Los resultados de tres ECCA sugieren que bamlinivimab podría no mejorar significativamente el tiempo a resolución de los síntomas. 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 sugiere 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 tromboprofilácticas.

• **Antiinflamatorios no esteroideos (AINES):** Hasta el momento, el uso de AINES 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:** La continuación del tratamiento con IECA y ARB en pacientes con COVID-19 podría no aumentar la mortalidad ni los requerimientos de ventilación mecánica invasiva. 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 anterior versión

• **Iodo povidona (spray nasal):** La nueva evidencia incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

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

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

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

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

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

• **XAV-19 (anticuerpos policlonales de cerdo):** La nueva evidencia incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

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

• **PNB001 (antagonista CCK-A):** La nueva evidencia incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

• **Lactococcus Lactis (intranasal):** La nueva evidencia incluida modifica la interpretación de los resultados o la certeza de la evidencia.

• **Neem (Azadirachta Indica A. Juss):** La nueva evidencia incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

• **Miel + Nigella Sativa:** La nueva evidencia incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

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

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

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

• **Lenzilumab:** La nueva evidencia 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 nueva evidencia, 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&section=methods. The repository is continuously updated, and the information is transmitted in real-time to the L·OVE platform, however, it was last checked for this review on May 6, 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); 3) Intervention's characteristicas (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.[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.

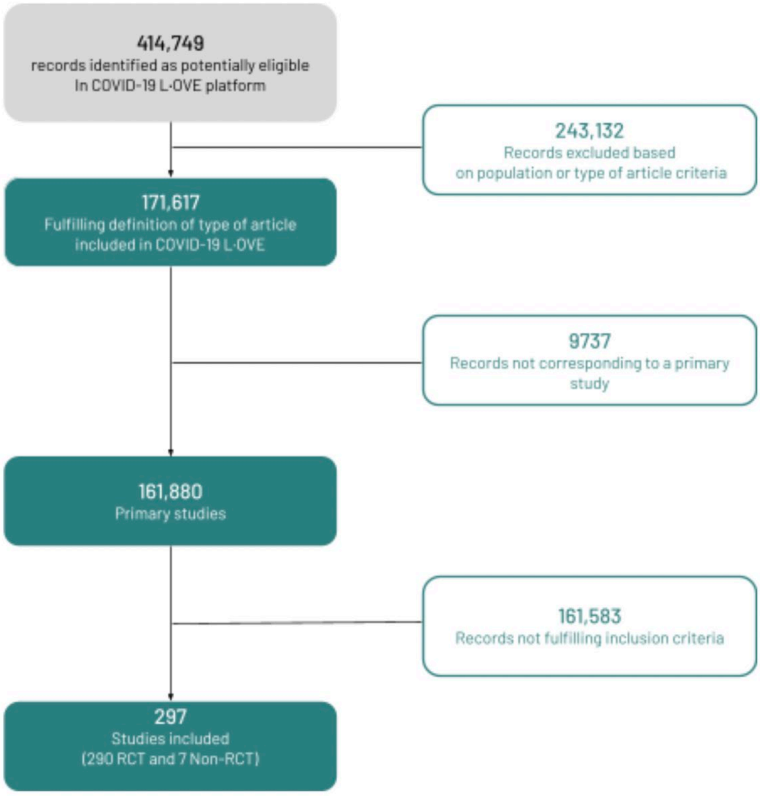
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in figure 1. A total of 297 studies were selected for inclusion, 290 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 misssing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result	Overall Risk-of-bias judgement	
						Mortality and Invasive mechanical ventilation	Symptoms, infection and adverse events
RECOVERY - Dexamethasone	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
RECOVERY - Hydroxychloroquine	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
BCN PEP CoV-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	NA	Some Concerns
ACTT-1	Low	Low	Low	Some Concerns	Low	Low	Low
COVID-19 PEP	Low	Low	High	Low	Low	NA	High
Cavalcanti et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kamran SM et al	High	Some Concerns	Low	High	Low	NA	High
COVID-19 PET	Low	Low	Low	Low	Low	Low	Low
SIMPLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BCN PEP CoV-2	High	Some Concerns	Low	High	Low	NA	High
Chen C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CAP-China remdesivir 2	Low	Low	Low	Low	Low	Low	Low
LOTUS China	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Tang et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hung IF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
GRECCO-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Li L et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RASTAVI	Low	Some Concerns	Low	High	Low	NA	High
Chen, Zeng et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zheng et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ELACOI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CONCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
GLUCOCOVID	High	Some Concerns	Low	Low	Low	High	High
CloroCOVID19	Low	Low	Low	Some Concerns	Low	Low	Low
Davoudi-Monfared et al	High	Some Concerns	Low	Low	Low	High	High
Chen et al	High	Some Concerns	Low	Low	Low	High	High
Davoodi L et al	High	Some Concerns	Low	Low	Low	High	High
Ivashchenko AA et al	High	Some Concerns	Low	Low	Low	High	High
Rasheed AM et al	High	Some Concerns	Low	Low	Low	High	High
Chen et al	High	Some Concerns	Low	Low	Low	High	High
Cao Y et al	Low	Some Concerns	Low	Low	Low	Low	Low
Chen PC et al	High	Some Concerns	Low	Low	Low	High	High
HC-nCoV	High	Some Concerns	Low	Low	Low	High	High
Lou Y et al	High	Some Concerns	Low	Low	Low	High	High
Vlaar APJ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Guvenmez O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Huang et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Yuan et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ren Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mehboob R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zhong et al	Low	Some Concerns	Low	Low	Low	Low	High
Sakoulas et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Hu K, Wang M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ESPERANZA	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopes et al	High	Low	Low	Low	Low	High	High
Duarte M et al	High	Some Concerns	Low	Some Concerns	Some Concerns	High	High
Metcovid	Low	Low	Low	Low	Low	Low	Low
Mansour E et al	Low	Low	Low	Some Concerns	Low	Low	High
Zhang J et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - Lopinavir-ritonavir	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Miller J et al	High	Some Concerns	Low	Some Concerns	Some Concerns	High	High
Abbaspour Kasgari H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sadeghi A et al	High	Some Concerns	Low	Low	Low	High	High
Shu L et al	High	Some Concerns	Low	Some Concerns	Low	High	High
SIMPLE 2	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
Abd-Elsalam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sekhavati E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zagazig University	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahmani H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ConPlas-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CoDEX	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVIDIOL	High	Some Concerns	Low	Some Concerns	Low	High	High
CAPE COVID	Low	Low	Low	Low	Low	Low	Low
COVACTA	Low	Low	Low	Low	Low	Low	Low
COALITION II	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Li T et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Wang D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mohiuddin ATMM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLACID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Gharebaghi N et al	High	Low	Low	Low	Low	Some Concerns	Some Concerns
TX-COVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
Cheng LL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Farahani R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kimura KS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATENEA-Co-300	High	Some Concerns	Low	Some Concerns	Low	High	High
Wu X et al	Low	Low	Low	Low	Low	Low	Low
Balcells ME et al (Pontificia Universidad Catolica de Chile)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Edalatifard M et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PREP	Low	Low	Low	Low	Low	Low	Low
Wang M, Hu K et al (Renmin Hospital of Wuhan University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Doi Y et al (Fujita Health University Hospital)	High	Some Concerns	Low	Some Concerns	Low	High	High
Podder CS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Edalatifard M et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PREP	Low	Low	Low	Low	Low	Low	Low
Wang M, Hu K et al (Renmin Hospital of Wuhan University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Doi Y et al (Fujita Health University Hospital)	High	Some Concerns	Low	Some Concerns	Low	High	High

Podder CS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
TEACH	High	Low	Low	Some Concerns	Low	High	High
Nojomi et al (Iran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PrEP_COVID	Low	Low	Low	Low	Low	Low	Low
de Alencar JCG et al (Universidade de São Paulo)	Low	Low	Low	Low	Low	Low	Low
Fu W et al (Shanghai Public Health Clinical Center)	High	Some Concerns	Low	Some Concerns	Low	High	High
Salehzadeh F (Ardabil University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
Dabbous H et al (Ain Shams University)	High	Some Concerns	Low	Some Concerns	Low	High	High
PATCH	Low	Low	Low	Low	Low	Low	Low
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLASM-AR	Low	Low	Low	Low	Low	Low	Low
COVID-19-MCS	Low	Low	Low	Some Concerns	High	Low	High
Ansarin K (Tabriz University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
WHO SOLIDARITY - HCQ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - LPV/r	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - remdesivir	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - IFN	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - IFN	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Yethindra V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shi L et al	Low	Low	Low	Low	Low	Low	Low
RCT-TCZ-COVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BACC Bay Tocilizumab Trial	Low	Low	Low	Low	Low	Low	Low
SARITA-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
Ghaderkhani S et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PEP (University of Washington)	Low	Low	Low	Low	Low	NA	Low
Hashim HA et a (Alkarkh Health Directorate-Baghdad)	High	Some Concerns	Low	Some Concerns	Low	High	High
ILBS-COVID-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PROBIOZOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Padmanabhan U et al (Medical Education and Drugs Departmen	High	Low	Low	Low	Low	High	High
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khamis F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BLAZE-1	High	Low	Low	Low	Low	High	High
PETAL	Low	Low	Low	Low	Low	Low	Low
Lanzoni G et al	High	Low	Low	Low	Low	High	High
Ruzhentsova T et al (R-Pharm)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Lenze E et al	Low	Low	Low	Low	Low	Low	Low
Monk P et al	Low	Low	Low	Low	Low	Low	Low
SHADE trial	High	Some Concerns	Low	Some Concerns	Low	High	High
Yakoot M et al (Pharco Corporate)	High	Some Concerns	Low	Some Concerns	Low	High	High
Ghandehari S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HAHPS	Low	High	Low	Some Concerns	Low	High	High
Elgazzar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgazzar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgazzar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Tabarsi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAV052020 (Promomed, LLC)	High	Some Concerns	Low	Some Concerns	Low	High	High
Murai IH et al (University of Sao Paulo)	Low	Low	Low	Low	Low	Low	Low
Udwadia ZF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-TOCI 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EMPACTA	Low	Low	Low	Low	Low	Low	Low
HYCOVID	Low	Low	Low	Low	Low	Low	Low
Krolewiecki A et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ILIAD	Low	Low	Low	Low	Low	Low	Low
AB-DRUG-SARS-004	High	Low	Low	Low	Low	High	High
Q-PROTECT	Low	Low	Low	Low	Low	Low	Low
Hassan M et al	High	Low	Low	Low	Low	High	High
FundacionINFANT-Plasma	Low	Low	Low	Low	Low	Low	Low
COVID-Lambda	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Niaee MS et al	Low	Some Concerns	Low	Some Concerns	Low	Low	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 S et al	High	Low	Low	Low	Low	High	High
ITOLI-C19-02-I-00	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Prolectin-M	High	Some Concerns	Low	Some Concerns	Low	High	High
Maldonado V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
GARGLES	High	Some Concerns	Low	Some Concerns	Low	High	High
ERSul	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
SAINT	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 AZ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Balykova LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Babalola et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REMAP-CAP - tocilizumab	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Abdelmaksoud AA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kirti R et al	Low	Low	Low	Low	Low	Low	Low
Kumari P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FK/FAV00A-CoV/2020	High	Low	Low	Low	Low	High	High
IVERCAR-TUC	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIFERON	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY-Plasma	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Interferon in COVID (Alavi Darazam I et al)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AB-DRUG-SARS-004 (Cadegiani FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
JamaliMoghadamSiahkali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedighiyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Roostaei A et al	High	Low	Low	Low	Low	High	High
Bee-Covid	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEOT	High	Some Concerns	Low	Some Concerns	Low	High	High
RIVET-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Rezai M et al	Low	Low	Low	Low	Low	Low	Low
Spoorthi V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Raad H et al	High	Low	Low	Low	Low	High	High
IVE-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Okumus	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	Some Concerns	Some Concerns
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
Famoosh G et al	Some Concerns	Some Concerns	High	Some Concerns	Low	High	High
Khalili H et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Baklaushev VP et al	High	Some Concerns	Low	Some Concerns	Low	High	High
KILLER	High	Some Concerns	Low	Some Concerns	Low	High	High
HYDRA	Low	Some Concerns	Low	Low	Low	Low	Low
Sali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
NITFQM0320OR	High	Some Concerns	Low	Some Concerns	Low	High	High
SVU-MED-CHT019-420860	High	Some Concerns	Low	Some Concerns	Low	High	High
STOIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Borges M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY-TCZ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDAtoZ -Zinc	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVIDAtoZ - Vit C	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVID-19 Early Treatment	Low	Some Concerns	Low	Low	Low	Low	Low
Shogenova LV et al	High	Some Concerns	Low	Some Concerns	Low	High	High
EFC16844	Low	Some Concerns	Low	Low	Low	Low	Low
ARTI-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Purwati	High	Some Concerns	Low	Some Concerns	Low	High	High
VB-N-IVIG-COVID-19/2020-CT2	High	Some Concerns	Low	Some Concerns	Low	High	High
Jamaati H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Beltran-HCQ	High	Some Concerns	Low	Some Concerns	Low	High	High
Beltran-Ivermectin	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-Vaskeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopez-Medina	Low	Some Concerns	Low	Low	Low	Low	Low
Lakkireddy M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Silva	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High
Bermejo Galan	Low	Some Concerns	Low	Low	Low	Low	Low
Pott-Junior	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mikhaylov	Low	Some Concerns	Low	Some Concerns	Low	Low	High
2GAMMACOVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
AAAS9924	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Tolouian et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ElZein R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PEGI.20.002	High	Some Concerns	Low	Some Concerns	Low	High	High
MASH-COVID	Low	Some Concerns	Low	Low	Low	Low	Low
INSPIRATION	Low	Some Concerns	Low	Low	Low	Low	Low
Zarychanski	Low	Some Concerns	Low	Low	Low	Low	Low
Santos PSS et al	Low	Some Concerns	Low	Low	Low	Low	Low
Solaymani-Dodaran M et al	Low	Some Concerns	Low	Low	Low	Low	Low
TD-0903-0188	High	Some Concerns	Low	Some Concerns	Low	High	High
DISCOVER	Low	Some Concerns	Low	Low	Low	Low	Low
SURG-2020-28683	Low	Some Concerns	Low	Low	Low	Low	Low
Alavi-Moghaddam M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CT-P59 3.2	Low	Some Concerns	Low	Low	Low	Low	Low
Yadollahzadeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BBCovid	Low	Some Concerns	Low	Low	Low	Low	Low
Hanna Huang Y et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Gaynitdinova VV et al	High	Some Concerns	Low	Some Concerns	Low	High	High
K031-120	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Beltran Gonzalez JL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Doaei S et al	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High
COVID-AIV	High	Some Concerns	Low	Some Concerns	Low	High	High
Amra B et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ribakov AR et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kishoria N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CERC-002-CVID-201	High	Low	High	Some Concerns	Low	High	High
Mahajan L et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Pouladzadeh M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
HBOTCOVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
RESIST	High	Some Concerns	Low	Some Concerns	Low	High	High
CARR-COV-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Seet	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SBU-COVID19-ConvalescentPlasma	Low	Some Concerns	Low	Low	Low	Low	Low
TOGETHER	Low	Some Concerns	Low	Low	Low	Low	Low
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High

OSCAR	Low	Some Concerns	Low	Low	Low	Low	Low
POLYCOR	Low	Some Concerns	Low	Low	Low	Low	Low
Vanguard	Low	Some Concerns	Low	Low	Low	Low	Low
Samimagham HR et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CamoCO-19	Low	Some Concerns	Low	Low	Low	Low	Low
BCR-PNB-001	High	Some Concerns	Low	Some Concerns	Low	High	High
ATOMIC2	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Siami Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CLOROTRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High
PROBCO	High	Some Concerns	Low	Some Concerns	Low	High	High
Nesari TM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PISCO	High	Some Concerns	Low	Some Concerns	Low	High	High
HNS-COVID-PK	Low	Some Concerns	Low	Low	Low	Low	Low
Rashad A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Moni M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
FACCT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COV-BARRIER	Low	Some Concerns	Low	Low	Low	Low	Low
LIVE-AIR	Low	Some Concerns	Low	Low	Low	Low	Low

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 1.)
- 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 2. and 3.)

Figure 1. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19

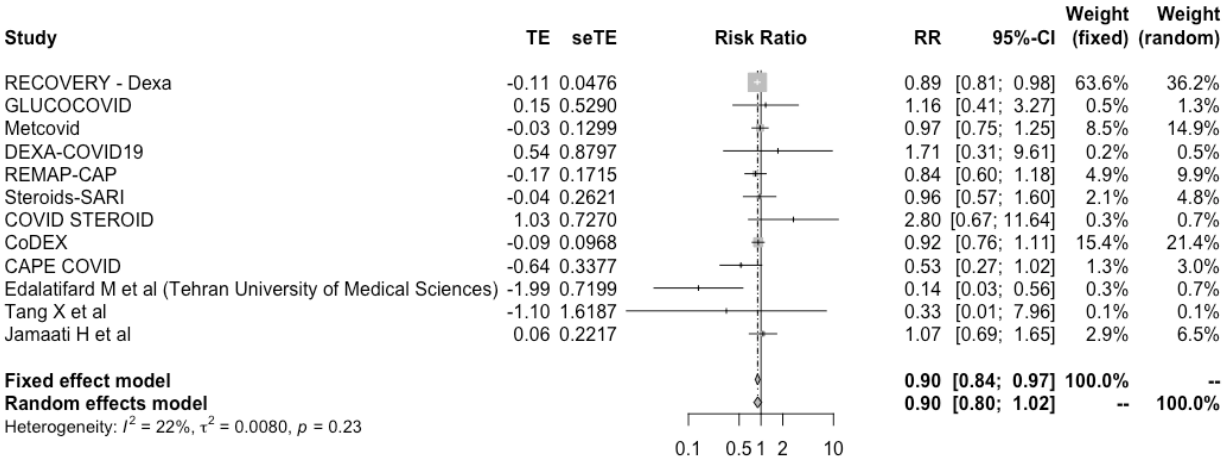


Figure 2. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

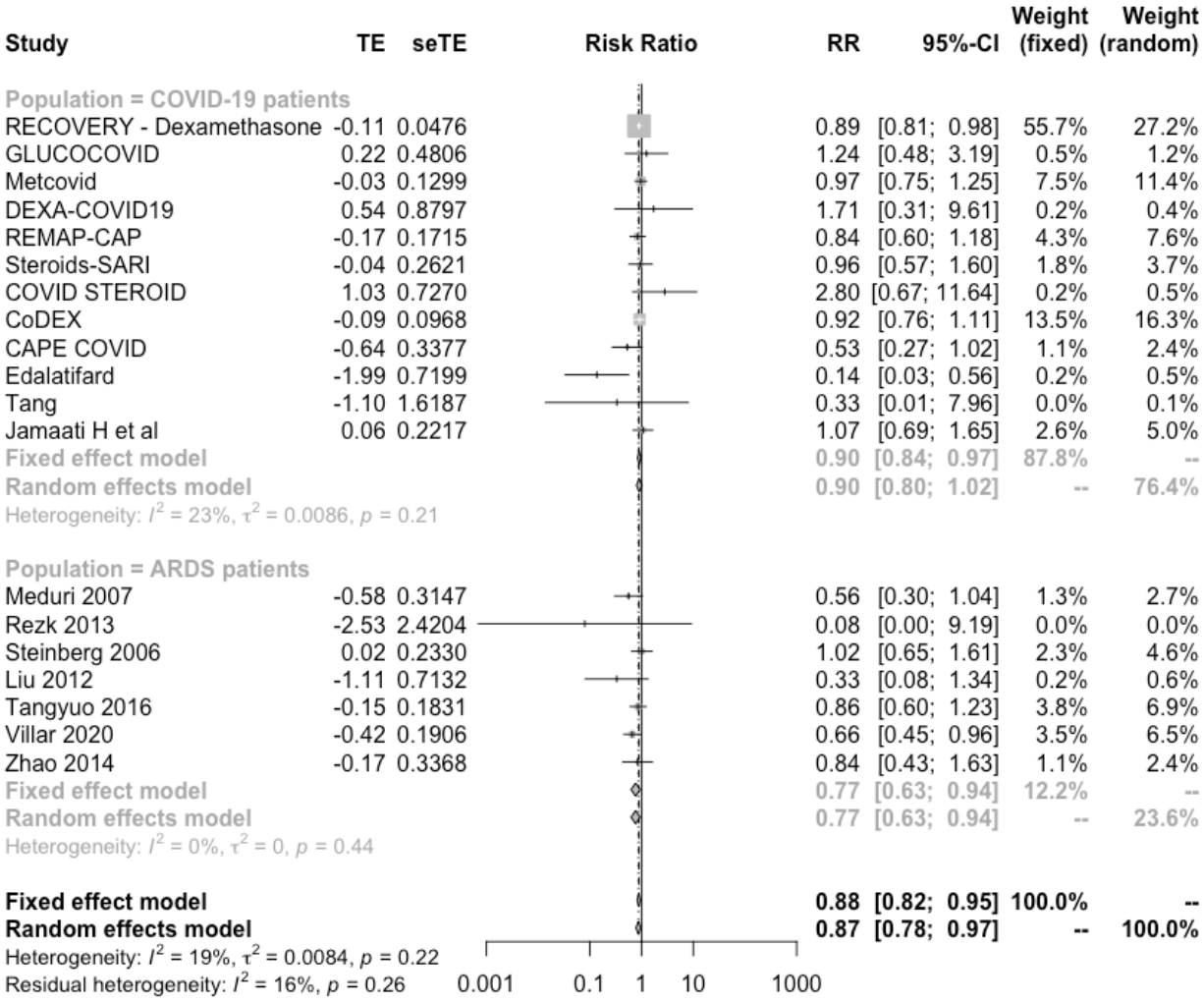
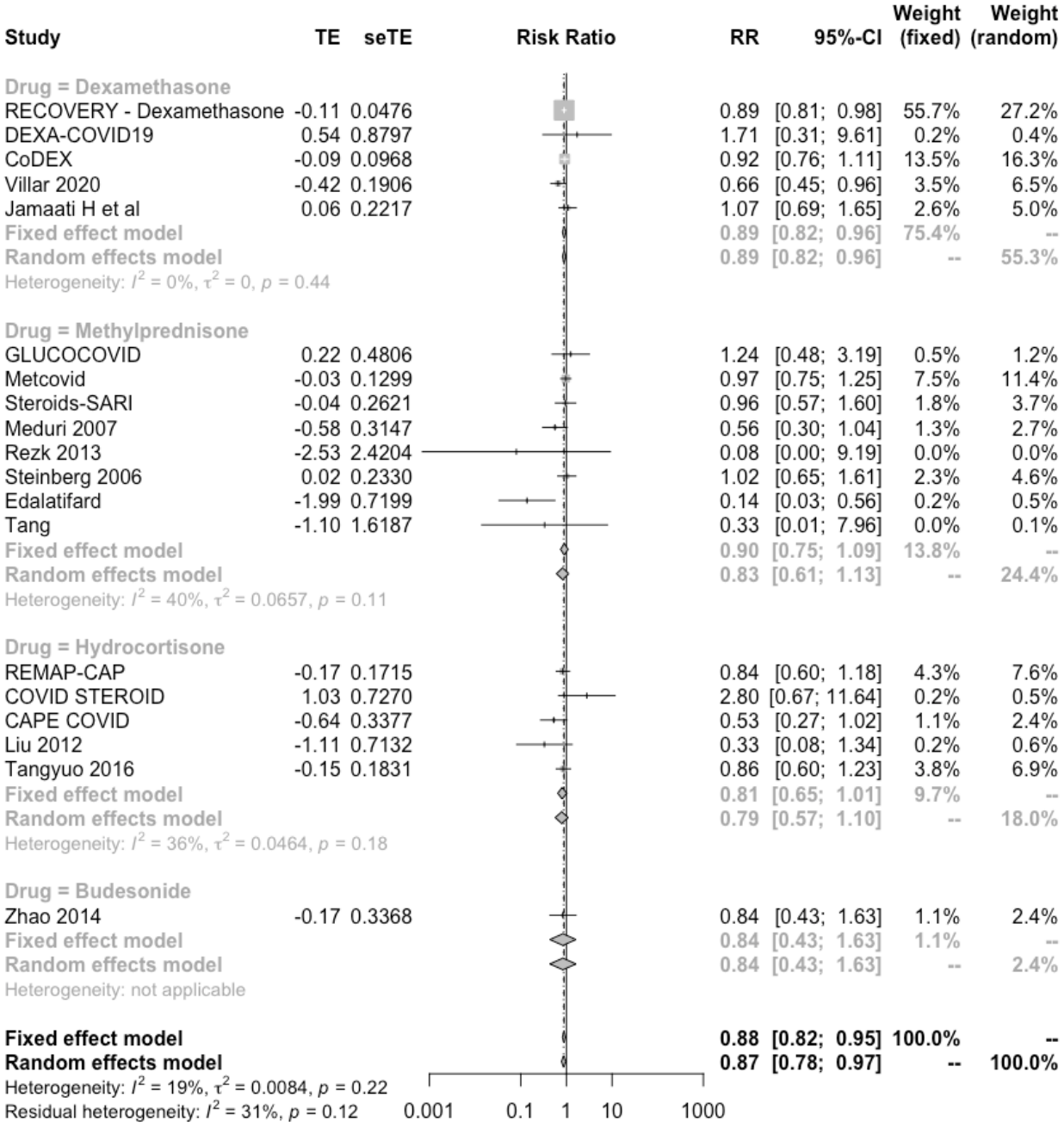


Figure 3. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19



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 4.)
- 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 5.)
- 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 6.)
- 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 4. All-cause mortality with remdesivir use vs. standard of care in randomized control trials including COVID-19 patients

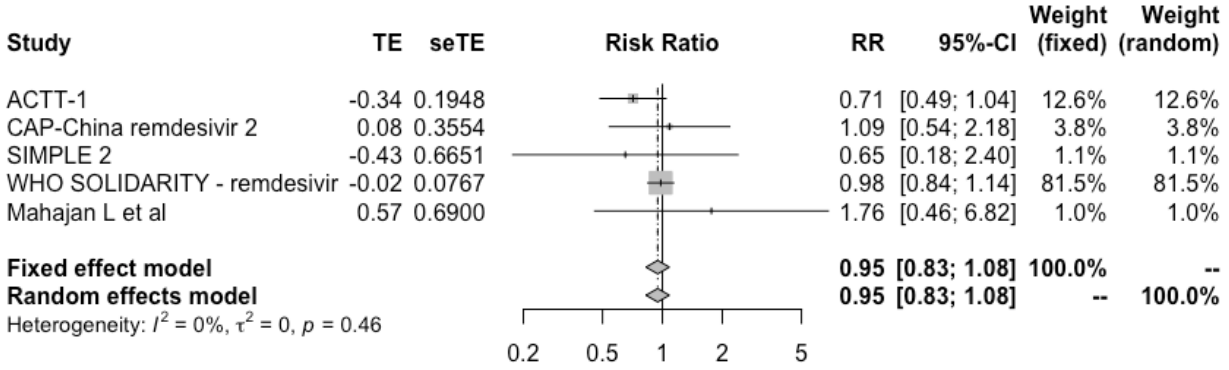


Figure 5. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

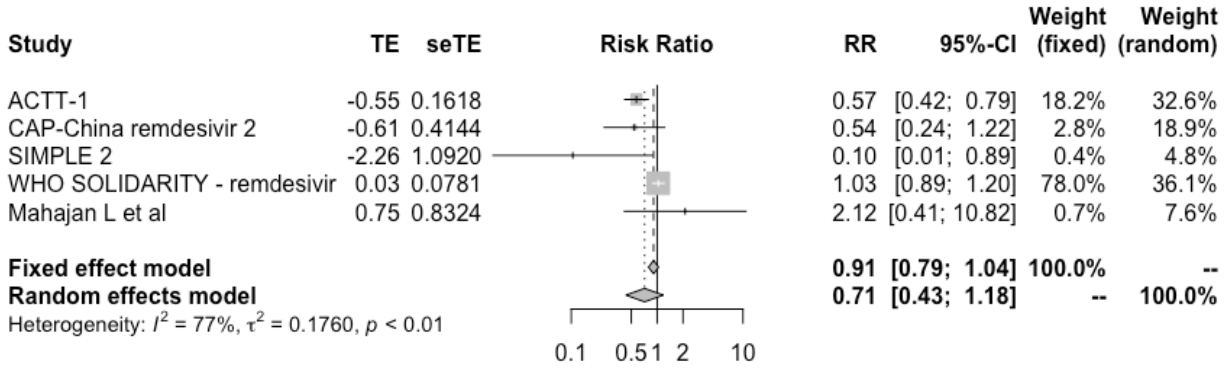
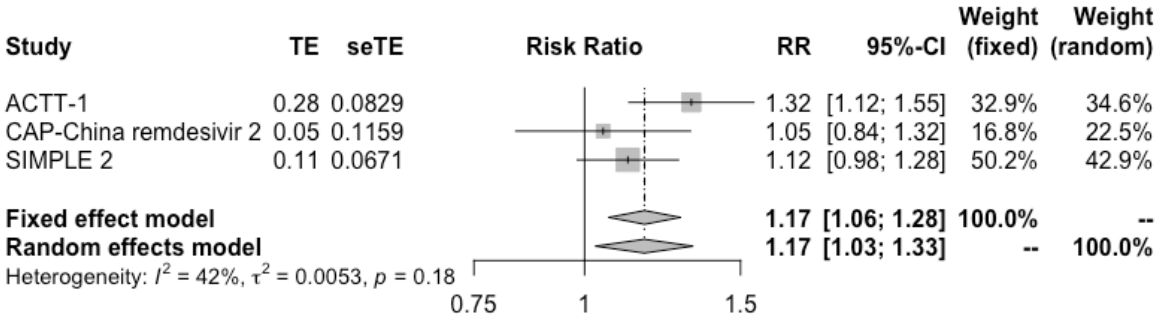


Figure 6. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 41 RCTs including 19,699 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 7.)
- Hydroxychloroquine or chloroquine probably does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.91 to 1.26); RD 1.2% (95%CI -1.6% to 4.5%); 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 8.) (based on low risk of bias studies)
- Hydroxychloroquine or chloroquine may not significantly increase the risk of severe adverse events, RR 0.9 (95%CI 0.59 to 1.37); RD -1% (95%CI -4.2% to 3.8%); 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 7. All-cause mortality in RCTs comparing hydroxychloroquine or chloroquine with standard of care in patients with COVID-19

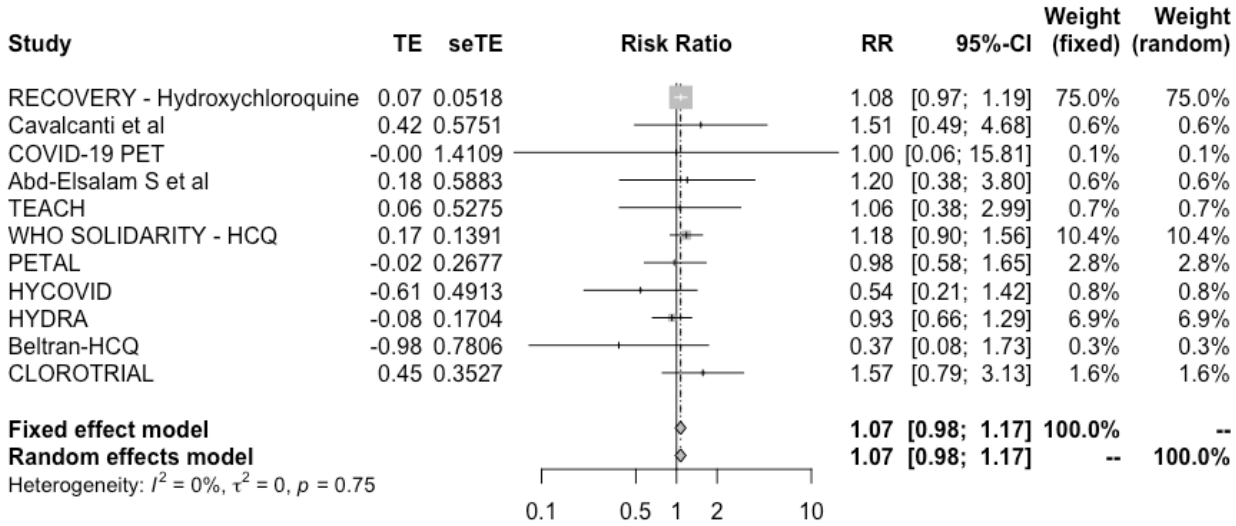
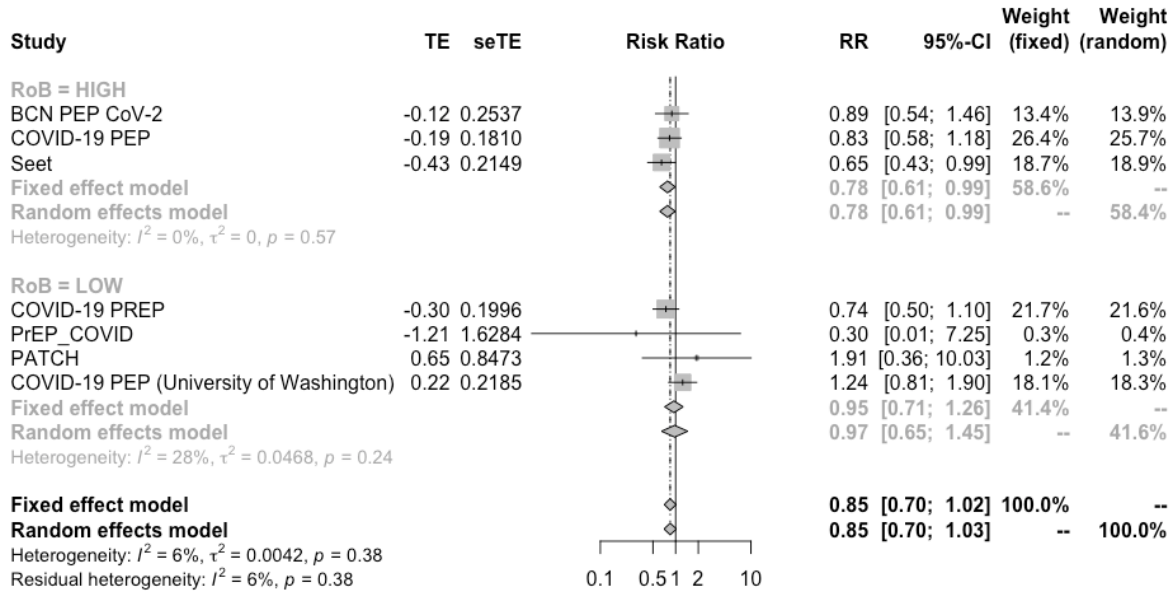


Figure 8. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



In addition, we identified a systematic review[10] that included 12 unpublished studies providing information on mortality outcome. Overall pooled estimates did not differ when including unpublished information (OR 1.08, 95%CI 0.99 to 1.18).

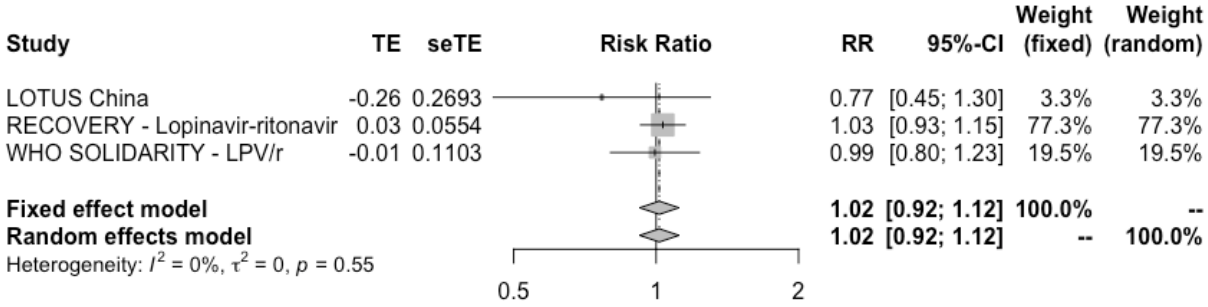
Lopinavir-Ritonavir

See Summary of findings Table 4, Appendix 1

We identified thirteen RCTs including 9,421 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 1.02 (95%CI 0.92 to 1.22); RD 0.3% (95%CI -1.3% to 1.9%); Moderate certainty ⊕⊕⊕◯ (Figure 9.)
- 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 9. All-cause mortality in RCTs comparing lopinavir–ritonavir with standard of care for treatment of patients with COVID-19



Convalescent plasma

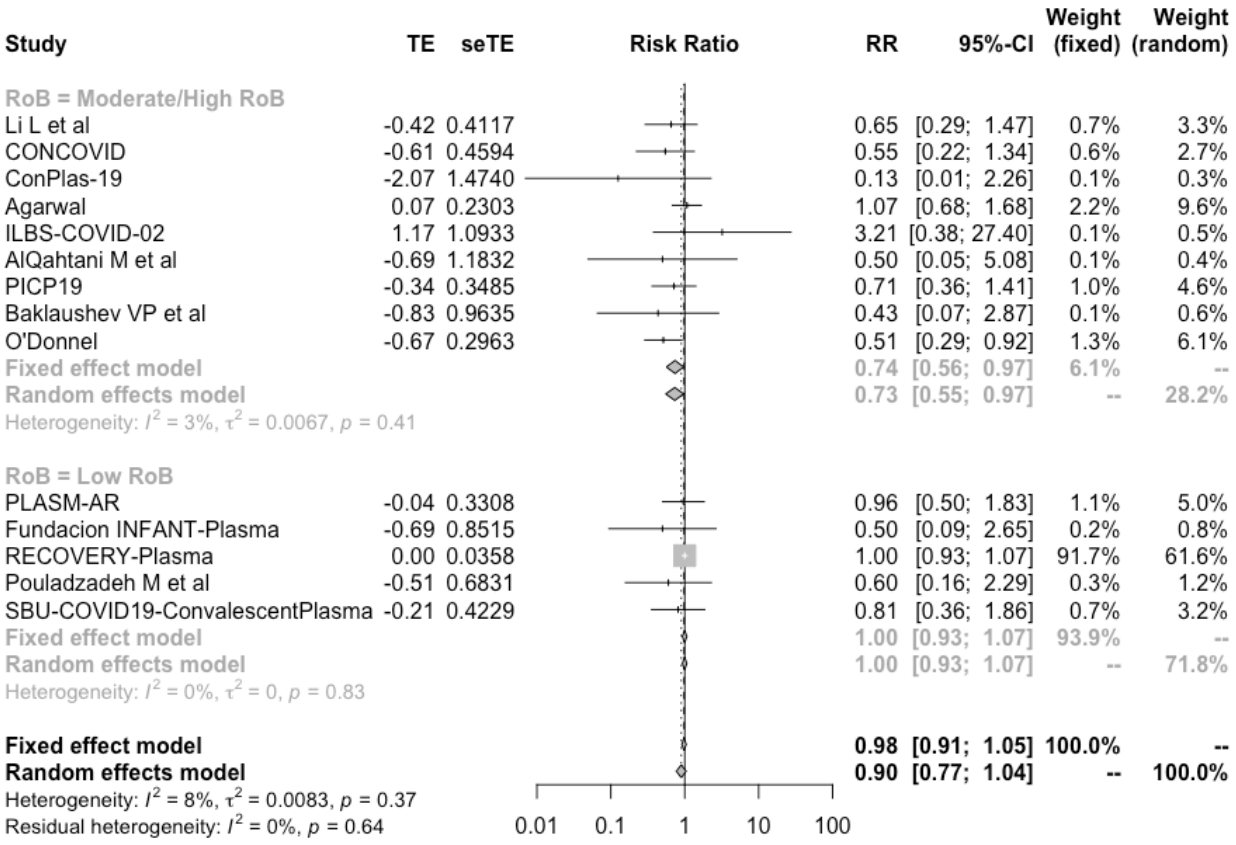
See summary of findings table 5 in appendix 1

We identified sixteen RCT including 13605 patients in which convalescent plasma was compared against standard of care or other treatments. RECOVERY was the biggest study including 11588 patients. Most studies (14/16) 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 1 (95%CI 0.93 to 1.07); RD 0% (95%CI -1.1% to 1.1%); Moderate certainty ⊕⊕⊕◯ (figure 10.) (based on low risk of bias studies)
- Convalescent plasma probably does not significantly reduces invasive mechanical ventilation requirements, RR 0.91 (95% CI 0.77 to 1.07); RD -1.6% (95%CI -4% to 1.2%); Moderate certainty ⊕⊕⊕◯ (based on low risk of bias studies).
- 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 ⊕⊕⊕◯
- It is uncertain if convalescent plasma increases severe adverse events, RR 0.97 (95% CI 0.67 to 1.41); RD -0.3% (95%CI -3.4% to 4.2%); Very 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 10. 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 ⊕◯◯◯ 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 eleven RCTs including 6589 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 0.89 (95%CI 0.77 to 1.03); RD -1.8% (95%CI -3.7% to 0.5%); Moderate certainty ⊕⊕⊕◯ (Figure 11.)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.83 (95%CI 0.77 to 0.89); RD -2.9% (95%CI -4% to -1.9%); High certainty ⊕⊕⊕⊕ (Figure 12.)
- 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, RR 0.89 (95%CI 0.75 to 1.07); RD -1.1% (95%CI -2.5% to 0.7%); Moderate certainty ⊕⊕⊕◯

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

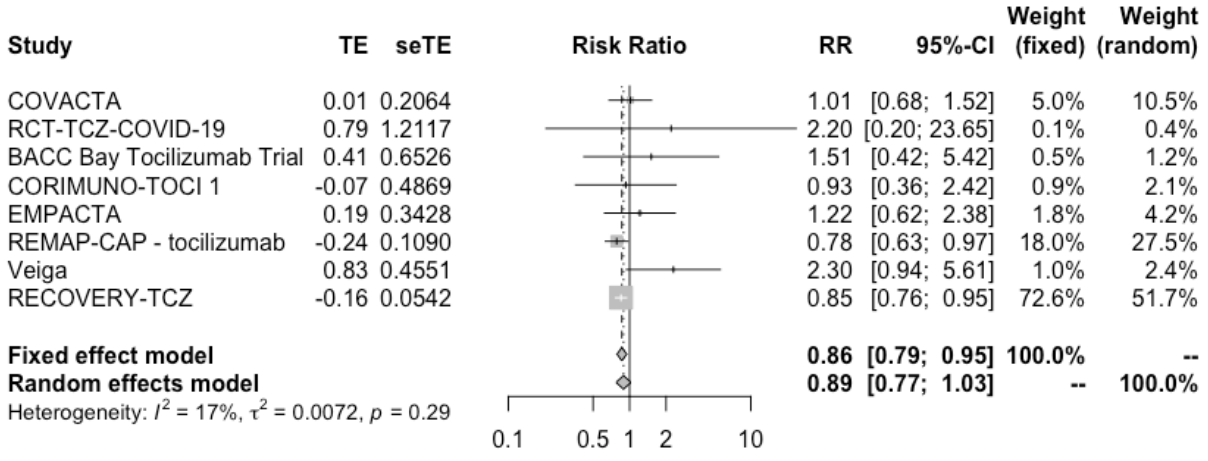
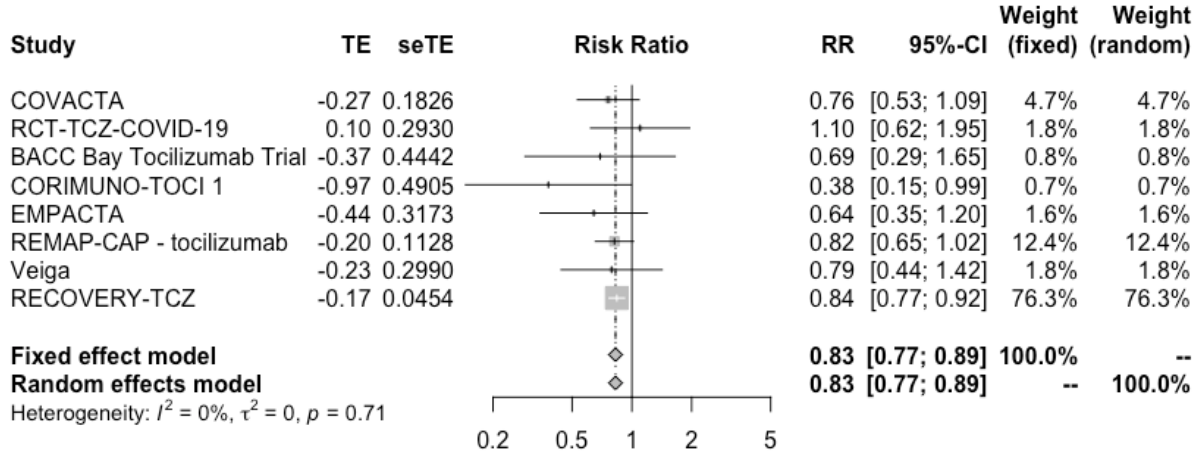


Figure 12. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



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

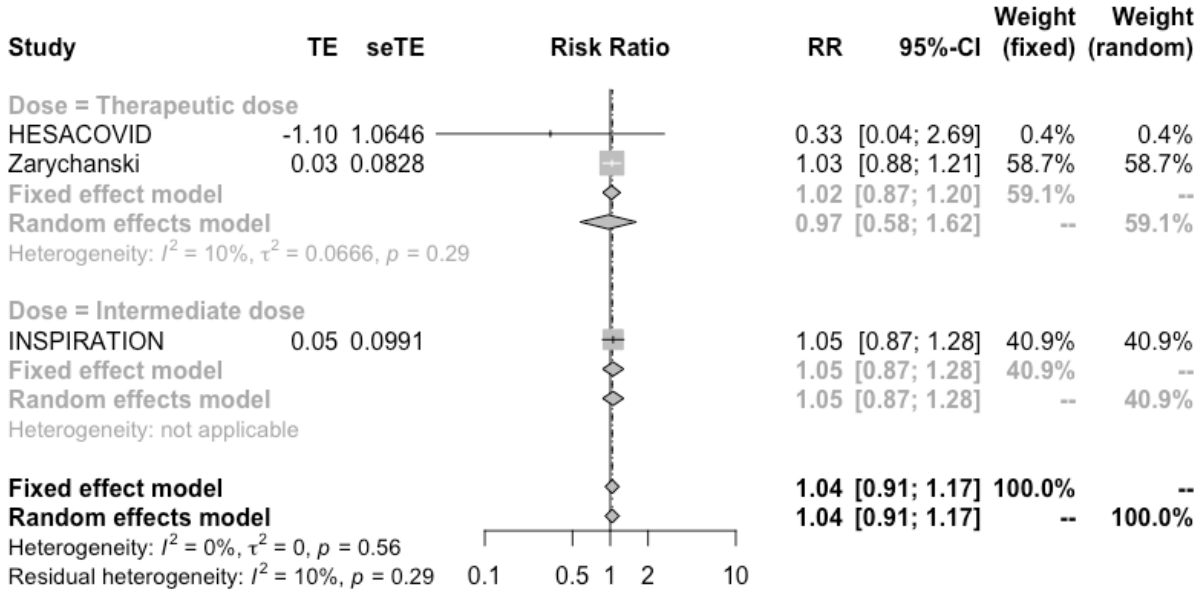
See Summary of findings Table 7, Appendix 1

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 three RCTs including 1656 patients that compared anticoagulants in intermediate (i.e enoxaparin 1mg/kg a day) or full dose (i.e enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e enoxaparin 40mg 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 1.04 (95%CI 0.91 to 1.17); RD 0.6% (95%CI -1.4% to 2.7%); Moderate certainty ⊕⊕⊕◯ (Figure 13.)
- Anticoagulants in intermediate dose may slightly reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.93 (95%CI 0.38 to 2.26); RD -0.5% (95%CI -4.3% to 8.8%); Low certainty ⊕⊕◯◯

- Anticoagulants in full dose may reduce venous thromboembolic events in comparison with prophylactic dose, RR 0.58 (95%CI 0.37 to 0.91); RD -2.9% (95%CI -4.4% to 0.6%); Low certainty ⊕⊕◯◯
- Anticoagulants in intermediate dose or full dose may increase major bleeding in comparison with prophylactic dose, RR 1.43 (95%CI 0.76 to 2.71); RD 0.8% (95%CI -0.4% to 3.2%); Low certainty ⊕⊕◯◯

Figure 13. All-cause mortality in RCTs using anticoagulants in therapeutic dose, intermediate dose or prophylactic dose for treatment of hospitalized patients with COVID-19



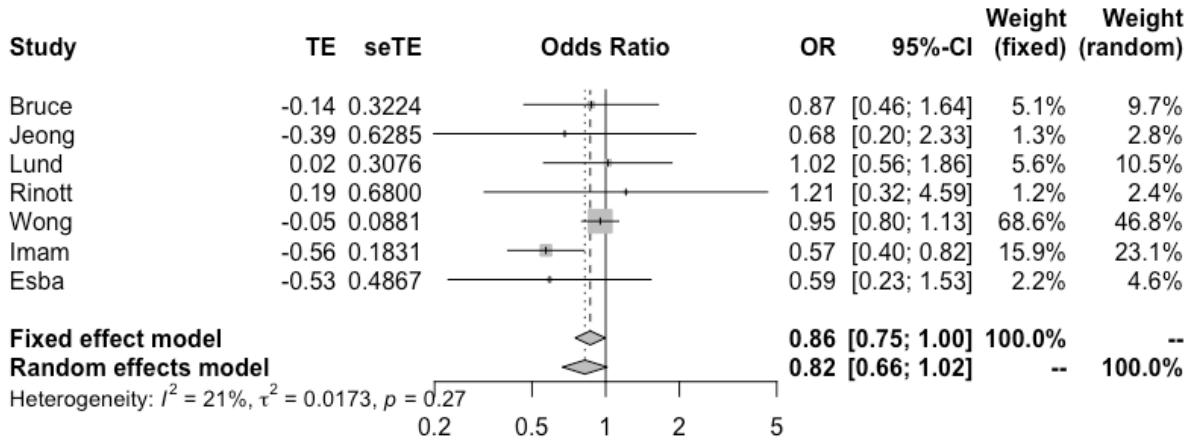
NSAIDs

See Summary of findings table 8, Appendix 1

We identified seven non-RCTs including at least 100 patients in which COVID-19 mortality risk was compared between groups of patients exposed to NSAIDs and those that were not. Populations 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 14.)

Figure 14. All-cause mortality in non-RCTs comparing exposure to NSAIDs with no exposure in individuals exposed to or infected with COVID-19



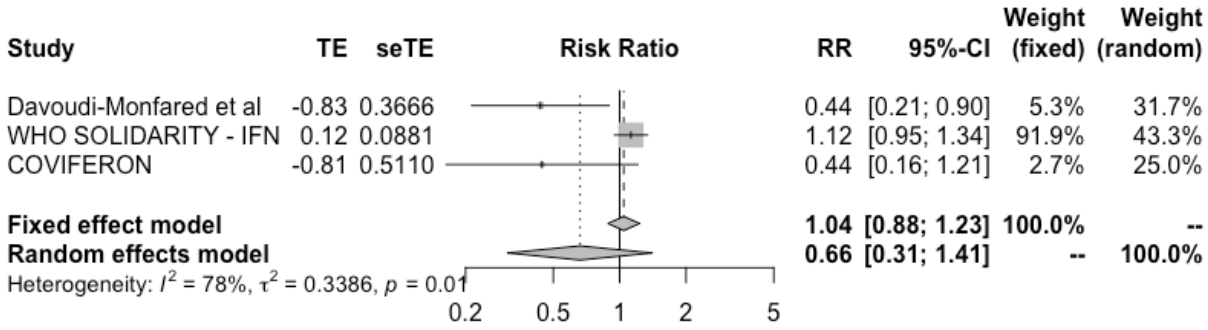
Interferon Beta-1a

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 15.)
- 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 15. All-cause mortality with IFN beta-1a vs. standard of care in randomized studies including COVID-19 patients

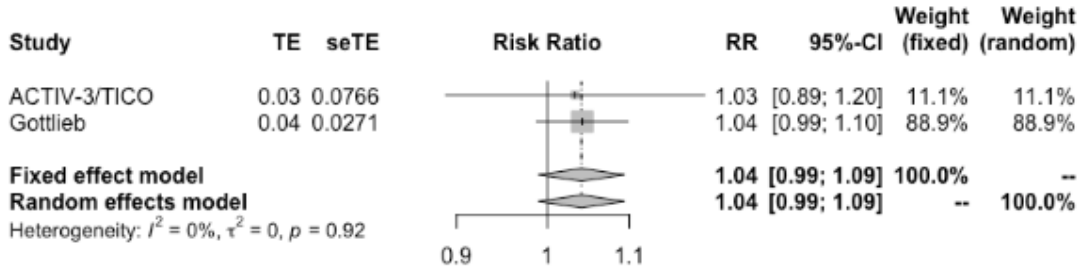


Bamlanivimab (monoclonal antibody)

We identified three RCT including 1187 patients in which bamlanivimab was compared against standard of care. The studies included mild to moderate patients as 0 to 3% patients died. Our results showed:

- It is uncertain if bamlanivimab reduces mortality or mechanical ventilation requirements; 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 16.)
- It is uncertain if bamlanivimab increases the risk of severe adverse events; Very low certainty ⊕◯◯◯
- It is uncertain if bamlanivimab affects hospitalizations in patients with non-severe disease; Very low certainty ⊕◯◯◯

Figure 16. Symptom resolution or improvement with bamanivimab vs. standard of care in randomized studies including COVID-19 patients



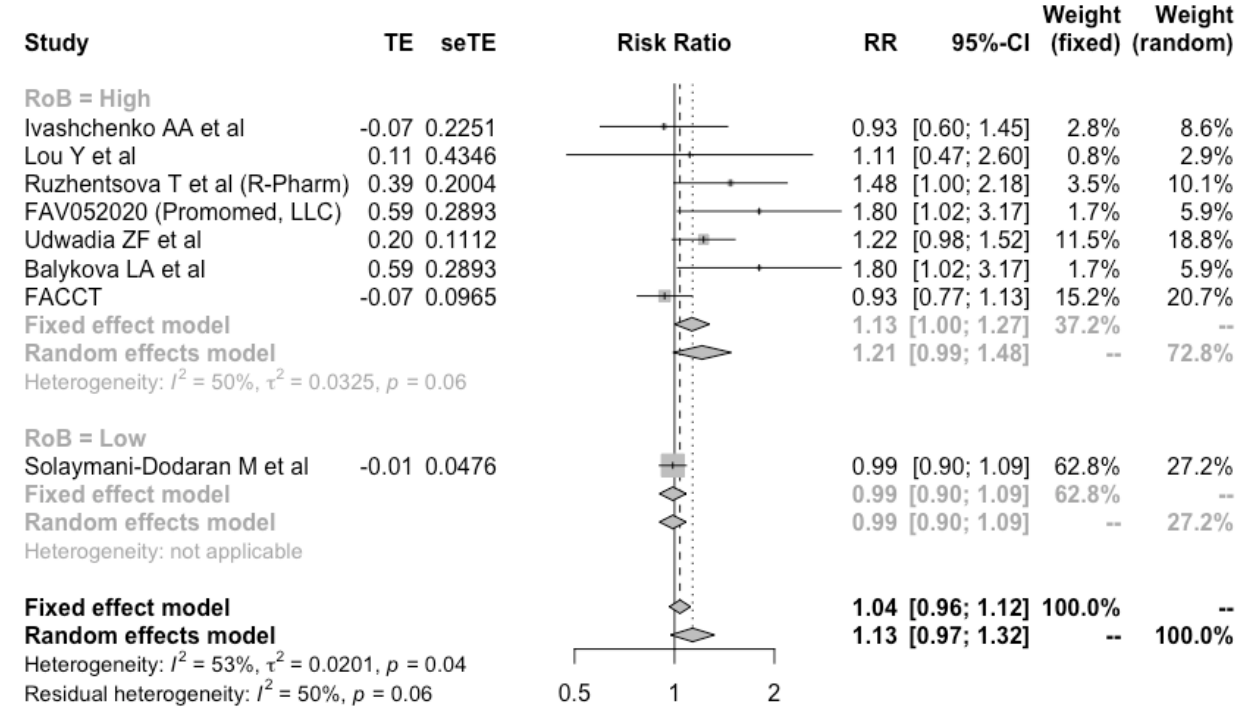
Favipiravir

See Summary of findings Table 10, 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 17.) (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 17. 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 11, Appendix 1

We identified twenty eight RCT including 4837 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 have important methodological limitations including inappropriate randomization process and lack of allocation concealment. Our results showed:

- Ivermectin may not significantly reduce mortality, RR 0.94 (95%CI 0.51 to 1.73); RD -0.96% (95%CI -7.8% to 11.7%); Low certainty ⊕⊕◯◯ (Figure 18) (based on low risk of bias studies)
- It is uncertain if ivermectin affects mechanical ventilation requirements, RR 0.89 (95%CI 0.38 to 2.07); RD -1.9% (95%CI -10.7% to 18.5%); Very low certainty ⊕◯◯◯

- Ivermectin probably does not improve symptom resolution or improvement, RR 1 (95%CI 0.9 to 1.11); RD 0% (95%CI -6% to 6.6%); Moderate certainty ⊕⊕⊕◯ (figure 19) (based on low risk of bias studies)
- It is uncertain if ivermectin affects symptomatic infection, RR 0.22 (95%CI 0.09 to 0.53); RD -13.6% (95%CI -15.8% to -8.2%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects severe adverse events, RR 1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.2%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects hospitalizations in non-severe patients, RR 0.66 (95%CI 0.69 to 2.30); RD 2.5% (95%CI -6% to 9.6%); Very low certainty ⊕◯◯◯

Figure 18. Mortality in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19

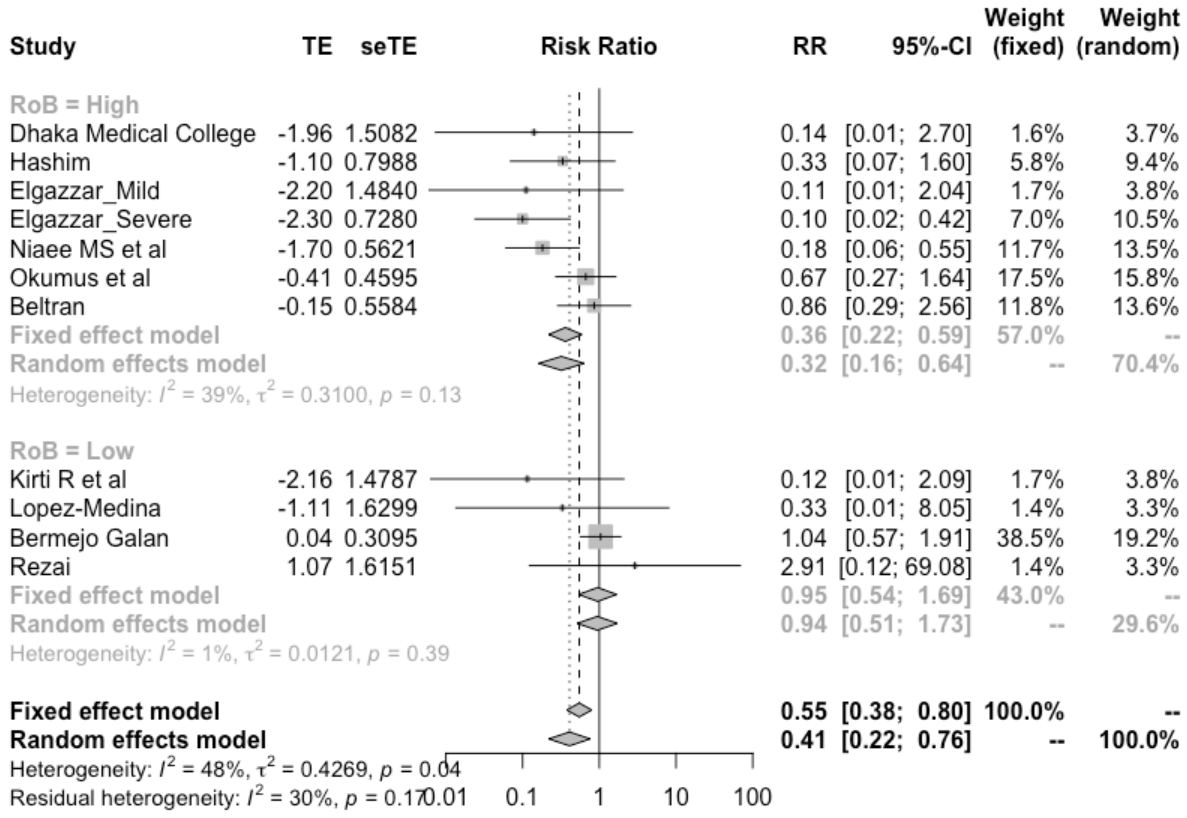
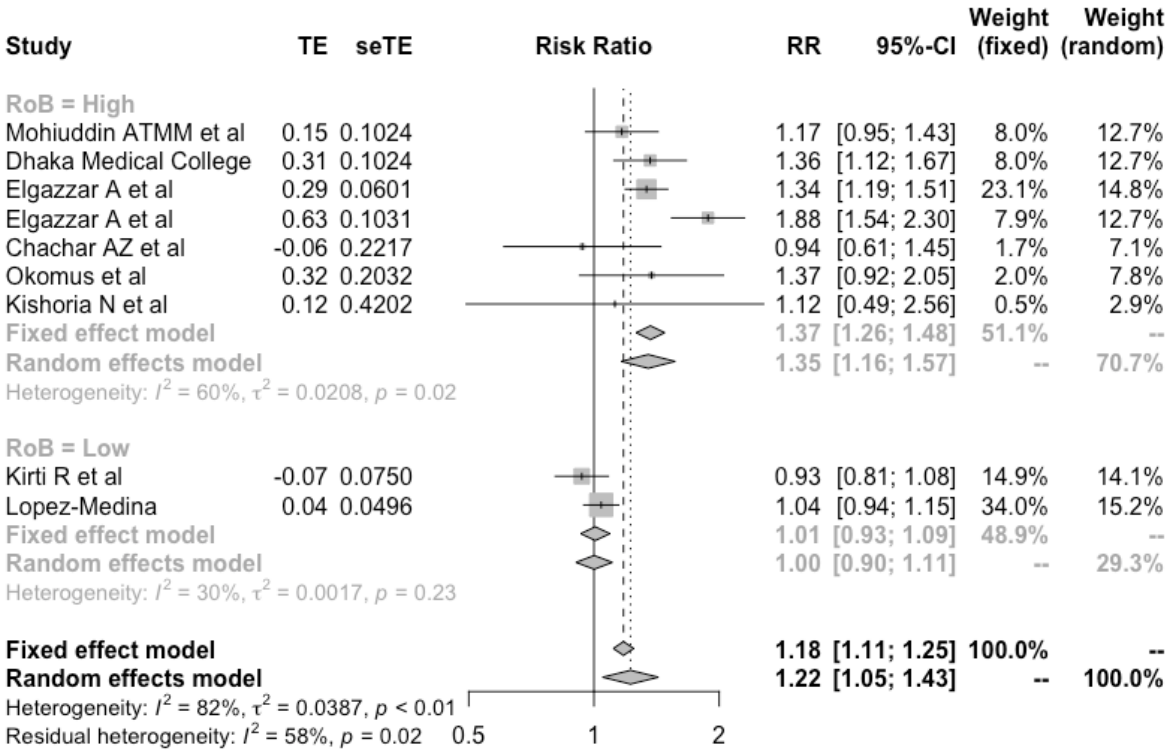


Figure 19. Symptom resolution or improvement in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



Although pooled estimates suggest significant benefits with ivermectin for some critical outcomes, included studies methodological limitations, small overall number of events and the possibility of publication bias results in very low certainty of the evidence. Further research is needed to confirm or discard those findings.

Baricitinib

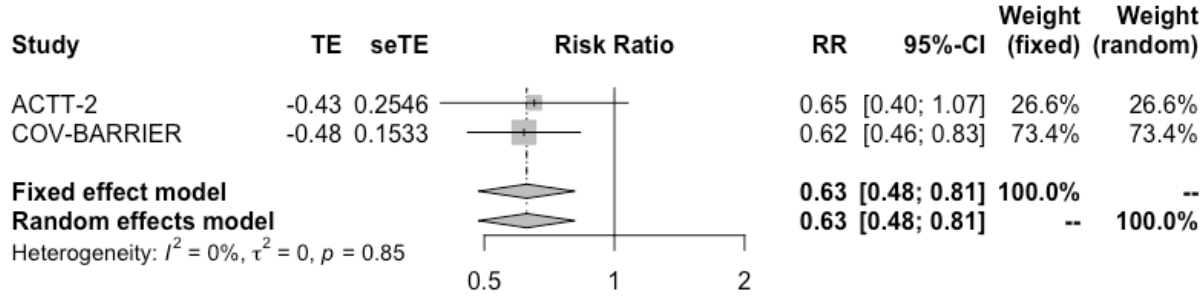
See Summary of findings Table 12, Appendix 1

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 20.)
- 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 20. Mortality in randomized studies comparing baricitinib with standard of care in patients with COVID-19



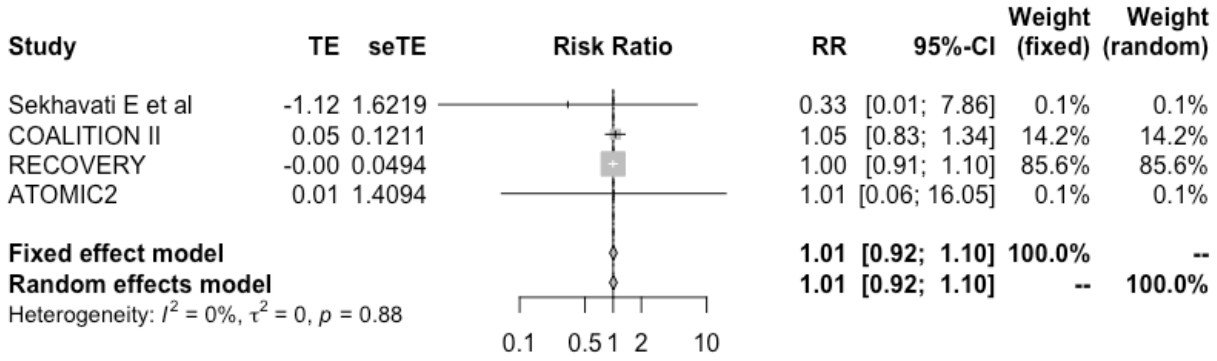
Azithromycin

See Summary of findings Table 13, 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:

- Azithomycin 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 21.)
- Azithomycin 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 21. Mortality in randomized studies comparing azithromycin with standard of care in patients with COVID-19

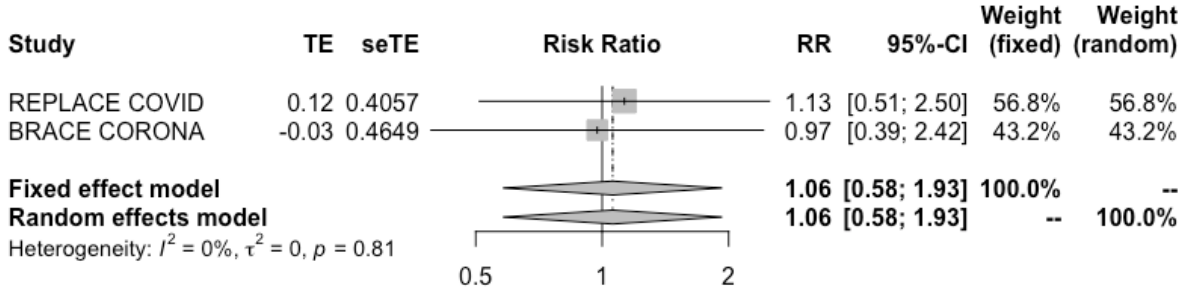


ACEI/ARB discontinuation

We identified two RCT including 811 patients in which patients with COVID-19 were randomized to discontinue or continue ACEI/ARB treatment. Our results showed:

- ACEI/ARB discontinuation may not reduce mortality, RR 1.01 (95%CI 0.58 to 1.93); RD 1% (95%CI -6.7% to 14.9%); Low certainty ⊕⊕◯◯ (Figure 22.)
- ACEI/ARB discontinuation may not reduce mechanical ventilation requirements, RR 0.94 (95%CI 0.63 to 1.39); RD -1.04% (95%CI -6.4% to 6.7%); Low certainty ⊕⊕◯◯ (Figure 20.)

Figure 22. Mortality in randomized studies comparing discontinuation vs continuation of ACEI/ARB in patients with COVID-19



Colchicine

See Summary of findings Table 14, Appendix 1

We identified four RCT including 4731 patients in which colchicine was compared against standard of care or other treatments. The COLCORONA trial was the biggest, with 2,235 patients assigned to intervention and 2,253 to control. Studies included patients with mild to severe disease, as shown by the mortality rates in the control arms, which ranged from 0% to 7%. Our results showed:

- Colchicine may reduce mortality, RR 0.45 (95%CI 0.18 to 1.12); RD -8.8% (95%CI -13.1% to 1.9%); Low certainty ⊕⊕◯◯ (Figure 23.)
- Colchicine may reduce mechanical ventilation requirements, RR 0.48 (95%CI 0.24 to 0.96); RD -9% (95%CI -13.1% to -0.7%); Low certainty ⊕⊕⊕◯ (Figure 24.)
- 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 not significantly increase pulmonary embolism, RR 0.8 (95%CI 0.62 to 1.03); RD -1.5% (95%CI -2.8% to 1.9%); Low certainty ⊕◯◯◯

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

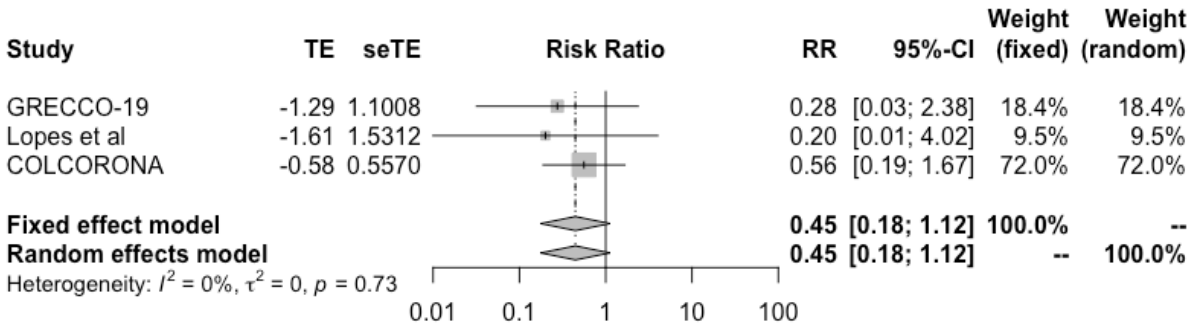
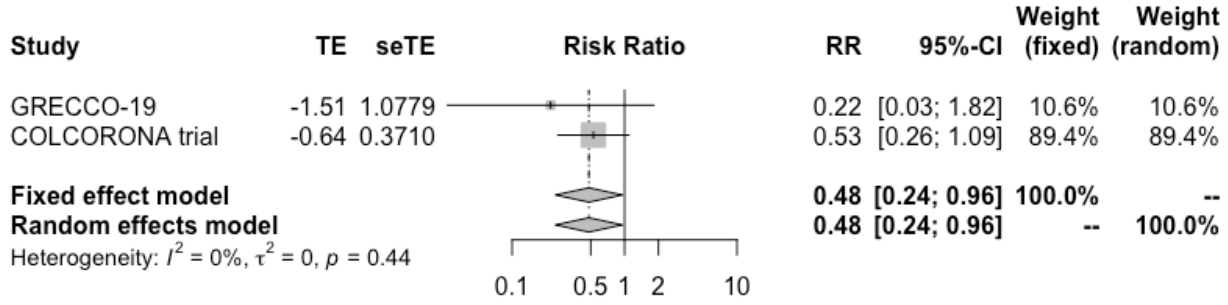


Figure 24. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



Recently a press release reported that RECOVERY trial, which included hospitalized patients with COVID-19, stopped enrolment to colchicine arm because of futility. Caution should be exerted until results of RECOVERY trial and other ongoing studies are available and subgroup analysis can be performed.

Sofosbuvir +/- daclatasvir or ledipasvir

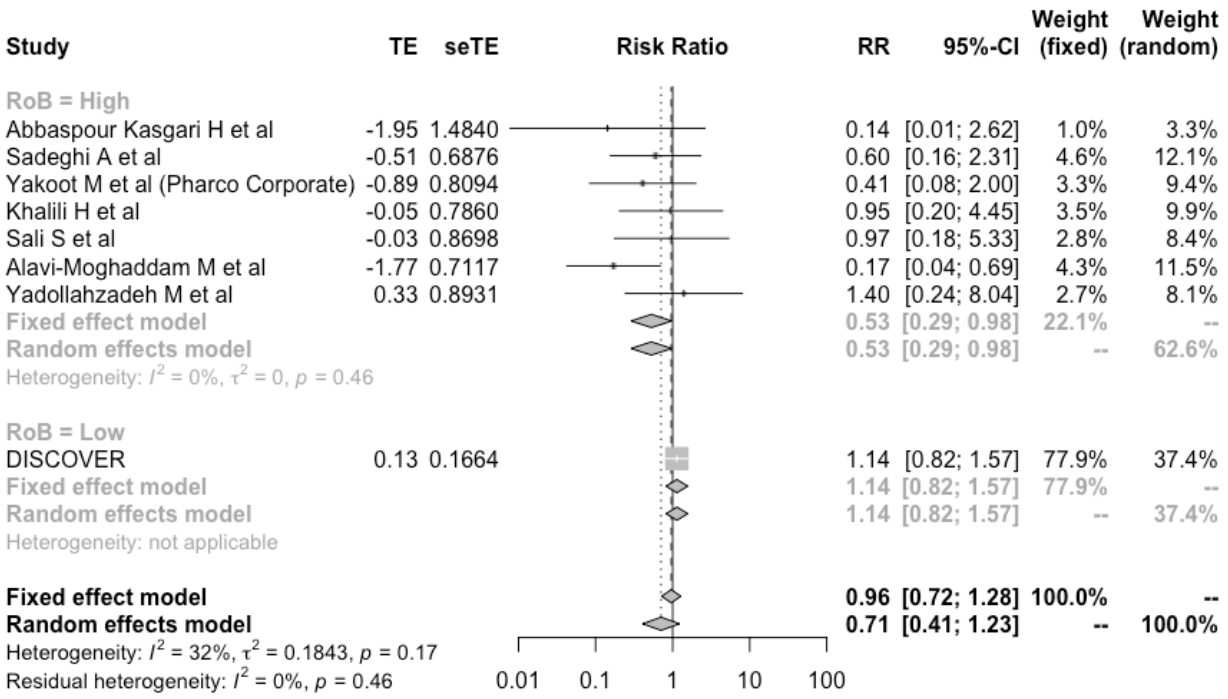
See Summary of findings Table 15, Appendix 1

We identified eight RCT including 1686 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 one study compared sofosbuvir + ledipasvir vs. standard of care. As there is moderate to high certainty that lopinavir-ritonavir is not related to significant benefits, we assumed that intervention as equivalent to standard of care. The DISCOVER trial was the biggest, with 1,083 patients and the only one categorized as with low risk of bias. Studies included patients with mild to severe disease. Our results showed:

- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mortality, RR 1.14 (95%CI 0.82 to 1.57); RD 2.2% (95%CI -2.9% to 9.1%) ; Low certainty ⊕⊕◯◯ (Figure 25.) (based on low risk of bias studies)
- Sofosbuvir +/- daclatasvir or ledipasvir may not reduce mechanical ventilation requirements, RR 1.5 (95%CI 0.73 to 3.09); RD 8.6% (95%CI -4.7% to 36.1%); Low certainty ⊕⊕◯◯ (based on low risk of bias studies)

- Sofosbuvir +/- daclatasvir or ledipasvir probably does not improve time to symptom resolution, RR 1 (95%CI 0.94 to 1.07); RD 0% (95%CI -3.6% to 4.2%); Moderate certainty ⊕⊕⊕◯

Figure 25. Mortality in randomized studies comparing sofosbuvir +/- daclatasvir or ledipasvir 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 125mg 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) continuation Continuing ACEIs OR ARBs may not increase mortality or mechanical ventilation requirements. 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 1.06 (95%CI 0.58 to 1.93); RD 1% (95%CI -6.7% to 14.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.63 to 1.39); RD -1.04% (95%CI -6.4% to 6.7%); Moderate certainty ⊕⊕◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
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.	

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) treatment Uncertainty in potential benefits and harms. Further research 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					
ATTRACT trial;[17] Tornling et al; Preprint; 2020	Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200mg a day for 7 days and 55 assigned to SOC	Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%	Steroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Nouri-Vaskeh et al;[18] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan 50mg a day for 14 days and 39 assigned to Amlodipine 5mg a day for 14 days	Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
SURG-2020-28683 trial;[19] Puskarich et al; Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to losartan 25 mg a day for 10 days and 59 assigned to SOC	Age (35-54) 46%, male 51.4%, hypertension 7.7%, diabetes 6%, COPD %, asthma 10.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

Anakinra Anakinra may not improve time to symptom resolution. Further research is needed to confirm or discard these findings					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CORIMUNO-ANA-1 trial;[20] Bureau et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 59 assigned to anakinra 400mg a day for 3 days followed by 200mg for 1 day followed by 100mg for 1 day and 55 assigned to SOC	Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD 31.6%, cancer 9.6%,	Steroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%, tocilizumab 0.8%, azithromycin 24.6%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.93 (95%CI 0.69 to 1.26); RD -4.2% (95%CI -18.8% to 15.8%) Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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 1mg/kg a day) or full dose (i.e enoxaparin 1mg/kg twice a day) probably does not decrease mortality in comparison with prophylactic dose (i.e enoxaparin 40mg 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;[21] Bertoldi Lemos et al; peer reviewed; 2020	Patients with critical COVID-19. Ten assigned to low molecular weight heparin therapeutic dose (i.e enoxaparin 1mg/kg twice a day) and ten assigned to prophylactic dose (i.e enoxaparin 40mg a day)	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, coronary heart disease 10%, immuno-suppression 5%	Steroids 70%, hydroxy-chloroquine 25%, azithromycin 90%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.04 (95%CI 0.91 to 1.17); RD 0.6% (95%CI -1.4% to 2.7%) Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Venous thromboembolic events (intermediate dose):** RR 0.93 (95%CI 0.38 to 2.26); RD -0.5% (95%CI -4.3% to 8.8%) Low ⊕⊕◯◯ **Venous thromboembolic events (therapeutic dose):** RR 0.58 (95%CI 0.37 to 0.91); RD -2.9% (95%CI -4.4% to
REMAP-CAP, ACTIV-4a, ATTACC trial;[22] Zarychanski et al; Preprint; 2021	Patients with moderate to critical COVID-19 infection. 532 assigned low molecular weight heparin therapeutic dose (i.e enoxaparin 1mg/kg twice a day) and 557 assigned to prophylactic dose (i.e enoxaparin 40mg 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	
INSPIRATION trial;[23] Sadeghipour et al; Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 276 assigned to low molecular weight heparin intermediate dose (i.e enoxaparin 1mg/kg a day) and	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	

	286 assigned to low molecular weight heparin prophylactic dose (i.e enoxaparin 40mg a day)			assessors were blinded	0.6%) Low ⊕⊕◯◯ **Major bleeding:** RR 1.43 (95%CI 0.76 to 2.71); RD 0.8% (95%CI -0.4% to 3.2%) Low ⊕⊕◯◯ **Hospitalization:** No information
Aprepitant **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Mehboob et al;[24] preprint; 2020	Patients with mild to critical COVID-19 infection. 10 assigned to aprepitant 80mg once a day for 3-5 days and 8 assigned to standard of care	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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

Artemisinin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ARTI-19 trial;[25] Tieu et al; Preprint; 2020	Patients with mild to moderate COVID-19. 39 assigned to Artemisinin 500mg 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

Aspirin Uncertainty in potential benefits and harms. Further research 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					
RESIST trial;[26] Ghati et al; preprint; 2021	Patients with moderate to severe COVID-19 infection.	Mean age 53.1 ± 9.2, male 73.3%, hypertension 28.6%,	Steroids 27.3%, remdesivir 20.6%, hydroxychloroquine	High for mortality and mechanical ventilation; High for symptom	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive**

	221 assigned to aspirin 75mg once a day for 10 days and 219 assigned to SOC	diabetes 27.7%, CHD 1.1%, CKD 2.4%	9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	resolution, infection and adverse events Notes: Blinding and concealment probably inappropriate	**mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Auxora

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Miller et al;[27] 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).	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information **Hospitalization:** No information
Aviptadil **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
COVID-AIV trial;[28] Jihad et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 136 assigned to aviptadil three infusions of 50, 100 and 150pmol/kg/hr and 67 assigned to SOC	Mean age 61 ± NR, male 69%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Blinding and concealment probably inapropriate	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Azithomycin Azithrimycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Sekhavati et al;[29] 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.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.89 (95%CI 0.46 to 1.72); RD -0.8% (95%CI -4% to
Guvenmez et al;[30] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600mg twice a day for 5 days and 12 assigned to Azithromycin 500mg on first day followed by 250mg 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.	
COALITION II trial;[31] Furtado et al; peer-reviewed; 2020	Patients with severe COVID-19. 214 assigned to azithromycin 500mg 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.	

RECOVERY trial[32] Horby et al; preprint; 2020	Patients with moderate to critical COVID-19. 2582 assigned to azithromycin 500mg 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.	5.4%); Very low certainty ⊕◯◯◯
Rashad et al;[33] preprint ; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500mg a day for 7 days, 99 assigned to Clarithromycin 1000mg 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;[34] Butler et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 500 assigned to azithromycin 500mg a day for 3 days and 629 assigned to SOC	Mean age 60.7 ± 7.8, male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,	NR	Some Concerns for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	
ATOMIC2 trial;[35] Hinks et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 145 assigned to azithromycin 500mg 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;[36] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 10 assigned to Azvudine 5mg once a day and 10 assigned to standard of care	Median age 52 ± 59, male 60%, hypertension 5%, diabetes 5%, coronary heart disease 5%	Antivirals 100%, antibiotics 40%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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

Baricitinib Baricitinib may reduce mortality, mechanical ventilation requirements and may improve time to symptom resolution. However certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ACTT-2 trial;[37] Kalil et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 515 assigned to baricitinib + remdesivir 4mg a day for 14 days + 200mg once followed by 100mg 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 ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.25 (95%CI 1.11 to 1.41); RD 15.1% (95%CI 6.6% to 24.8%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.77 (95%CI 0.63 to 0.95); RD -2.3% (95%CI -3.7% to -0.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
COV-BARRIER trial;[38] Marconi et al; ; 2021	Patients with moderate to severe COVID-19 infection. 764 assigned to baricitinib 4mg 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	

Baloxavir

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Lou et al;[39] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to Baloxavir 80mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%	Antivirals 100%, interferon 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Bamlanivimab (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;[40] Chen et al; peer-	Patients with mild to moderate COVID-19.	Mean age 45 ± 68, male 55%	NR	High for mortality and mechanical ventilation;	**Mortality:** Very low certainty ⊕◯◯◯

reviewed; 2020	309 assigned to bamlanivimab 700 mg, 2800 mg or 7000 mg once and 143 assigned to standard of care			high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**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 ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯ **Hospitalization:** Very Low certainty ⊕◯◯◯
ACTIV-3/TICO trial;[41] Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000mg 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	
Gottlieb et al;[42] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to Bamlanivimab 700-7000mg 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	

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;[42] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to Bamlanivimab 700-7000mg once, 112 assigned to Bamlanivimab + etesevimab and 156	Mean age 44.7 ± 15.7, male 45.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom**

	assigned to SOC				**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 ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯

BCG **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Padmanabhan et al;[43] preprint; 2020	Patients with severe COVID-19. 30 assigned to BCG 0.1ml once and 30 assigned to standard of care	Mean age 45.2 ± 36.5, male 60%, obesity 23%	Remdesivir 6.6%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Bioven Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Rybakov et al;[44] 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 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

Bromhexine hydrochloride Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Li T et al;[45] peer-reviewed; 2020	Patients with severe to critical COVID-19. 12 assigned to bromhexine	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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very

	hydrochloride 32mf three times a day for 14 days and 6 assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Ansarin et al;[46] 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 inappropriate.	
Mikhaylov et al;[47] Preprint; 2021	Patients exposed to COVID-19 infection. 25 assigned to bromhexine 12mg 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;[48] Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 48 assigned to bromhexine 32mg 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**
RCT					
CamoCO-19 trial;[49] Gunst et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 137 assigned to camostat mesilate 200mg a day for 5 days and 68 assigned to SOC	Median age 61 ± 23, male 60%, hypertension 34%, diabetes 17%, COPD 10%, asthma 13%, CHD 19%, cancer 14%, obesity 33%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

CERC-002 (monoclonal antibody) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Perlin et al;[50] preprint; 2021	Patients with mild to moderate COVID-19 infection. 31 assigned to CERC-002 16mg/kg once and 31 assigned to SOC	Mean age 58.5 ± 14, male 69.5%	Steroids 91.5%, remdesivir 68.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Significant lost to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Chloroquine nasal drops Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Thakar et al;[51] Peer reviewed; 2020	Patients with mild COVID-19. 30 assigned to	Mean age 34.9 ± 10.35, male 78.3%	NR	High for mortality and mechanical ventilation; High for symptom	**Mortality:** No information

	Chloroquine nasal drops 0.03% six times a day for 10 days and 30 assigned to SOC			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
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;[52] Cruz et al; preprint; 2020	Patients with mild to moderate COVID-19. 10 assigned to CIGB-325 2.5 mg/kg/day during 5-consecutive days) and 10 assigned to standard of care	Mean age 45.3 ± 12, male 70%, hypertension 25%, diabetes 0%, cancer 5%, obesity 25%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:**

					Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Clarithromycin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Rashad et al;[33] preprint ; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500mg a day for 7 days, 99 assigned to Clarithromycin 1000mg 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 **Hospitalization:** No information

Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
COVID-19-MCS trial;[53] Altay et al; preprint; 2020	Patients with mild to moderate COVID-19. 71 assigned to Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 22 assigned to standard of care	Mean age 35.6 ± 47, male 60%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Outcome assessors not blinded. Possible reporting bias.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Colchicine Colchicine may reduce mortality and mechanical ventilation requirements, however 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;[54] 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 0.45 (95%CI 0.18 to 1.12); RD -8.8% (95%CI -13.1% to 1.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.48 (95%CI 0.24 to 0.96); RD -9% (95%CI -13.1% to -0.7%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** No information **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 ⊕⊕⊕⊕ **Pulmonary embolism:** RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕⊕◯◯
Lopes et al;[55] 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.	
Salehzadeh et al;[56] preprint; 2020	Patients with moderate to critical COVID-19. 50 assigned to colchicine 1 mg a day for 6 days and 50 assigned to standard of care	Mean age 56, male 41%, hypertension 11%, diabetes 11%, chronic lung disease 4%, coronary heart disease 15%, chronic kidney disease 5%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	

				inappropriate.	**Hospitalization:** RR 0.8 (95%CI 0.62 to 1.03); RD -1.5% (95%CI -2.8% to 1.9%); Low certainty ⊕⊕◯◯
Tardif et al;[57] Preprint; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe disease. 2235 assigned to colchicine 1mg a day for 3 days followed by 0.5mg 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	

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;[58] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 52 assigned to convalescent plasma 4 to 13 mL/kg of recipient body weight and 51 assigned to standard of care	Median age 70 ± 8, male 58.3%, hypertension 54.3%, diabetes 10.6%, coronary heart disease 25%, chronic kidney disease 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%	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, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 1 (95%CI 0.93 to 1.07); RD 0% (95%CI -1.1% to 1.1%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.91 (95% CI 0.77 to 1.07); RD -1.6% (95%CI -4% to 1.2%); Moderate certainty ⊕⊕⊕◯ **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 ⊕⊕⊕◯
CONCOVID trial; Gharbharan et al;[59] 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.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.97 (95% CI 0.67 to 1.41); RD -0.3% (95%CI -3.4% to 4.2%); Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Avendaño-Solá et al;[60] 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.	
PLACID trial;[61] Agarwal et al; preprint; 2020	Patients with severe COVID-19. 235 assigned to convalescent plasma 200 ml twice in 24hs and 229 assigned to standard of care	Median age 52 ± 18, male 76.3%, hypertension 37.3%, diabetes 43.1%, chronic lung disease 3.2%, coronary heart disease 6.9%, chronic kidney disease 3.7%, cerebrovascular disease 0.9%, cancer 0.2%, obesity 7.1%	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 introduced bias to symptoms and adverse events outcomes results.	
PLASM-AR trial;[62] 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;[63] 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;[64] 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;[65] Libster et al; preprint; 2020	Patients with mild to moderate COVID-19. 80 assigned to convalescent plasma 250 ml and 80 assigned to standard of care	Mean age 77.1 ± 8.6, male 47.5%, hypertension 71.2%, diabetes 22.5%, COPD 4.4%, asthma 3.8%, coronary heart disease 13.1%, chronic kidney disease 2.5%, cancer 3.8%, obesity 7.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
PICP19 trial;[66] 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;[67] Horby et al; Other; 2020	Patients with severe to critical COVID-19 infection. 5795 assigned to CP 275ml 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;[68] peer reviewed; 2020	Patients with moderate to severe COVID-19. 46 assigned to CP 640ml 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;[69] Preprint; 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;[70] 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;[71] peer reviewed; 2021	Patients with severe COVID-19 infection. 30 assigned to CP 500ml once or twice and 30 assigned to	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	

	SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SBU-COVID19 - Convalescent Plasma trial;[72] Bennett-Guerrero et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 59 assigned to CP 480ml once and 15 assigned to SOC	Mean age 65.5 ± 16.6, male 59.5%, hypertension 68.9%, diabetes 33.7%, COPD 12.1%, CHD 17.6%, CKD 9.5%, cerebrovascular disease 14.8%, immunosuppressive therapy 8.1%	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	
Balcells et al;[73] peer reviewed; 2020	Patients with moderate to severe COVID-19. 28 assigned to convalescent plasma at enrolment, 200 mg twice and 30 assigned to convalescent plasma when clinical deterioration was observed (43.3% received CP in this arm)	Mean age 65.8 ± 65, male 50%, hypertension 67.2%, diabetes 36.2%, chronic lung disease %, asthma 5.1%, coronary heart disease %, chronic kidney disease 8.6%, cerebrovascular disease 5.1%, immunosuppression 12%, cancer 7%, obesity 12%	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 study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very Low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯ **Hospitalization:** No information
Non-RCT					
Joyner et al;[74] 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%
Darunavir-Cobicistat **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DC-COVID-19 trial;[75] Chen et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 15 assigned to darunavir-Cobicistat 800mg/150 mg once a day for 5 days and 15 assigned to standard of care	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, coronary heart disease 26.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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

Dutasteride Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
AB-DRUG-SARS-004 trial;[76] Cadegiani et al; preprint; 2020	Patients with mild COVID-19. 64 assigned to dutasteride (dosage not reported) and 66 assigned to standard of care	Mean age 42 ± 12, male 100 %, diabetes 11%, COPD 0%, asthma 1%, coronary heart disease 1%, cancer 0%, obesity 15.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very Low certainty ⊕◯◯◯[1]
EAT-DUTA AndroCoV trial;[77] Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 43 assigned to Dutasteride 0.5mg 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	

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;[78] 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	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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

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	39 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
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;[79] Preprint; 2020	Patients with moderate to severe COVID-19. assigned to enisamium 500mg 4 times a day for 7 days or SOC. Number of patients in each arm not reported.	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

					Hospitalization: No information
Famotidine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
Non-RCT					
Samimagham et al;[80] preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to famotidine 160mg for up to 14 days and 10 assigned to SOC	Mean age 47.5 ± 13, male 60%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Favipiravir **Favipiravir may not reduce mortality nor mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al; preprint;[81] 2020	Patients with moderate to critical	Mean age not reported male 46.6%,	NR	High for mortality and invasive mechanical	**Mortality:** RR 1.09 (95%CI 0.72 to

	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	hypertension 27.9%, diabetes 11.4%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	1.64); RD 1.4% (95%CI -4.5% to 10.2%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.24 (95%CI 0.72 to 2.12); RD 4.2% (95%CI -4.8% to 19.5%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 0.99 (95%CI 0.9 to 1.09); RD -0.6% (95%CI -6% to 5.6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Ivashchenko et al;[82] 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.	
Lou et al;[39] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%,	Antivirals 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Doi et al;[83] 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) 1800mg 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;[84] 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;[85] 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;[86] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 44 assigned to favipiravir + inhaled interferon beta-1B 1600 mg once followed by 600 mg twice a day for 10 days + 8million UI for 5 days and 45 assigned to standard of care	Mean age 55 ± 14, male 58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart disease 15%, chronic kidney disease 20%	Steroids 67%, tocilizumab 35%, convalescent plasma 58%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ruzhentsova et al;[87] preprint; 2020	Patients with mild to moderate COVID-19. 112 assigned to favipiravir 1800 mg once followed by 800mg 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;[88] 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;[89] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 100 assigned to favipiravir 3200mf once followed by 1200mg 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;[90] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 190 assigned to favipiravir 1800mg 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;[91] peer reviewed; 2021	Patients with COVID-19 infection who were	Mean age 55.7 ± 13.6, male 45.5%,	Steroids 3.6%, remdesivir 0%,	High for mortality and mechanical ventilation;	

	discharged from hospital. 36 assigned to Favipravir 3200mg once followed by 1200mg a day for 7 days and 19 assigned to SOC	hypertension 30.9%, diabetes 14.5%, CHD 7.3%, cancer 7.3%	hydroxychloroquine 5.5%, lopinavir-ritonavir 16.4%,	high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
FACCT trial;[92] Bosaeed et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 125 assigned to favipiravir + HCQ 3600mg + 800mg once followed by 2400mg + 400mg 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;[93] 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
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;[94] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 80 assigned to fluvoxamine incremental dose to 100 mg three times a day for 15 days and 72 assigned to standard of care	Median age 45.5 ± 20.5, male 28.2%, hypertension 19.7%, diabetes 11%, asthma 17.1%, obesity 56.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Helium (inhaled)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Shogenova et al;[95] 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.	**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

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;[96] Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + nigella sativa	> 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

	1gr + 80mg/kg three times a day for 13 days and 156 assigned to SOC				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;[97] 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 0.91 to 1.26); RD 1.2% (95%CI -1.6% to 4.5%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.05 (95%CI 0.95 to
Huang et al;[98] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to chloroquine 500 mg	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	

	twice a day for 10 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.	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 ⊕⊕◯◯ **Severe Adverse events:** RR 0.9 (95%CI 0.59 to 1.37); RD -1% (95%CI -4.2% to 3.8%); Low certainty ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
RECOVERY - Hydroxychloroquine trial;[99] Horby et al; preprint; 2020	Patients with Mild to critical COVID-19 infection. 1561 assigned to hydroxychloroquine 800 mg once followed by 400 mg twice a day for 9 days and 3155 assigned to standard of care	Mean age 65.3 ± 15.3, male %, diabetes 26.9%, chronic lung disease 21.9%, asthma NR%, coronary heart disease 25.4%, chronic kidney disease 7.8%, HIV 0.4%	NR	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BCN PEP CoV-2 trial;[100] 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;[101] 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;[102] Cavalcanti et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 159 assigned to hydroxychloroquine 400 mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to standard of care	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%, diabetes 19.1%, chronic lung disease 1.8%, asthma 16%, coronary heart disease 0.8%, chronic kidney disease 1.8%, cancer 2.9%, obesity 15.5%	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 introduced bias to symptoms and adverse events outcomes results.	
Kamran SM et al trial;[103] 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;[104] 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;[105] 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;[106] 2020	Patients with mild to moderate COVID-19 infection. 75 assigned to hydroxychloroquine	Mean age 46.1 ± 14.7, male 54.7%, hypertension 6%, diabetes 14%, other	Steroids 7%, lopinavir-ritonavir 17%, umifenovir 47%, oseltamivir 11%,	Low for mortality and invasive mechanical ventilation; high for symptom resolution,	

	1200 mg daily for three days followed by 800 mg daily to complete 7 days and 75 assigned to standard of care	comorbidities 31%	entecavir 1%, ATB 39%, ribavirin 47%	infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcome results.	
Chen et al;[107] 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;[108] 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;[109] 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;[110] Jun et al; peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 15 assigned to hydroxychloroquine	Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%, chronic	Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	400 mg once a day for 5 days and 15 assigned to standard of care	lung disease 3.3%		infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abd-Elsalam et al;[111] 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;[112] 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;[113] 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.	
PrEP_COVID trial;[114] Grau-Pujol et al; preprint; 2020	Patients exposed to COVID-19. 142 assigned to hydroxychloroquine	Median age 39 ± 20, male 26.8%, hypertension 1.8%, diabetes 0.4%, chronic	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution,	

	400 mg daily for four days followed by 400 mg weekly for 6 months and 127 assigned to standard of care	lung disease 2.6%		infection and adverse events	
PATCH trial;[115] Abella et al; peer-reviewed; 2020	Patients exposed to COVID-19. 64 assigned to hydroxychloroquine 600 mg a day for 8 weeks and 61 assigned to standard of care	Median age 33 ± 46, male 31%, hypertension 21%, diabetes 3%, asthma 17%	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	
WHO SOLIDARITY trial;[116] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 947 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 10 days and 906 assigned to standard of care	Age < 70 years 61%, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%, chronic kidney disease %	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.	
Davoodi et al;[93] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to Febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-19 PEP (University of Washington) trial; Barnabas et al;[117] Abstract; 2020	Patients exposed to COVID-19. 381 assigned to hydroxychloroquine 400mg for three days followed by 200 mg for 11 days and 400	Median age 39 ± 24, male 40%	NR	Low for symptom resolution, infection and adverse events	

	assigned to standard of care				
PETAL trial;[118] 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;[119] 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;[120] 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;[121] Omrani et al; peer-reviewed; 2020	Patients with mild COVID-19. 152 assigned to hydroxychloroquine 600 mg daily for 7 days and 152 assigned to hydroxychloroquine + azithromycin	Mean age 41 ± 16, male 98.4%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Dabbous et al;[122] peer reviewed; 2020	Patients with mild to moderate COVID-19. 44 assigned to favipiravir 3200mg	Mean age 35.5 ± 16.8, male 48.9%, comorbidities 18.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and	

	once followed by 600 mg twice a day for 10 days and 48 assigned to CQ			adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
HYDRA trial;[123] Hernandez-Cardenas et al; Preprint; 2020	Patients with severe to critical COVID-19. 106 assigned to HCQ 400mg 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;[124] Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to HCQ 800mg once followed by 400mg a day for 10 days, 65 assigned to HCQ + AZT 500mg once followed by 250mg 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;[125] peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to Lopinavir-Ritonavir 500/100 a day, 123 assigned to HCQ 200mg 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.	
Beltran et al;[126] Preprint; 2020	Patients with moderate to severe COVID-19. 33 assigned to HCQ 800mg once followed by 400mg 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;[127] Amaravadi et al; Preprint; 2020	Patients with mild COVID-19 infection. 17 assigned to HCQ 400mg 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;[128] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to Ivermectin 42mg 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;[129] peer reviewed; 2021	Patients exposed to COVID-19 infection. 432 assigned to HCQ 400mg once followed by 200mg 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;[130] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to HCQ 800mg once followed by 400mg 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	
CLOROTRIAL trial;[131] Réa-Neto et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to HCQ 800mg once followed by 400mg a day for 5 days and 52	Median age 53 ± , male 66.7%, hypertension 38.1%, diabetes 25.7%, COPD 8.6%, immunosuppresive therapy 5.7%	Steroids 72.4%, azithromycin 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hyperbaric oxygen **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hadanny et al;[132] preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric Oxygen two sesions 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 inapropriate	**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

Icatibant / iC1e/K Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Mansour et al;[133] 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
IFX-1 Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Vlaar et al;[134] peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1 800 mg IV with a maximum of seven	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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

	doses and 15 assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
INM005 (polyclonal fragments of equine antibodies) **INM005 may not improve symptom resolution and may not increase severe adverse events. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Lopardo et al;[135] peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005 4mg/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 Notes: Symptom resolution was reported as a composite outcome with hospital discharge. In the original protocol the outcome was not a composite.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.06 (95%CI 0.96 to 1.66); RD 3.6% (95%CI -2.4% to 10.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Interferon alpha-2b and Interferon gamma **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ESPERANZA trial;[136] 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;[137] preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three times a week and 39 assigned to standard of care	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	Steroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to 3.7%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
WHO SOLIDARITY;[116] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2050 assigned to Interferon beta-1a three doses over six days of 44µg 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.	
COVIFERON trial;[138] 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 0.25mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes	

				results.	
Darazam et al;[139] 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;[140] et al; peer-reviewed ; 2020	Patients with mild to severe COVID-19. 48 assigned to Interferon beta-1a nebulized once a day for 15 days and 50 assigned to standard of care	Mean age 57.1 ± 13.2, male 59.2%, hypertension 54.7%, diabetes 22.6%, COPD 44.2%, asthma %, coronary heart disease 24.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Interferon beta-1b Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Rahmani et al;[141] peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to Interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to standard of care	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%	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 inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
COVIFERON trial;[138] 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 0.25mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Interferon gamma Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Myasnikov et al;[142] 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

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;[143] peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2 mg	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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

	once a day for six days and 40 assigned to standard of care			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	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;[144] Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin +Iota-Carrageenan 12mg 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.	**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 ⊕◯◯◯
CARR-COV-02 trial;[145] 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.	**Hospitalization:** Very low certainty ⊕◯◯◯
Itolizumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ITOLI-C19-02-I-00 trial;[146] 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 ⊕◯◯◯ **Hospitalization:** No information

Ivermectin Ivermectin may not reduce mortality and probably does not improve time to symptom resolution. It is uncertain if it affects mechanical ventilation requirements, symptomatic infection as prophylaxis or severe adverse events.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zagazig University trial;[147] Shouman et al; Other; 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 0.94 (95%CI 0.51 to 1.73); RD -0.96% (95%CI -7.8% to 11.7%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.89 (95%CI 0.38 to 2.07); RD -1.9% (95%CI -10.7% to 18.5%); Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1 (95%CI 0.9 to 1.11); RD 0% (95%CI -6% to 6.6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):**RR 0.14 (95%CI 0.09 to 0.21); RD -15% (95%CI -13.7% to -15.8%); Very low certainty ⊕◯◯◯ **Adverse events:** RR 1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.2%); Very low
Chowdhury et al;[148] 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.	
Podder et al;[149] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 µgm/kg once and 30 assigned to standard of care	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Hashim HA et a (Alkarkh Health Directorate-Baghdad) trial;[150] Hashim et al; 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.	certainty ⊕◯◯◯ **Hospitalization:** RR 0.66 (95%CI 0.69 to 2.30); RD 2.5% (95%CI -6% to 9.6%); Very low certainty ⊕◯◯◯
Mahmud et al; NCT04523831; Other; 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	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Elgazzar et al (mild);[151] 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);[151] preprint; 2020	Patients with severe COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 58.9 ± 19.5, male 71%, hypertension 16%, diabetes 20%, COPD %, asthma 13%, coronary heart disease 7.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Elgazzar et al (prophylaxis);[151] preprint; 2020	Patients exposed to COVID-19. 100 assigned to ivermectin 400 µgm/kg twice (second dose after one week)	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	and 100 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Krolewiecki et al;[152] preprint; 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;[153] 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;[154] peer-reviewed; 2020	Patients with mild COVID-19. 55 assigned to ivermectin 12 mg a day for 5 days +/- doxycycline and 23 assigned to standard of care	Mean age 42 , male 46%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
SAINT trial;[155] 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;[156] peer-reviewed; 2020	Patients with mild COVID-19. 25 assigned to ivermectin 36mg 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;[157] Preprint; 2020	Patients with mild to severe COVID-19. 42 assigned to ivermectin 12 to 24mg 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%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Kirti et al;[158] Preprint; 2020	Patients with mild to moderate COVID-19. 55 assigned to ivermectin 24mg 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;[144] Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin + iota-carrageenan 12mg 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;[159] Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to Ivermectin 0.2-0.4 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.	
Rezai et al;[159] Unpublished; 2020	Patients with moderate to severe COVID-19 assigned to Ivermectin 0.2 mg/kg once or SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment from secondary sources as publication not available.	
Spoorthi et al;[159] 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.	
Raad et al;[159] Unpublished; 2020	Patients with mild COVID-19. 100 assigned to Ivermectin 0.2 mg/kg once and assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. RoB assessment from secondary sources as publication not available.	

Bukhari et al;[160] Preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to Ivermectin 12 mg once and 41 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Okumus et al;[161] Preprint; 2021	Patients with severe COVID-19. 30 assigned to Ivermectin 0.2 mg/kg for 5 days and 30 assigned to SOC	Mean age 62 ± 12, male 66%, hypertension 21.6%, diabetes 45%, COPD 1.6%, CHD 1.6%, cancer 1.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Beltran et al;[126] Preprint; 2021	Patients with moderate to severe COVID-19. 36 assigned to Ivermectin 12-18 mg once and 37 assigned to SOC	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	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.	
Lopez-Medina et al;[162] 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;[128] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to Ivermectin 42mg 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;[163] 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;[164] other; 2021	Patients with moderate to severe COVID-19 infection. 19 assigned to ivermectin 12mg 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;[129] peer reviewed; 2021	Patients exposed to COVID-19 infection. 617 assigned to ivermectin 12gr once and 619 assigned to SOC (vitamin C)	Mean age 33 , male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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;[165] 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 ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯ **Hospitalization:** No information
Gharebaghi et al;[166] 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.	
Tabarsi et al;[167] 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.	
Raman et al;[168] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 50	Mean age 48.7 ± 12, male 33%, hypertension 31%,	NR	High for mortality and mechanical ventilation; High for symptom	

	assigned to IVIG 0.4/gr/kg for 5 days and 50 assigned to SOC	obesity 16%		resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
KB109 (microbiome modificator) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Haran et al;[169] preprint; 2021	Patients with mild to moderate COVID-19 infection. 169 assigned to KB109 9-36gr twice a day for 14 days and 172 assigned to SOC	Median age 36 ± 56, male 40.8%, hypertension 18%, diabetes 2.5%, COPD 8.8%, cerebrovascular disease 2.3%, cancer 0.8%, obesity 3.7%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:**Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯ **Hospitalization:** No information

Lactococcus lactis (intranasal)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PROBCO trial;[170] 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

Leflunomide

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hu et al;[171] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned	Mean age 52.5 ± 11.5, male 30%, hypertension 60%,	Umifenovir 100%	High for mortality and invasive mechanical ventilation; high for	**Mortality:** No information

	to Leflunomide 50mg every 12hs (three doses) followed by 20 mg a day for 10 days and 5 assigned to standard of care	chronic lung disease 10%		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
Wang et al;[172] 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
RCT					
LIVE-AIR trial;[173] Temesgen et al; preprint; 2021	Patients with severe COVID-19 infection. 236 assigned to lenzilumab 1800mg 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

					information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.82 (95%CI 0.62 to 1.07); RD -1.8% (95%CI -3.9% to 0.7%); Low certainty ⊕⊕⊕◯ **Hospitalization:** No information
Levamisole **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Roostaei et al;[174] Preprint; 2020	Patients with mild to moderate COVID-19. 25 assigned to levamisole 150mg a day for 3 days and 25 assigned to SOC	Mean age 36.6 ± 13.7, male 60%,	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement: Mortality:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty

					⊕◯◯◯ **Hospitalization:** No information
Lincomycin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Guvenmez et al;[30] 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

Lopinavir-Ritonavir **Lopinavir-ritonavir probably does not reduce mortality with moderate certainty. Lopinavir-ritonavir may not be associated with a significant increase in severe adverse events. However, the certainty is low because of risk of bias and imprecision.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
LOTUS China trial;[175] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to Lopinavir-Ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Steroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.02 (95%CI 0.92 to 1.22); RD 0.3% (95%CI -1.3% to 1.9%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** 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 ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
ELACOI trial;[176] 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.	
RECOVERY - Lopinavir-ritonavir trial;[177] 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.	
Huang et al; peer-reviewed;[98] 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zheng et al; preprint;[178] 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;[179] 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;[116] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 1399 assigned to lopinavir-ritonavir 200/50 mg	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	

	twice a day for 14 days and 1372 assigned to standard of care			adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Sali et al;[180] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to Sofosbuvir 400mg a day and 32 assigned to Lopinavir-Ritonavir 400/100mg 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;[181] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to Lopinavir-Ritonavir 500/100 a day, 123 assigned to HCQ 200mg 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;[182] 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;[183] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/daclatasvir 400/60mg a day for	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	10 days and 54 assigned to lopinavir-ritonavir 400/100mg twice a day for 7 days	immunosuppression 3.6%, cancer 10.7%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
TOGETHER trial;[130] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 244 assigned to Lopinavir-Ritonavir 1600mg/400mg once followed by 800mg/200mg 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	

Mavrilimumab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
MASH-COVID trial;[184] Cremer et al; Peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 21 assigned to mavrilimumab 6 mg/kg once and 19 assigned to SOC	Mean age 56.7 ± 23.8, male 65%, hypertension 55%, diabetes 43%, COPD 8%, CKD 8%, cerebrovascular disease 3%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

					Hospitalization: No information
Melatonin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Farnoosh et al;[185] Preprint; 2020	Patients with mild to moderate COVID-19. 24 assigned to melatonin 9mg 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 **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and 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;[186] peer-reviewed; 2020	Patients with severe COVID-19 infection.	Median age 61 ± 10, male 58.5%,	Steroids 100%, antibiotics 87.8%,	High for mortality and invasive mechanical	**Mortality:** Very low certainty ⊕◯◯◯

	12 assigned to mesenchymal stem cell 2 × 10^6 cells/kg one infusion and 29 assigned to standard of care	hypertension 22%, diabetes 19.5%	antivirals 100%	ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Shi et al;[187] preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem cell three infusions with 4.0×107 cells each and 35 assigned to standard of care	Mean age 60.3 ± 8.4, male 56%, hypertension 27%, diabetes 17%, COPD 2%	Steroids 22%	Low for mortality and mechanical ventilation	
Lanzoni et al;[188] preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell 100±20 x106 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.	

Metisoprinol

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Borges et al;[189] peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to metisoprinol 1500 mg/kg/day for 14 days and 30 assigned to SOC	Mean age 33.2 ± 16, male 53.3%, COPD 10%, CKD 16.6%, cancer 3.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or**

				inappropriate.	**improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Molnupiravir **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Painter et al;[190] Preprint; 2020	Patients with mild to moderate COVID-19. 64 assigned to Molnupiravir 80 to 1600mg twice a day for 5.5 days	Mean age 39.6 ± 39, male 82.8%,	NR	Low for adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Mouthwash Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Mukhtar et al;[191] 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 ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
GARGLES trial;[192] 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 ± nr, 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.	
KILLER trial;[193] Guenezan et al; peer reviewed; 2020	Patients with mild COVID-19. 12 assigned to Mouthwash with 25ml of 1% povidone iodine and 12 assigned to SOC	Mean age 45 ± 23, male 33%, hypertension 12.5%, diabetes 4%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Elzein et al;[194] preprint; 2021	Patients with mild to severe COVID-19 infection. 52 assigned to mouthwash with povidone or	Mean age 45.3 ± 16.7, male 40.9%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	chlorhexidine and 9 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Santos et al;[195] 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;[196] Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to Mouthwash with ß-cyclodextrin-citrox three times a day and 78 assigned to SOC	Mean age 43.8 ± 15.5, male 45.7%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Huang et al;[197] peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 66 assigned to mouthwash chlorhexidine 0.12% 15ml 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.	

N-acetylcysteine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
de Alencar et al;[198] peer-reviewed; 2020	Patients with severe COVID-19. 68 assigned to NAC 21	Mean age 58.5 ± 22.5, male 59.2%, hypertension 46.6%,	NR	Low for mortality and invasive mechanical ventilation; low for	**Mortality:** Very low certainty ⊕◯◯◯

	gr once and 67 assigned to standard of care	diabetes 37.7%, cancer 12.6%,		symptom resolution, infection and adverse events	**Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯ **Hospitalization:** No information
Gaynitdinova et al;[199] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 24 assigned to NAC 1200-1500mg 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.	

Nasal hypertonic saline

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Kimura et al;[200] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 14 assigned to nasal hypertonic saline 250 cc twice daily, 14 assigned to nasal hypertonic saline plus surfactant and 17 assigned to standard of care	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%, diabetes 6.6%, chronic lung disease 15.5%, coronary heart disease 4.4%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information **Hospitalization:** No information
Neem (Azadirachta Indica A. Juss) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Nesari et al;[201] other; 2021	Patients exposed to COVID-19 infection. 70 assigned to neem 50mg 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;[202] Rocco et al; preprint; 2020	Patients with mild COVID-19. 194 assigned to nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	Age range 18 - 77 , male 47%, comorbidities 13.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant lost to follow up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Fontanesi et al;[203] preprint ; 2020	Patients with mild to critical COVID-19. 25 assigned to nitazoxanide 1200mg a day for 7 days and 25 assigned to SOC	age > 65 46% , male 30%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Silva et al;[204] 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;[205] Rossignol et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 184	Mean age 40.3 ± 15.4, male 43.5%, comorbidities 34%	NRazithromycin %, convalescent plasma %	Low for mortality and mechanical ventilation; low for symptom	

	assigned to nitazoxanide 600mg a day for 5 days and 195 assigned to SOC			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;[206] preprint; 2021	Patients with severe COVID-19 infection. 14 assigned to iNO pulses of 30min 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

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;[178] preprint; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-Ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-Ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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

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
Non-RCT					
Eilidh et al;[207] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 54 received NSAID	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%, coronary heart disease	NR	High for mortality Notes: Non-randomized study with retrospective	**Mortality:** OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕◯◯◯

	and 1168 received alternative treatment schemes	22.3%, chronic kidney disease 38.7%,		design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function)	
Jeong et al;[208] preprint; 2020	Patients with moderate to severe COVID-19 infection. 354 received NSAID and 1470 received alternative treatment schemes	Age >65 36%, male 41%, hypertension 20%, diabetes 12%, chronic lung disease 16%, asthma 6%, chronic kidney disease 2%, cancer 6%	NR	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and IPTW were implemented to adjust for potential confounders (age, sex, health insurance type, hypertension, hyperlipidemia, diabetes mellitus, malignancy, asthma, chronic obstructive pulmonary disease, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal, conditions, and use of co-medications)	
Lund et al;[209] 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	
Rinott et al;[210] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 87 received NSAID and 316 received alternative treatment schemes	Median age 45 ± 37, male 54.6%, diabetes 9.4%, coronary heart disease 12.9%,	NR	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. No adjustment for potential confounders.	
Wong et al;[211] 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;[212] 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;[213] 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).	
Omega-3 fatty acids **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Sedighiyan et al;[214] Preprint; 2020	Patients with mild to moderate COVID-19. 15 assigned to omega-3 670mg 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 **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Doaei et al;[215] peer reviewed; 2021	Patients with critical COVID-19 infection. 28 assigned to omega-3 1000mg 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 inappropiate. Significant lost to follow up.	

Otilimab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
OSCAR trial;[216] Patel et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 386 assigned to Otilimab 90mg 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ozone Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
PROBIOZOVID trial;[217] Araimo et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 14 assigned to Ozone	Mean age 61.7 ± 13.2, male 50%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive**

	250 ml ozonized blood and 14 assigned to standard of care			adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
SEOT trial;[218] Shah et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to Ozone 150ml rectal insufflation plus 5ml 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.	

Peg-interferon (IFN) alfa

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PEGI.20.002 trial;[219] 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: Very No information **Hospitalization:** No information
Peg-interferon (IFN) lamda **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ILIAD trial;[220] 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 ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
COVID-Lambda trial;[221] Jagannathan et al; preprint; 2020	Patients with mild COVID-19. 60 assigned to Peg-IFN lambda 180 mcg subcutaneous injection once and 60 assigned to standard of care	Median age 36 ± 53, male 68.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Pentoxifylline Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Maldonado et al;[222] 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
PNB001 (CCK-A antagonist) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BCR-PNB-001 trial;[223] Lattaman et al; preprint; 2021	Patients with moderate COVID-19 infection. 20 assigned to PNB001 200mg a	Mean age 52, 65% male	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical**

	day for 14 days and 20 assigned to SOC			adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Povidone iodine spray **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Seet et al;[129] 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 ⊕◯◯◯
Progesterone **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Ghandehari et al;[224] preprint; 2020	Patients with severe COVID-19. 18 assigned to progesterone 100 mg twice a day for 5 days and 22 assigned to standard of care	Mean age 55.3 ± 16.4, male 100%, hypertension 48%, diabetes 25%, obesity 45%	Steroids 60%, remdesivir 60%, hydroxychloroquine 2.5%, tocilizumab 12.5%, azithromycin 50%, convalescent plasma 5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Prolectin-M

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Prolectin-M trial;[225] 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 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;[226] Duarte Silveira et al; Preprint; 2020	Patients with moderate to critical COVID-19. 82 assigned to propolis 400-800mg a day for	Mean age 50 ± 12.8, male 69.4%, hypertension 45.2%, diabetes 21%, COPD 7.3%, asthma %,	Steroids 80.6%, hydroxychloroquine 3.2%, azithromycin 95.2%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very

	7 days and 42 assigned to SOC	obesity 51.6%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	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;[227] Preprint; 2020	Patients with mild COVID-19. 114 assigned to proxalutinde 200mg 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 ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No
AB-DRUG-SARS-004 trial;[228] Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 171 assigned to Proxalutide 200mg 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.	

					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;[229] Fragoso-Saavedra et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 94 assigned to pyridostigmine 60mg 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;[230] Preprint; 2020	Patients with moderate to severe COVID-19. 52 assigned to Quercetin 1000mg and 395 assigned to SOC	Age > 50 65.7% , male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma 13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ramipril Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
RASTAVI trial;[231] Amat-Santos et al; preprint; 2020	Patients exposed to COVID-19. 50 assigned to Ramipril 2.5 mg a day	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%, diabetes 20.65%,	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution,	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical**

	progressively increased to 10 mg a day and 52 assigned to standard of care	chronic lung disease 7.35%, coronary heart disease 22.45%, chronic kidney disease 34.15%, cerebrovascular disease 11.15%		infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information

Recombinant Super-Compound Interferon

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Li et al;[232] 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.	**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
REGN-COV2 (Regeneron) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Weinreich et al;[233] Peer reviewed; 2020	Patients with mild COVID-19. 143 assigned to REGN-COV2 (Regeneron) 2.4 to 8gr single infusion and 78 assigned to SOC	Median age 44 ± 17, male 49%, obesity 42%, comorbidities 64%	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:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Regdanvimab (monoclonal antibody) Regdabivimab may improve time to symptom resolution. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Eom et al;[234] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 204 assigned to Regdanvimab 40-80mg/kg once and 103 assigned to SOC	Mean age 51 ± 20, male 44.6%, comorbidities 73%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.94 (95%CI 0.82 to 1.08); RD 13.9% (95%CI 1.8% to 27.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Remdesivir Remdesivir may slightly reduce mortality, mechanical ventilation requirement and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ACTT-1 trial; Beigel et al;[235] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 541 assigned to remdesivir intravenously 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death and 522 assigned to standard of care	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 0.95 (95%CI 0.83 to 1.08); RD -0.8% (95%CI -2.7% to 1.3%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.71 (95%CI 0.43 to 1.18); RD -5% (95%CI -9.9% to 3.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.8 (95%CI 0.48 to 1.33); RD -2% (95%CI -5.3% to 3.4%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
SIMPLE trial; Goldman et al;[236] peer-reviewed; 2020	Patients with severe COVID-19 infection. 200 assigned to remdesivir (5 days) 200 mg once followed 100mg for 5 days and 197 assigned to remdesivir (10 days)	Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CAP-China remdesivir 2 trial;[237] 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	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	

	single daily infusions and 79 assigned to standard of care				
SIMPLE 2 trial; Spinner et al;[238] 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;[116] 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;[239] peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 34 assigned to Remdesivir 200mg once followed by 100mg once a day for 5 days and 36 assigned to SOC	Mean age 57.7 ± 13.1, male 65.5%, hypertension 45.7%, diabetes 60%, asthma 1.4%, CHD 12.9%, CKD 4.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

rhG-CSF (in patients with lymphopenia)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cheng et al;[240] 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.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ribavirin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Chen et al;[179] preprint; 2020	Patients with mild to moderate COVID-19 infection. 33 assigned	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** No information **Invasive**

	to ribavirin 2 gr IV loading dose followed by orally 400-600mg every 8 hs for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-Ritonavir			symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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;[241] 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;[242] peer-reviewed; 2020	Patients with severe COVID-19 infection. 22 assigned to ruxolitinib 5mg twice a day and 21	Mean age 63 ± 10, male 58.5%, hypertension 39%, diabetes 19.5%, coronary heart disease	Steroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse	**Mortality:** No information **Invasive mechanical ventilation:** No

	assigned to standard of care	7.3%,		events	information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Sarilumab **Sarilumab may reduce mortality and mechanical ventilation requirements. However certainty of the evidence is low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
REMAP-CAP - tocilizumab trial;[243] Gordon et al; preprint; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8mg/kg once or twice, 48 assigned to sarilumab 400mg 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.	**Mortality:** RR 0.75 (95%CI 0.48 to 1.16); RD -4% (95%CI -8.3% to 2.5%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.67 (95%CI 0.42 to 1.05); RD -5.6% (95%CI -10% to 0.8%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 0.95 (95%CI 0.85 to 1.06); RD -3% (95%CI -9% to 3.7%); Low certainty
Lescure et al;[244] peer-reviewed; 2020	Patients with severe to critical COVID-19. 332 assigned to sarilumab 200-400mg 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	Steroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

		20.7%			⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 1.17 (95%CI 0.77 to 1.79); RD 1.8% (95%CI -2.3% to 8.1%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information

Sofosbuvir +/- daclatasvir or ledipasvir

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;[182] 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 1.14 (95%CI 0.82 to 1.57); RD 2.2% (95%CI -2.9% to 9.1%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.5 (95%CI 0.73 to 3.09); RD 8.6% (95%CI -4.7% to 36.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1 (95%CI 0.94 to 1.07); RD 0% (95%CI -3.6% to
Sadeghi et al;[245] 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	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%,	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	

	standard of care	obesity 25.7%		assessors and data analysts were blinded. Concealment of allocation probably inappropriate.	4.2%); Moderate certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Yakoot et al;[246] preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 10 days and 45 assigned to standard of care	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %, asthma 1%, coronary heart disease 8%	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Roozbeh et al;[247] Peer reviewed; 2020	Patients with moderate COVID-19. 27 assigned to sofosbuvir/daclatasvir 400/60mg 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;[180] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to Sofosbuvir 400mg a day and 32 assigned to Lopinavir-Ritonavir 400/100mg 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;[248] Mobarak et al; Preprint; 2021	Patients with moderate to severe COVID-19 infection. 541 assigned to sofosbuvir/daclatasvir 400/60mg a day for 10 days and 542 assigned to SOC	Median age 58 ± 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;[249] Preprint; 2021	Patients with severe to critical COVID-19 infection. 27 assigned to Sofosbuvir 400mg a da 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;[183] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/daclatasvir 400/60mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100mg 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;[250] 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.	

Statins

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
RCT					
RESIST trial;[26] Ghati et al;	Patients with moderate to severe	Mean age 53.1 ± 9.2, male 73.3%,	Steroids 27.3%, remdesivir 20.6%,	High for mortality and mechanical ventilation;	**Mortality:** Very low certainty ⊕◯◯◯

preprint; 2021	COVID-19 infection. 221 assigned to atorvastatin 40mg once a day for 10 days and 219 assigned to SOC	hypertension 28.6%, diabetes 27.7%, CHD 1.1%, CKD 2.4%	hydroxychloroquine 9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	High for symptom resolution, infection and adverse events Notes: Blinding and concealment probably inappropriate	**Invasive mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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
RCT					
GLUCOCOVID trial;[251] Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone 40mg 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.	**Mortality:** RR 0.90 (95%CI 0.80 to 1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR
Metcovid trial;[252] Prado Jeronimo et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 194 assigned to methylprednisolone 0.5mg/kg twice a day	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse	

	for 5 days and 199 assigned to standard of care	0.5%, asthma 2.5%, coronary heart disease 6.9%, alcohol use disorder 27%, liver disease 5.5%		events	1.27 (95%CI 0.98 to 1.65); RD 16.4% (95%CI -1.2% to 39.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
RECOVERY - Dexamethasone trial;[253] Horby et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 2104 assigned to Dexa 6mg 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.	
DEXA-COVID19 trial;[254] 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;[255] 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;[256] Arabi et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 278 assigned to hydrocortisone 50 mg every 6 hours for 7	Mean age 59.9 ± 13, male 71%, diabetes 32%, chronic lung disease 20.3%, coronary heart disease	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	

	days and 99 assigned to standard of care	7.5%, chronic kidney disease 9.2%, immunosuppression 4.9%		events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVID STEROID trial;[254] 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;[257] Dequin et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 76 assigned to Hydrocortisone 200mg a day progressively reduced to 50mg 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;[254] 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;[258] preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to methylprednisolone 1000 mg/day for three days followed by prednisolone 1 mg/kg for 10 days, and 15 assigned to standard of care	Mean age 64 ± 13.5	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Edalatifard et al;[259] 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;[260] 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;[261] Peer-reviewed ; 2020	Patients with moderate to severe COVID-19. 25 assigned to dexamethasone 20mg a day for 5 days followed by 10mg 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;[262] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 75 assigned to dexamethasone 4mg/kg a day for 3 days followed by 8mg a day for 10 days and 74 assigned to TCZ	Mean age 62, male 56.9%, hypertension 47.7%, diabetes 28.4%, COPD 1.8%, asthma 2.7%, CHD 12.8%, CKD 8.2%, cancer 0.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. Significant lost to follow-up as patients who died in the first 3 days after randomization were excluded.	

Ranjbar et al;[263] Preprint; 2020	Patients with severe to critical COVID-19 infection. 44 assigned to Methylprednisolone 2mg/kg daily for 5 days followed by tapering using same scheme at half dose every 5 days, 42 assigned to dexamethasone 6mg 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 hos[pitalizations. Further research is needed.

Study; publication status	Patients and 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;[264] Ramakrishnan et al; peer reviewed ; 2020	Patients with mild to moderate COVID-19. 71 assigned to budesonide (inh) 800µg twice a day and 69 assigned to SOC	Mean age 45 ± 56, male 42.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** Very low 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;[265] Yu et al; preprint;	Patients with mild to moderate COVID-19	Mean age 68.2 , male 46.3%, hypertension	NR	Some Concerns for mortality and	

2021	infection. 751 assigned to budesonide (inh) 800µg twice daily for 14 days and 1028 assigned to SOC	21.9%, diabetes 20.5%, COPD 18.3%, CHD 15.4%, disease 6.2%		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**
RCT					
ERSul trial;[266] 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 **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
RCT					
Singh et al;[267] Preprint; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to TD-0903 1-10mg 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

Telmisartan

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Duarte et al;[268] preprint; 2020	Patients with mild to severe COVID-19	Mean age 61.9 ± 18.2, male 61.5%,	NR	High for mortality and invasive mechanical	**Mortality:** Very low certainty ⊕◯◯◯

	infection. 38 assigned to Telmisartan 80 mg twice daily and 40 assigned to standard of care	hypertension 30.7%, diabetes 11.5%, chronic lung disease 11.5%, asthma 1.3%, chronic kidney disease 2.6%, cerebrovascular disease 7.7%, obesity 12.8%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[269] preprint; 2021	Patients with severe COVID-19 infection. 28 assigned to thalidomide 100mg 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.	**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
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;[270] peer-reviewed; 2020	Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned to standard of care	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, coronary heart disease 28%, obesity 20.5%	Steroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 0.89 (95%CI 0.77 to 1.03); RD -1.8% (95%CI -3.7% to 0.5%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.83 (95%CI 0.77 to 0.89); RD -2.9% (95%CI -4% 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 ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.89 (95%CI 0.75 to 1.07); RD -1.1% (95%CI -2.6%
Wang et al;[271] 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.	
Zhao et al;[91] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600mg twice a day for 7 days, 7 assigned to tocilizumab 400 mg once or twice and 5	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	

	assigned to favipiravir plus tocilizumab			inappropriate.	to 0.7%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
RCT-TCZ-COVID-19 trial;[272] Salvarani et al; peer-reviewed; 2020	Patients with severe COVID-19. 60 assigned to tocilizumab 8 mg/kg twice on day 1 and 66 assigned to standard of care	Median age 60 ± 19, male 61.1%, hypertension 44.4%, diabetes 15.1%, COPD 3.2%, obesity 32.2%	Hydroxychloroquine 91.3%, azithromycin 20.6%, antivirals 41.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BACC Bay Tocilizumab Trial trial;[273] Stone et al; peer-reviewed; 2020	Patients with severe COVID-19. 161 assigned to tocilizumab 8 mg/kg once and 81 assigned to standard of care	Median age 59.8 ± 15.1, male 58%, hypertension 49%, diabetes 31%, COPD 9%, asthma 9%, coronary heart disease 10%, chronic kidney disease 17%, cancer 12%,	Steroids 9.5%, remdesivir 33.9%, hydroxychloroquine 3.7%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
CORIMUNO-TOCI 1 trial;[274] 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;[275] 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;[243] Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8mg/kg once or twice, 48 assigned to sarilumab 400mg 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%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %	Low for mortality and mechanical ventilation; 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;[276] peer reviewed; 2020	Patients with severe to critical COVID-19. 65 assigned to TCZ 8mg/kg once and 64 assigned to SOC	Mean age 57.4 ± 14.6, male 68%, hypertension 49.6%, diabetes 32.6%, COPD 3%, CHD 5.5%, cancer 7%,	Steroids 71.3%	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY-TCZ trial;[277] Horby et al; peer reviewed; 2020	Patients with severe to critical COVID-19. 2022 assigned to TCZ 400-800mg 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.	

Triazavirin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Wu et al;[278] 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Umifenovir Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al;[81] preprint; 2020	Patients with moderate to critical COVID-19 infection.	Mean age NR ± NR, male 46.6%, hypertension 27.9%,	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** No information

	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	diabetes 11.4%		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
ELACOI trial; Li et al;[176] 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.	
Nojomi et al;[279] 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;[280] 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;[281] 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
RCT					
Zhang et al;[282] 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 ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Kumari et al;[283] Peer reviewed; 2020	Patients with severe COVID-19. 75 assigned to Vit C 50mg/kg a day and 75 assigned to SOC	Mean age 52.5 ± 11.5	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Jamali Moghadam Siahkali et al;[284] Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5gr a day for 5 days	Mean age 59.2 ± 17, male 50%, hypertension 41.6%, diabetes 38.3%, COPD	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and	

	and 30 assigned to SOC	10%,		adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVIDAtoZ - Vit C trial;[285] Thomas et al; peer reviewed; 2020	Patients with mild COVID-19. 48 assigned to Vit C 8000mg 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;[286] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to vitamin D 0.532 once followed by 0.266 twice and 26 assigned to standard of care	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, coronary heart disease 3.9%, immunosuppression 9.2%, cancer %, obesity %	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information
SHADE trial;[287] 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	Mean age 48.7 ± 12.4, male 50%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	assigned to standard of care			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Murai et al;[288] peer-reviewed; 2020	Patients with severe COVID-19. 117 assigned to vitamin D 200,000 IU once and 120 assigned to standard of care	Mean age 56.3 ± 14.6, male 56.3%, hypertension 52.5%, diabetes 35%, COPD %, asthma 6.3%, coronary heart disease 13.3%, chronic kidney disease 1%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Lakkireddy et al;[289] preprint; 2021	Patients with mild to moderate with low plasmatic vitamin D COVID-19 infection. 44 assigned to Vit D 60000 IU a day for 8 to 10 days and 43 assigned to SOC	Mean age 45.5 ± 13.3, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

XAV-19 (swine glyco-humanized polyclonal antibodies)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
POLYCOR trial;[290] 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Zinc **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and 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;[291] preprint; 2020	Patients with mild to critical COVID-19. 49 assigned to zinc 220 mg twice a day and 56 assigned to standard of care	Mean age 45.9 ± 17.5, male 58.2%, hypertension 10.4%, diabetes 11.2%, coronary heart disease 3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Abd-Elsalam et al;[292] 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.	
Abdelmaksoud et al;[293] Peer reviewed; 2020	Patients with mild to critical COVID-19. 49 assigned to Zinc 220mg 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;[285] Thomas et al; ; 2020	Patients with mild COVID-19. 58 assigned to Zinc 50mg 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;[294] Patel et al; Peer reviewed; 2020	Patients with severe to critical COVID-19. 15 assigned to Zinc 0.24 mg/kg a day for 7 days and 18 assigned to SOC	Mean age 61.8 ± 16.9, male 63.6%, hypertension 48.4%, diabetes 18.2%, COPD 6%, CHD 21.2%,	Steroids 75.8%, remdesivir 30.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Seet et al;[129] peer reviewed; 2021	Patients exposed to COVID-19 infection. 634 assigned to zinc 80 mg and 500mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33 , male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

α-Lipoic acid Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zhong et al;[295] preprint; 2020	Patients with critical COVID-19 infection. 8 assigned to α-Lipoic acid 1200 mg infusion once daily for 7 days and 9 assigned to standard of care	Median age 63 ± 7, male 76.5%, hypertension 47%, diabetes 23.5%, coronary heart disease 5.9%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Appendix 1. Summary of findings tables

Summary of findings table 1.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 Difference: **16 fewer per 1000** (CI 95% 32 fewer - 3 more)	**Moderate** Due to serious imprecision[1]	Steroids probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 5942 patients in 6 studies Follow up 28	**172** per 1000	**150** per 1000 Difference: **22 fewer per 1000** (CI 95% 48 fewer - 9 more)	**Moderate** Due to serious imprecision[2]	Steroids probably decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.27 (CI 95% 0.98 - 1.65) Based on data from 646 patients in 5 studies	**606** per 1000	**770** per 1000 Difference: **164 more per 1000** (CI 95% 12 fewer - 394 more)	**Moderate** Due to serious risk of bias[3]	Steroids probably increases symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.89 (CI 95% 0.68 - 1.17) Based on data from 833 patients in 6 studies	**102** per 1000	**91** per 1000 Difference: **11 fewer per 1000** (CI 95% 33 fewer - 17 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Steroids may have little or no difference on severe adverse events

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 Difference: **10 fewer per 1000** (CI 95% 29 fewer - 13 more)	**Low** Due to serious imprecision, Due to serious risk of bias[1]	Remdesivir may decrease mortality slightly
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 Difference: **61 fewer per 1000** (CI 95% 106 fewer - 19 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Remdesivir may decrease mechanical ventilation requirements
Symptom resolution or improvement 28 days	Relative risk: 1.17 (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 Difference: **103 more per 1000** (CI 95% 18 more - 200 more)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Remdesivir may improve symptom resolution or improvement
Severe adverse events	Relative risk: 0.8 (CI 95% 0.48 - 1.33) Based on data from 1869 patients in 3 studies	**102** per 1000	**82** per 1000 Difference: **20 fewer per 1000** (CI 95% 53 fewer - 34 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Remdesivir may have little or no difference on severe adverse events

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

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

Summary of findings table 3.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 15 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 8944 patients in 11 studies Follow up Median 15 days	**160** per 1000	**171** per 1000 Difference: **11 more per 1000** (CI 95% 3 fewer - 27 more)	**Moderate** Due to serious risk of bias[1]	HCQ probably increases mortality
Mechanical ventilation 15 days	Relative risk: 1.07 (CI 95% 0.91 - 1.26) Based on data from 7255 patients in 8 studies Follow up Median 15 days	**173** per 1000	**185** per 1000 Difference: **12 more per 1000** (CI 95% 16 fewer - 45 more)	**Moderate** Due to serious risk of bias[2]	Hcq probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.05 (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 Difference: **30 more per 1000** (CI 95% 30 fewer - 97 more)	**Moderate** Due to serious inconsistency[3]	Hcq probably has little or no difference on symptom resolution or improvement
COVID-19 infection (in exposed individuals) (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 Difference: **5 fewer per 1000** (CI 95% 61 fewer - 78 more)	**Low** Due to very serious imprecision[4]	Hcq may have little or no difference on covid-19 infection (in exposed individuals)
	Relative risk: 0.82 (CI 95% 0.49 - 1.36)	**74** per 1000	**61** per 1000	**Very Low**	We are uncertain whether hcq increases

Hospitalizations (in patients with non-severe disease)	Based on data from 1195 patients in 4 studies	Difference: **13 fewer per 1000** (CI 95% 38 fewer - 27 more)	Due to serious risk of bias, Due to very serious imprecision[5]	or decreases hospitalizations
Severe adverse events	Relative risk: 0.9 (CI 95% 0.59 - 1.37) Based on data from 6536 patients in 12 studies	**102** per 1000 **92** per 1000 Difference: **10 fewer per 1000** (CI 95% 42 fewer - 38 more)	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Hcq may have little or no difference on severe adverse events

1. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
3. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** I2 82%; **Imprecision: No serious.** Secondary to inconsistency;
4. **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
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	LPV	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 1.02 (CI 95% 0.92 - 1.12) Based on data from 8010 patients in 3 studies Follow up Median 28 days	**160** per 1000	**163** per 1000 Difference: **3 more per 1000** (CI 95% 13 fewer - 19 more)	**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 7580 patients in 3 studies Follow up Median 28 days	**173** per 1000	**185** per 1000 Difference: **12 more per 1000** (CI 95% 3 fewer - 29 more)	**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 Difference: **18 more per 1000** (CI 95% 48 fewer - 91 more)	**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 study	**102** per 1000	**61** per 1000 Difference: **41 fewer per 1000** (CI 95% 64 fewer - 2 fewer)	**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 Difference: **18 more per 1000** (CI 95% 30 fewer - 115 more)	**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** SOC	CP	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality (Low RoB studies)[1] 28 days	Relative risk: 1.0 (CI 95% 0.93 - 1.07) Based on data from 12111 patients in 4 studies Follow up Median 28 days	**160** per 1000	**160** per 1000 Difference: **0 fewer per 1000** (CI 95% 11 fewer - 11 more)	**Moderate** Due to serious imprecision[2]	Convalescent plasma probably has little or no difference on mortality
Mechanical ventilation (Low RoB studies)[1] 28 days	Relative risk: 0.91 (CI 95% 0.77 - 1.07) Based on data from 7558 patients in 4 studies Follow up Median 28 days	**173** per 1000	**157** per 1000 Difference: **16 fewer per 1000** (CI 95% 40 fewer - 12 more)	**Moderate** Due to serious imprecision[3]	Cp probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.03 (CI 95% 0.92 - 1.15) Based on data from 12554 patients in 5 studies Follow up 28 days	**606** per 1000	**624** per 1000 Difference: **18 more per 1000** (CI 95% 48 fewer - 91 more)	**Moderate** Due to serious inconsistency[4]	Cp probably has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.26 (CI 95% 0.83 - 1.9) Based on data from 81 patients in 1 study	**102** per 1000	**129** per 1000 Difference: **27 more per 1000** (CI 95% 17 fewer - 92 more)	**Very Low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[5]	We are uncertain whether cp increases or decreases 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: Very 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
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	TCZ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.89 (CI 95% 0.77 - 1.03) Based on data from 6350 patients in 8 studies Follow up Median 28 days	**160** per 1000	**142** per 1000 Difference: **18 fewer per 1000** (CI 95% 37 fewer - 5 more)	**Moderate** Due to serious imprecision[1]	TCZ probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.83 (CI 95% 0.77 - 0.89) Based on data from 5352 patients in 8 studies Follow up Median 28 days	**173** per 1000	**144** per 1000 Difference: **29 fewer per 1000** (CI 95% 40 fewer - 19 fewer)	**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 Difference: **61 more per 1000** (CI 95% 6 fewer - 133 more)	**Low** Due to serious imprecision, Due to serious risk of bias[3]	TCZ may increase symptom resolution or improvement
Severe adverse events	Relative risk: 0.89 (CI 95% 0.75 - 1.07) Based on data from 2312 patients in 8 studies	**102** per 1000	**91** per 1000 Difference: **11 fewer per 1000** (CI 95% 25 fewer - 7 more)	**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 1mg/kg a day) or full dose (i.e enoxaparin 1m/kg twice a day)
Comparator: Anticoagulants in prophylactic dose (i.e enoxaparin 40mg a day)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	ACO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 1.04 (CI 95% 0.94 - 1.17) Based on data from 1656 patients in 3 studies	**160** per 1000	**166** per 1000 Difference: **6 more per 1000** (CI 95% 10 fewer - 27 more)	**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: 0.93 (CI 95% 0.38 - 2.26) Based on data from 563 patients in 1 study	**70** per 1000	**65** per 1000 Difference: **5 fewer per 1000** (CI 95% 43 fewer - 88 more)	**Low** Due to very serious imprecision[2]	Anticoagulantes in intermediate dose may slightly reduce venous thromboembolic events
Venous thromboembolic events (full dose)	Relative risk: 0.58 (CI 95% 0.37 - 0.91) Based on data from 1110 patients in 1 study	**70** per 1000	**41** per 1000 Difference: **29 fewer per 1000** (CI 95% 44 fewer - 6 fewer)	**Low** Due to very serious imprecision[3]	Anticoagulantes in full dose may reduce venous thromboembolic events
Major bleeding	Relative risk: 1.43 (CI 95% 0.76 - 2.71) Based on data from 1671 patients in 2 studies	**19** per 1000	**27** per 1000 Difference: **8 more per 1000** (CI 95% 5 fewer - 32 more)	**Low** Due to very serious imprecision[4]	Anticoagulantes in intermediate or full dose may increase major bleeding events

1. **Imprecision: Serious.** 95%CI includes small benefits and harms;
2. **Imprecision: Very Serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: Very Serious.** Few patients and events;
4. **Imprecision: Very Serious.** 95%CI includes benefits and harms;

Summary of findings table 8.

Population: Patients with COVID-19 infection
Intervention: Non-steroids anti-inflammatory drugs
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC NSAID	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 Difference: **23 fewer per 1000** (CI 95% 48 fewer - 7 more)	**Very Low** Due to very serious risk of bias[1]	We are uncertain whether NSAID increases or decreases mortality

1. **Risk of bias: Very Serious.**

Summary of findings table 9.

Population: Patients with COVID-19 infection
Intervention: Interferon Beta-1a
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	IFN	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 Difference: **6 more per 1000** (CI 95% 19 fewer - 37 more)	**Moderate** Due to serious imprecision[1]	IFN 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 Difference: **3 fewer per 1000** (CI 95% 29 fewer - 28 more)	**Moderate** Due to serious imprecision[2]	IFN 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 Difference: **35 more per 1000** (CI 95% 157 fewer - 219 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether IFN 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 Difference: **264 more per 1000** (CI 95% 11 more - 381 more)	**Low** Due to very serious imprecision[5]	IFN (inhaled) may increase symptom resolution or improvement

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

Summary of findings table 10.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Favipravir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 Difference: **28 more per 1000** (CI 95% 130 fewer - 753 more)	**Low** Due to very serious imprecision[1]	Favipravir may have little or no difference on mechanical ventilation
Mortality 28 days	Relative risk: 1.16 (CI 95% 0.7 - 1.94) Based on data from 672 patients in 4 studies Follow up Median 28 days	**160** per 1000	**186** per 1000 Difference: **26 more per 1000** (CI 95% 48 fewer - 150 more)	**Low** Due to very serious imprecision[2]	Favipravir 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 Difference: **12 more per 1000** (CI 95% 412 fewer - 1351 more)	**Very Low** Due to very serious imprecision[4]	We are uncertain whether favipravir increases or decreases severe adverse events
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.9 - 1.09) Based on data from 373 patients in 1 study Follow up 28 days	**606** per 1000	**600** per 1000 Difference: **6 fewer per 1000** (CI 95% 61 fewer - 55 more)	**Moderate** Due to serious imprecision[5]	Favipravir probably has little or no difference on symptom resolution or improvement
	Relative risk: 0.75 (CI 95% 0.13 - 4.36)	**606** per 1000	**455** per 1000	**Very Low**	We are uncertain whether favipravir

Hospitalization (in patients with non-severe disease)	Based on data from 168 patients in 1 study Follow up 28 days	Difference: **151 fewer per 1000** (CI 95% 527 fewer - 2036 more)	Due to serious risk of bias, Due to very serious imprecision[6]	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 11.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality (Low risk of bias studies)[1]	Relative risk: 0.94 (CI 95% 0.51 - 1.73) Based on data from 747 patients in 4 studies	**160** per 1000	**150** per 1000 Difference: **10 fewer per 1000** (CI 95% 78 fewer - 117 more)	**Low** Due to very serious imprecision[2]	Ivermectin may have little or no difference on mortality
Mechanical ventilation	Relative risk: 0.89 (CI 95% 0.38 - 2.07) Based on data from 312 patients in 3 studies	**173** per 1000	**154** per 1000 Difference: **19 fewer per 1000** (CI 95% 107 fewer - 185 more)	**Very Low** Due to serious indirectness, Due to serious publication bias, Due to very serious imprecision[3]	We are uncertain whether ivermectin increases or decreases mortality
Symptom resolution or improvement (Low risk of bias studies)	Relative risk: 1.0 (CI 95% 0.9 - 1.11) Based on data from 508 patients in 2 studies	**606** per 1000	**606** per 1000 Difference: **0 fewer per 1000** (CI 95% 61 fewer - 67 more)	**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 Difference: **136 fewer per 1000** (CI 95% 158 fewer - 82 fewer)	**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 Difference: **4 more per 1000** (CI 95% 69 fewer - 243 more)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias, Due to serious publication bias[7]	We are uncertain whether ivermectin increases or decreases severe adverse events

Hospitalization (in non-severe patients)	Relative risk: 0.66 (CI 95% 0.19 - 2.3) Based on data from 398 patients in 1 study Follow up 28 days	**102** per 1000 **67** per 1000 Difference: **35 fewer per 1000** (CI 95% 83 fewer - 133 more)	**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. **Indirectness: Serious.** Most events from studies that compared ivermectin against hydroxychloroquine; **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: 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: Very Serious.** 95%CI includes significant benefits and absence of benefits ; **Publication bias: Serious.**
8. **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits ; **Publication bias: Serious.**

Summary of findings table 12.

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates SOC	Absolute effect estimates Baricitinib	Certainty of the Evidence (Quality of evidence)	Plain text summary
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 Difference: 59 fewer per 1000 (CI 95% 83 fewer - 30 fewer)	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 **Difference: 59 fewer per 1000 (CI 95% 93 fewer - 12 fewer)**	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 Difference: 152 more per 1000 (CI 95% 67 more - 248 more)	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 **Difference: 23 fewer per 1000 (CI 95% 38 fewer - 5 fewer)**	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 13.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
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 Difference: **2 more per 1000** (CI 95% 13 fewer - 16 more)	**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 Difference: **10 fewer per 1000** (CI 95% 38 fewer - 22 more)	**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 Difference: **12 more per 1000** (CI 95% 6 fewer - 24 more)	**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 Difference: **23 more per 1000** (CI 95% 50 fewer - 200 more)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias[4]	We are uncertain whether 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 14.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 0.45 (CI 95% 0.18 - 1.12) Based on data from 4665 patients in 3 studies	**160** per 1000	**72** per 1000 Difference: **88 fewer per 1000** (CI 95% 131 fewer - 19 more)	**Low** Due to serious imprecision, Due to very serious imprecision[1]	Colchicine may decrease mortality
Invasive mechanical ventilation	Relative risk: 0.48 (CI 95% 0.24 - 0.96) Based on data from 4593 patients in 2 studies Follow up 30 days	**173** per 1000	**83** per 1000 Difference: **90 fewer per 1000** (CI 95% 131 fewer - 7 fewer)	**Low** Due to very serious imprecision[2]	Colchicine may decrease invasive mechanical ventilation
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 1.0) Based on data from 4488 patients in 1 studies Follow up 30 days	**102** per 1000	**80** per 1000 Difference: **22 fewer per 1000** (CI 95% 40 fewer - 0 fewer)	**High** [3]	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 studies Follow up 30 days	**0.9** per 1000	**5.0** per 1000 Difference: **4.1 more per 1000** (CI 95% 0.21 more - 21.6 more)	**Low** Due to very serious imprecision[4]	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 studies Follow up 30 days	**74** per 1000	**59** per 1000 Difference: **15 fewer per 1000** (CI 95% 28 fewer - 2 more)	**Low** Due to very serious imprecision[5]	Colchicine may decrease hospitalization in patients with non-severe disease

1. **Imprecision: Very Serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals;
3. **Imprecision: No serious.** 95%CI includes significant benefits and absence of benefits ;

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

Summary of findings table 15.

Population: Patients with COVID-19 infection
Intervention: Sofosbuvir +/- daclatasvir or ledipasvir
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Sofosbuvir +/- daclatasvir or ledipasvir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 1.14 (CI 95% 0.82 - 1.57) Based on data from 1083 patients in 1 study	**160** per 1000	**182** per 1000 Difference: **22 more per 1000** (CI 95% 29 fewer - 91 more)	**Low** Due to serious imprecision, Due to very serious imprecision[1]	Sofosbuvir alone or in combination may have little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 1.5 (CI 95% 0.73 - 3.09) Based on data from 1083 patients in 1 study Follow up 30 days	**173** per 1000	**260** per 1000 Difference: **87 more per 1000** (CI 95% 47 fewer - 362 more)	**Low** Due to very serious imprecision[2]	Sofosbuvir alone or in combination may have little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.0 (CI 95% 0.94 - 1.07) Based on data from 1343 patients in 5 studies Follow up 7 days	**606** per 1000	**606** per 1000 Difference: **0 fewer per 1000** (CI 95% 36 fewer - 42 more)	**Moderate** Due to serious inconsistency[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. **Risk of bias: No 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; **Inconsistency: Serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.;

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БАГАТОЦЕНТРОВЕ РАНДОМІЗОВАНЕ ДОСЛІДЖЕННЯ З ОЦІНКИ ЕФЕКТИВНОСТІ ПРЕПАРАТУ БІОВЕН, ВИРОБНИЦТВА ТОВ «БІОФАРМА ПЛАЗМА», В КОМПЛЕКСНІЙ ТЕРАПІЇ ПАЦІЄНТІВ З ПНЕВМОНІЄЮ, ЩО ВИКЛИКАНА КОРОНАВІРУСНОЮ ІНФЕКЦІЄЮ COVID-19. Pain, Anaesthesia and Intensive Care. 2020;4(93):9–21.

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