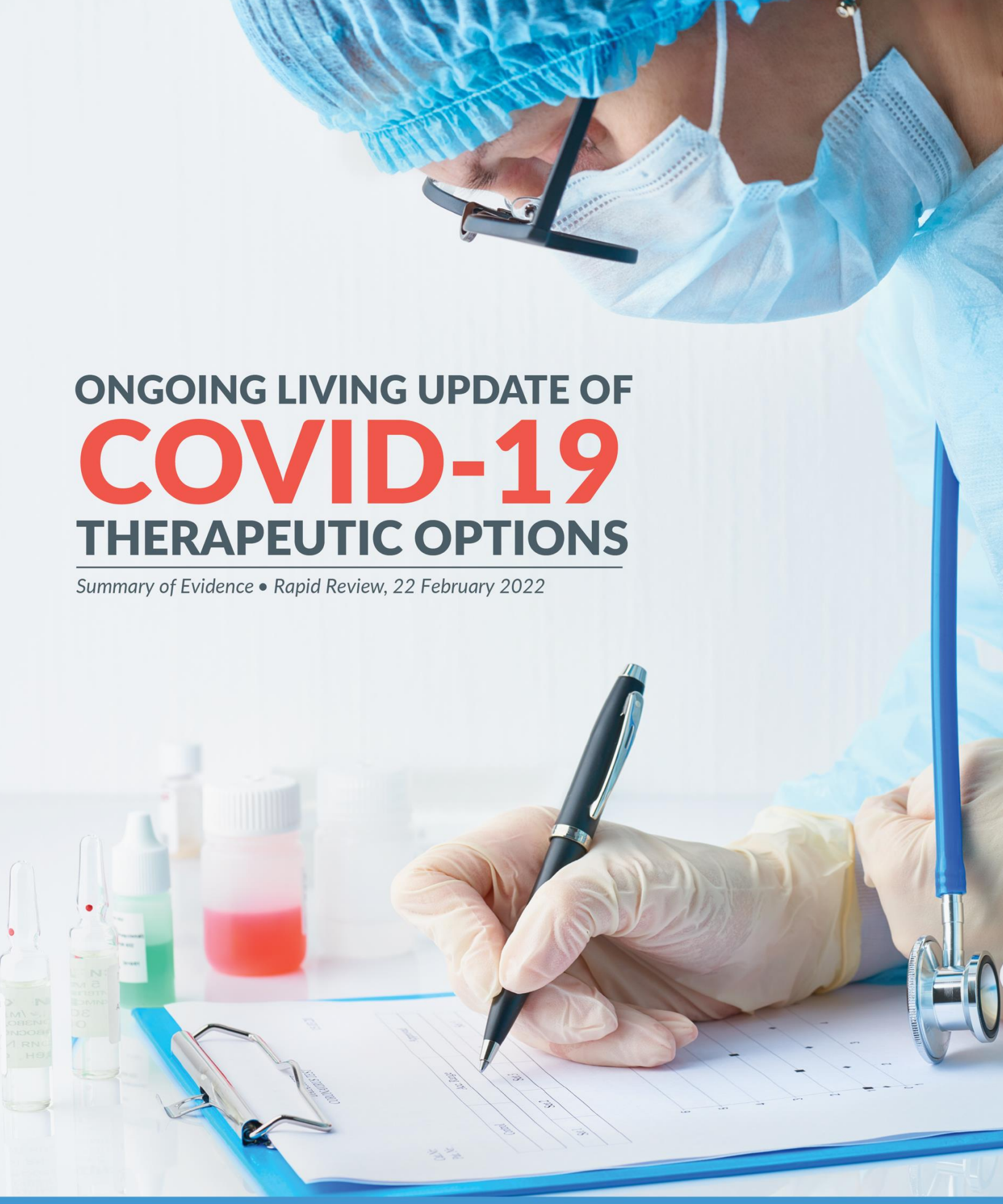

ONGOING LIVING UPDATE OF COVID-19 THERAPEUTIC OPTIONS

Summary of Evidence • Rapid Review, 22 February 2022

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, 22 February 2022

PAHO/IMS/EIH/COVID-19/22-0011

Disclaimer

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

Contents

Executive summary

Background

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 178 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=540)

Intervention		Overall number of studies including the intervention, n=540	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	54	13	9	10	7(*)	17	7
Ivermectin	NEW	35	6 (*)	6	4 (*)	4	6	5 (§)
Convalescent plasma	NEW	32	15(*)	9(*)	11		12	3 (§)
Tocilizumab		29	20	21	11		17	
Favipiravir		21	8	6	3(*)		7	3
Corticosteroids		20	17(@)	7	6		6	
Lopinavir-Ritonavir		17	4	4	2	1	2	1
Anticoagulants		13	11(@@)				5 (^)	
Sofosbuvir +/- Daclatasvir or others		13	2(*)	2(*)	2(*)			
Mouthwash		12	2	1	2			
ACEIs or ARBs		11	7(*)	9	3		1	1
Azithromycin		10	4	3	4		1	2
Colchicine	NEW	10	8(**)	5(**)	4(**)		3	2
REGEN-COV (casirivimab and imdevimab)	NEW	10	2(##)	2(##)	3(##)	3	3	3
Remdesivir		10	8 (#)	7	4		4	1
Sarilumab		9	9	7	7		6	
Bamlanivimab +/- etesevimab		8	3		3	1	6	3
Umifenovir		7	1	2			1	
Vitamin C		7	6	3	3			
Vitamin D	NEW	7	2	1			1	
Zinc		7	2	1	2		1	
Interferon beta-1a		6	5	4	2		2	
Corticosteroids (inhaled)		6	2	1	6			3
Bromhexine Hydrochloride		5	3	1	2	2	2	
IVIG		5	10	9				
Melatonin		5	2		3			
Mesenchimal cell tranplantation		5	4	1	2		2	
Anakinra		4	4	2	4		3	
Nasal hypertonic saline		4			1			
Nitazoxanide		5	1	1	1		2	2
Probiotics		4	2	1	1	1	1	1
Proxalutamide		4	3	3	2			2
Quercetin	NEW	4	3		2		1	1
Aspirin		3	2	2	1			
Baricitinib		3	3	1	3		3	
Cofactors		3	1		1		1	
Doxycycline	NEW	3	2	1	2		1	1
Hyperimmune anti-COVID-19 IVIG	NEW	3	3		1		2	
N-acetylcysteine		3	2	2			1	
Molnupiravir	NEW	5	2				2	3
Omega-3 fatty acids		3	2					
Beta glucans		2					1	
Camostat mesilate	NEW	2	1	1	1		1	1
Canakinumab		2	2	1	1		1	
Dutasteride		2			1			
Electrolyzed saline		2	2		1		1	
Fluvoxamine		2	1	1			2	2 (§)
Hyperbaric oxygen		2	2	2	1			
Iota-Carrageenan		2	1				2	1
Leflunomide		2						
Levamisole		2	1		1			2
Linagliptin		2	2	2				
Low-dose radiation therapy		2	1	1				
Niclosamide	NEW	2	1	1			1	1
Nigella sativa +/- Honey		2	1		1			1
Nitric oxide		2	1	1			2	
Peg-IFN alfa		2	2		2			
Pentoxifylline		2	2	2	1			
Regdanvimab		2			2		2	1
Resveratrol		2	2	2			2	2
Ruxolitinib		2	2	2	2		2	
Sotrovimab		2	1	1	1		1	1
Statins		2	2	1				
Tenofovir + emtricitabine		2	1				1	2
Thalidomide		2	1	1			1	
Tofacitinib	NEW	2	1		1		1	
99mTc-MDP		1						

Intervention		Overall number of studies including the intervention, n=540	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)
Adalimumab		1	1	1				
Ammonium chloride		1	1	1				
AMP5A (inhaled)		1	1				1	
Aprepitant		1						
Artemisinin		1			1		1	
Auxora		1	1		1		1	
Avdoralimab	NEW	1	1				1	
Aviptadil		1	1		1		1	
Azelastine (inhaled)		1			1		1	
Azvudine		1						
Baloxavir		1			1			
BCG		1	1					
Bioven		1	1				1	
Calcitriol		1	1				1	
Cannabidiol		1	1	1	1		1	1
CERC-002		1	1				1	
Chloroquine nasal drops		1						
CIGB-325		1			1		1	
Clarithromycin		1						
Clevudine		1					1	
Colchicine + rosuvastatin		1	1	1			1	
Corticosteroids (nasal)		1						
Crizanlizumab		1	1	1	1		1	
Darunavir-Cobicistat		1						
Dapagliflozin		1	1		1		1	
Dimethyl sulfoxide (DSMO)		1				1		
Electrolyzed saline		1	1		1			1
Emtricitabine/tenofovir		1	1	1			1	
Endothelial dysfunction protocol	NEW	1	1	1			1	
Enisamium		1			1			
Enzalutamide		1	1	1			1	
Famotidine		1	1					
Febuxostat		1						1
Finasteride		1	1					
Fostamatinib		1	1		1		1	
GB0139 (inhaled)		1	1				1	
Helium (inhaled)		1						
Hemadsorption		1	1		1			
Hesperidin		1	1	1	1		1	1
Icatibant/ iC1e/K		1	1					
Icosapent ethyl		1			1			
IFN-alpha2b + IFN-gamma		1						
IFX-1		1	1				1	
Imatinib		1	1	1			1	
Indomethacin		1	1	1			1	
Infliximab		1	1		1		1	
INM005 (equine antibodies)		1	1	1	1		1	
Interferon beta-1b		1	1	1	1			
Interferon beta-1a (inhaled)		1	1	1	1		1	
Interferon gamma		1						
Interferon kappa + TFF2		1	1				1	
Itolizumab		1	1	1			1	
Ivermectin (inhaled)		1			1			
KB109		1	1		1		1	
L-arginine		1	1				1	
Lactococcus Lactis (intranasal)		1			1		1	
Lactoferrin		1			1			
Lenzilumab		1	1	1			1	
Levilimab		1	1	1	1		1	
Lincomycin		1						
Mavrilimumab		1	1	1	1		1	
Mefenamic acid		1	1				1	1
Metformin		1	1				1	1
Metisoprinol		1						
Methylene blue		1	1					
Metoprolol		1	1					
Metronidazole		1			1			

Intervention		Overall number of studies including the intervention, n=540	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)
Montelukast		1	1					
Mupadolimab		1					1	
Mycobacterium w		1	1					
Nafamostat mesylate		1	1				1	
Namilumab		1	1		1		1	
Nano-curcumin		1					1	
Neem (Azadirachta Indica A. Juss)		1				1		
Nirmatrelvir-ritonavir	NEW	1	1				1	1
Novaferon		1						
NSAIDS		1	1		1		1	
Nutritional support		1	1	1				
Opaganib		1	1	1	1		1	
Otilimab		1	1				1	
P2Y12		1	1		1		1	
Peg-IFN lambda		1					1	
Plitidepsin		1	1	1			1	
PNB001 (CCK-A antagonist)		1	1		1			
Polymerized type I collagen (PT1C)		1						1
Povidone iodine		1	1				1	1
Progesterone		1	1	1			1	
Prolectin-M		1	1	1			1	
Propolis		1	1	1	1			
Prostacyclin		1	1				1	
Pyridostigmine		1	1	1	1		1	
Ramipril		1	1			1		
RD-X19 (light therapy)		1			1			
Recombinant Super-Compound IFN		1	1		1			
Ribavirin		1						
Ribavirin + Interferon beta-1b		1						
rhG-CSF		1	1		1		1	
rhG-CSF (inhaled)		1	1	1	1		1	
Secukinumab		1	1	1			1	
Short-wave diathermy		1	1		1		1	
Sildenafil		1	1	1			1	
Siltuximab		1	1	1				
Sitagliptin		1	1	1				
Spironolactone		1	1	1				
Stem-cell nebulization		1	1		1		1	
Sulodexide		1	1	1			1	1
TD-0903 (inhaled JAK-inhibitor)		1	1				1	
Tissue-plasminogen activator (tPA)		1	1				1	
Triazavirin		1	1		1		1	
XAV-19 (swine polyclonal antibodies)		1	1				1	
α-Lipoic acid		1	1					

(*) Based on low risk of bias subgroup of studies; (#) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-statistically significant mortality reduction (RR 0.95, 95%CI 0.83 - 1.08); (^) Major bleeding; (**) Observed results apply mostly to hospitalized patients with moderate to critical disease. The COLCORONA trial that included patients with recent onset mild disease showed a tendency to less hospitalizations, less mortality and less mechanical ventilation requirements. However the certainty on those potential benefits was low because of very serious imprecision as the number of events was low; (##) Subgroup of seronegative patients; (@) High dose schemes (i.e dexamethasone 12 mg a day) may not be more effective than standard dose schemes (i,e dexamethasone 6 mg a day); (@@) Excluding high risk of bias studies; (§) Observed effects would probably be considered important in patients with very high hospitalization risk.

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

Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=178), as at 22 February 2022

	Intervention	Summary of findings
1	**99mTc-MDP**	Uncertainty in potential benefits and harms. Further research is needed.
2	**Adalimumab**	Uncertainty in potential benefits and harms. Further research is needed.
3	**ACEIs or ARBs**	Continuing or initiating ACEIs or ARBs in patients with COVID-19 may increase mortality. However, the certainty of the evidence was low. Further research is needed.
4	**Ammonium chloride**	Uncertainty in potential benefits and harms. Further research is needed.
5	**AMP5A (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Anakinra**	It is uncertain if anakinra affects mortality, mechanical ventilation requirements, symptom resolution or increases severe adverse events. Further research is needed.
7	**Anticoagulants**	There are specific recommendations on the use of antithrombotic agents for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) may not decrease mortality in comparison with prophylactic dose (i.e.,

	Intervention	Summary of findings
		enoxaparin 40 mg a day). Anticoagulants in full dose decrease venous thromboembolic events but increase major bleeding in comparison with prophylactic dose. In mild ambulatory patients, anticoagulants in prophylactic dose, may not importantly improve time to symptom resolution.
8	**Aprepitant**	Uncertainty in potential benefits and harms. Further research is needed.
9	**Artemisinin**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Aspirin**	Aspirin probably does not reduce mortality, or mechanical ventilation and probably does not increase symptom resolution or improvement.
11	**Auxora**	Auxora may reduce mortality and may not increase severe adverse events. Further research is needed.
12	**Avdoralimab**	Avdoralimab may increase mortality and severe adverse events. Further research is needed.
13	**Aviptadil**	Uncertainty in potential benefits and harms. Further research is needed.
14	**Azelastine**	Uncertainty in potential benefits and harms. Further research is needed.
15	**Azithromycin**	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
16	**Azvudine**	Uncertainty in potential benefits and harms. Further research is needed.
17	**Baricitinib**	Baricitinib reduces mortality and time to symptom resolution without increasing severe adverse events. Certainty of the evidence was moderate because of risk of bias.
18	**Baloxavir**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
19	**Bamlanivimab +/- etesevimab (monoclonal antibody)**	Bamlanivimab probably reduces hospitalizations in patients with COVID-19 and it probably reduces symptomatic infections in exposed individuals. It is uncertain if it affects mortality or mechanical ventilation requirements. Further research is needed.
20	**BCG**	Uncertainty in potential benefits and harms. Further research is needed.
21	**Beta-glucans**	Uncertainty in potential benefits and harms. Further research is needed.
22	**Bioven**	Uncertainty in potential benefits and harms. Further research is needed.
23	**Bromhexine hydrochloride**	Bromhexine may reduce symptomatic infections in exposed individuals. Further research is needed.
24	**Calcitriol**	Uncertainty in potential benefits and harms. Further research is needed.
25	**Camostat mesilate**	Uncertainty in potential benefits and harms. Further research is needed.
26	**Canakinumab**	Uncertainty in potential benefits and harms. Further research is needed.
27	**Cannabidiol**	Uncertainty in potential benefits and harms. Further research is needed.
28	**CERC-002**	Uncertainty in potential benefits and harms. Further research is needed.
29	**Chloroquine nasal drops**	Uncertainty in potential benefits and harms. Further research is needed.
30	**CIGB-325**	Uncertainty in potential benefits and harms. Further research is needed.
31	**Clarithromycin**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
32	**Clevudine**	Uncertainty in potential benefits and harms. Further research is needed.
33	**Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)**	Uncertainty in potential benefits and harms. Further research is needed.
34	**Colchicine**	Colchicine probably does not reduce mortality, mechanical ventilation requirements or increase symptom resolution or improvement with moderate certainty. In patients with mild recent onset COVID-19 colchicine probably does not have an important effect on hospitalizations. However, the certainty of the evidence was low because of imprecision.
35	**Colchicine + rosuvastatin**	Uncertainty in potential benefits and harms. Further research is needed.
36	**Convalescent plasma**	Convalescent plasma does not reduce mortality or reduces mechanical ventilation requirements or improves time to symptom resolution with moderate to high certainty of the evidence. In patients with recent onset mild COVID-19 convalescent plasma probably does not have an important effect on hospitalizations. Convalescent plasma may not increase severe adverse events.
37	**Crizanlizumab**	Uncertainty in potential benefits and harms. Further research is needed.
38	**Dapagliflozin**	Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.
39	**Darunavir-cobicistat**	Uncertainty in potential benefits and harms. Further research is needed.
40	**Dimethyl sulfoxide (DSMO)**	Uncertainty in potential benefits and harms. Further research is needed.
41	**Doxycycline**	Doxycycline does not increase symptom resolution or improvement and may not reduce hospitalizations.
42	**Dutasteride**	Uncertainty in potential benefits and harms. Further research is needed**.**

	Intervention	Summary of findings
43	**Electrolyzed saline**	Uncertainty in potential benefits and harms. Further research is needed.
44	**Emtricitabine/tenofovir**	Uncertainty in potential benefits and harms. Further research is needed.
45	**Endothelial dysfunction protocol**	Uncertainty in potential benefits and harms. Further research is needed.
46	**Enisamium**	Uncertainty in potential benefits and harms. Further research is needed.
47	**Enzalutamide**	Uncertainty in potential benefits and harms. Further research is needed.
48	**Famotidine**	Uncertainty in potential benefits and harms. Further research is needed.
49	**Favipiravir**	Favipiravir may increase mortality and mechanical ventilation requirements, and it probably does not improve time to symptom resolution. Further research is needed.
50	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
51	**Finasteride**	Uncertainty in potential benefits and harms. Further research is needed.
52	**Fluvoxamine**	In patients with recent onset mild COVID-19 fluvoxamine probably does not have an important effect on hospitalizations and may not increase severe adverse events. Certainty of the evidence was low to moderate. Further research is needed.
53	**Fostamatinib**	Uncertainty in potential benefits and harms. Further research is needed.
54	**GB0139 (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
55	**Helium (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
56	**Hemadsorption**	Uncertainty in potential benefits and harms. Further research is needed.
57	**Hesperidin**	Hesperidin may not improve symptom resolution; however, the certainty of the evidence was low. Further research is needed.
58	**Hydroxychloroquine and chloroquine**	Hydroxychloroquine or chloroquine probably increases mortality, and probably does not reduce invasive mechanical ventilation or significantly improve time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19 it may reduce the risk of infection. However, certainty of the evidence is low because of risk of bias and imprecision.
59	**Hyperbaric oxygen**	Uncertainty in potential benefits and harms. Further research is needed.
60	**Hyperimmune anti-COVID-19 Intravenous Immunoglobulin (C-IVIG)**	Uncertainty in potential benefits and harms. Further research is needed.
61	**Icatibant/iC1e/K**	Uncertainty in potential benefits and harms. Further research is needed.
62	**Icosapent ethyl**	Uncertainty in potential benefits and harms. Further research is needed.
63	**IFX-1**	Uncertainty in potential benefits and harms. Further research is needed.
64	**Imatinib**	Uncertainty in potential benefits and harms. Further research is needed.
65	**Indomethacin**	Uncertainty in potential benefits and harms. Further research is needed.
66	**Infliximab**	Uncertainty in potential benefits and harms. Further research is needed.
67	**INM005 (polyclonal fragments of equine antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
68	**Interferon alpha-2b and interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
69	**Interferon beta-1a**	IFN beta-1a probably does not reduce mortality, invasive mechanical ventilation requirements or improve symptom resolution. Further research is needed.
70	**Interferon beta-1a (inhaled)**	Inhaled interferon beta-1a may improve time to symptom resolution. Further research is needed.
71	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
72	**Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
73	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.
74	**Iota-carrageenan**	Uncertainty in potential benefits and harms. Further research is needed.
75	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
76	**Ivermectin**	Although pooled estimates suggest significant benefits with ivermectin, included studies' methodological limitations and a small overall number of events result in very low certainty of the evidence. Based on the results reported by the RCTs classified as low risk of bias, ivermectin probably does not improve time to symptom resolution and may not have an important effect on hospitalizations. Further research is needed to confirm or discard these findings.
77	**Ivermectin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
78	**Intravenous immunoglobulin**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
79	**KB109**	Uncertainty in potential benefits and harms. Further research is needed.
80	**L-arginine**	Uncertainty in potential benefits and harms. Further research is needed.
81	***Lactococcus lactis* (intranasal)**	Uncertainty in potential benefits and harms. Further research is needed.
82	**Lactoferrin**	Uncertainty in potential benefits and harms. Further research is needed.
83	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
84	**Lenzilumab**	Lenzilumab may reduce mortality and mechanical ventilation requirements in severe patients. However, the certainty of the evidence is low because of imprecision. Further research is needed.
85	**Levamisole**	Uncertainty in potential benefits and harms. Further research is needed.
86	**Levilimab**	Levilimab may improve time to symptom resolution; however, the certainty of the evidence was low. Further research is needed.
87	**Linagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
88	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.
89	**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.
90	**Low-dose radiation therapy**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
91	**Mavrilimumab**	Uncertainty in potential benefits and harms. Further research is needed.
92	**Mefenamic acid**	Uncertainty in potential benefits and harms. Further research is needed.
93	**Melatonin**	Uncertainty in potential benefits and harms. Further research is needed.
94	**Mesenchymal stem-cell transplantation**	Mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence is low. Further research is needed.
95	**Metformin**	Metformin may not reduce hospitalizations in patients with recent onset mild disease. However, certainty of the evidence is low because of imprecision. Further research is needed.
96	**Methylene blue**	Uncertainty in potential benefits and harms. Further research is needed.
97	**Metisoprinol**	Uncertainty in potential benefits and harms. Further research is needed.
98	**Metoprolol**	Uncertainty in potential benefits and harms. Further research is needed.
99	**Metronidazole**	Uncertainty in potential benefits and harms. Further research is needed.
100	**Molnupiravir**	In patients with recent onset mild COVID-19 molnupiravir probably reduces hospitalizations and may not increase severe adverse events.

	Intervention	Summary of findings
101	**Montelukast**	Uncertainty in potential benefits and harms. Further research is needed.
102	**Mouthwash**	Mouthwash may improve time to symptom resolution. Uncertainty in potential benefits and harms on other outcomes. Further research is needed.
103	**Mupadolimab**	Uncertainty in potential benefits and harms. Further research is needed.
104	**Mycobacterium w**	Uncertainty in potential benefits and harms. Further research is needed.
105	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.
106	**Nafamostat mesylate**	Uncertainty in potential benefits and harms. Further research is needed.
107	**Namilumab**	Uncertainty in potential benefits and harms. Further research is needed.
108	**Nano-curcumin**	Uncertainty in potential benefits and harms. Further research is needed.
109	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
110	**Neem (*Azadirachta indica* A. Juss)**	Uncertainty in potential benefits and harms. Further research is needed.
111	**Niclosamide**	Uncertainty in potential benefits and harms. Further research is needed.
112	***Nigella sativa* +/- honey**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
113	**Nirmatrelvir-ritonavir**	Nirmatrelvir-ritonavir probably reduces hospitalizations in patients with mild recent onset COVID-19 and risk factors for severity, and it probably does not increase severe adverse events.
114	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.
115	**Nitric oxide**	Uncertainty in potential benefits and harms. Further research is needed.
116	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
117	**Non-steroidal anti-inflammatory drugs (NSAIDs)**	Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However, the certainty of the evidence is very low because of the risk of bias. Further research is needed.
118	**Nutritional support**	Uncertainty in potential benefits and harms. Further research is needed.
119	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed
120	**Opaganib**	Uncertainty in potential benefits and harms. Further research is needed
121	**Otilimab**	Uncertainty in potential benefits and harms. Further research is needed
122	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
123	**P2Y12 inhibitors**	P2Y12 inhibitors may increase mortality and may nor improve time to symptom resolution. However, certainty of the evidence was low because of imprecision. Further research is needed.

	Intervention	Summary of findings
124	**Peg-interferon alfa**	Uncertainty in potential benefits and harms. Further research is needed.
125	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
126	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.
127	**Plitidepsin**	Uncertainty in potential benefits and harms. Further research is needed.
128	**PNB001 (CCK-A antagonist)**	Uncertainty in potential benefits and harms. Further research is needed.
129	**Polymerized type I collagen (PT1C)**	Uncertainty in potential benefits and harms. Further research is needed.
130	**Povidone iodine (nasal spray)**	Uncertainty in potential benefits and harms. Further research is needed.
131	**Probiotics**	Uncertainty in potential benefits and harms. Further research is needed.
132	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed
133	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed
134	**Propolis**	Uncertainty in potential benefits and harms. Further research is needed
135	**Prostacyclin**	Uncertainty in potential benefits and harms. Further research is needed
136	**Proxalutamide**	Uncertainty in potential benefits and harms. Further research is needed

	Intervention	Summary of findings
137	**Pyridostigmine**	Uncertainty in potential benefits and harms. Further research is needed
138	**Quercetin**	Uncertainty in potential benefits and harms. Further research is needed
139	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
140	**RD-X19 (light therapy)**	Uncertainty in potential benefits and harms. Further research is needed.
141	**Recombinant super-compound interferon**	Uncertainty in potential benefits and harms. Further research is needed.
142	**REGEN-COV (casirivimab and imdevimab)**	In seronegative patients with severe to critical disease, REGEN-COV probably reduces mortality and increases symptom resolution and improvement. In patients with recent onset mild disease, REGEN-COV probably reduces hospitalizations and time to symptom resolution without increasing severe adverse events, and in asymptomatic exposed individuals REGEN-COV reduces symptomatic infections. The certainty of the evidence was high for symptomatic infections and low to moderate because of imprecision and indirectness for the remaining outcomes.
143	**Regdanvimab**	Regdanvimab may improve time to symptom resolution in mild to moderate patients. Its effects on mortality and mechanical ventilation are uncertain. Further research is needed.
144	**Remdesivir**	Remdesivir may not reduce mortality, but it may improve time to symptom resolution without significantly increasing the risk of severe adverse events. In patients with recent onset mild COVID-19, it may reduce hospitalizations. However, the certainty is low because of risk of bias and imprecision.
145	**Resveratrol**	Uncertainty in potential benefits and harms. Further research is needed.
146	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
147	**rhG-CSF (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
148	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.
149	**Ribavirin + interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
150	**Ruxolitinib**	Ruxolitinib may not improve time to symptom resolution; however, the certainty of the evidence was low. Further research is needed.
151	**Sarilumab**	Sarilumab may not reduce mortality and probably does not improve time to symptom resolution but may decrease mechanical ventilation requirements without increasing severe adverse events. However, the certainty is low because of imprecision and inconsistency.
152	**Secukinumab**	Uncertainty in potential benefits and harms. Further research is needed.
153	**Short-wave diathermy**	Uncertainty in potential benefits and harms. Further research is needed.
154	**Sildenafil**	Uncertainty in potential benefits and harms. Further research is needed.
155	**Siltuximab**	Uncertainty in potential benefits and harms. Further research is needed.
156	**Sitagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
157	**Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir or ravidasvir**	Sofosbuvir with or without daclatasvir or ledipasvir may not reduce mortality or mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.
158	**Sotrovimab**	Sotrovimab probably reduce hospitalizations in patients with recent onset mild COVID-19.

	Intervention	Summary of findings
159	**Spironolactone**	Uncertainty in potential benefits and harms. Further research is needed.
160	**Statins**	Uncertainty in potential benefits and harms. Further research is needed.
161	**Stem-cell nebulization**	Uncertainty in potential benefits and harms. Further research is needed.
162	**Steroids (corticosteroids)**	Corticosteroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Corticosteroids may not significantly increase the risk of severe adverse events. Higher-dose schemes (i.e., dexamethasone 12 mg a day) may not be more effective than standard dose schemes (i.e., dexamethasone 6 mg a day).
163	**Steroids (corticosteroids, inhaled)**	Inhaled corticosteroids probably improve time to symptom resolution. Its effects on other important outcomes are uncertain. Further research is needed.
164	**Steroids (corticosteroids, nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
165	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
166	**TD-0903 (inhaled JAK-inhibitor)**	Uncertainty in potential benefits and harms. Further research is needed.
167	**Tenofovir + emtricitabine**	Uncertainty in potential benefits and harms. Further research is needed.
168	**Thalidomide**	Uncertainty in potential benefits and harms. Further research is needed.
169	**Tissue-plasminogen activator (tPA)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
170	**Tocilizumab**	Tocilizumab reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
171	**Tofacitinib**	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low, further research is needed.
172	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.
173	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
174	**Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
175	**Vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
176	**XAV-19 (swine glyco-humanized polyclonal antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
177	**Zinc**	Uncertainty in potential benefits and harms. Further research is needed.
178	**α-lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** According to WHO International Clinical Trials Registry Platform (ICTRP), hundreds of potential interventions are being assessed in more than 10,000 clinical trials and observational studies. In this review, we identified and examined 178 therapeutic options.

• **Corticosteroids:** The body of evidence on corticosteroids, which includes 21 RCTs, shows that low- or moderate-dose treatment schemes (RECOVERY trial dose was 6 mg of oral or intravenous preparation once daily for 10 days) are probably effective in reducing mortality in patients with severe COVID-19 infection. These results remained robust after including studies in which patients with acute respiratory distress syndrome (ARDS) secondary to alternative etiologies (not COVID-19 related) were randomized to corticosteroids or placebo/no corticosteroids. Higher-dose schemes (i.e., dexamethasone 12 mg a day) may not be more effective than standard dose schemes (i.e., dexamethasone 6 mg a day).

• **Remdesivir:** In the WHO SOLIDARITY trial, remdesivir resulted in little or no effect on overall mortality, initiation of ventilation and duration of hospital stay among hospitalized patients. When combining those findings with those from seven other RCTs, remdesivir may not have an important effect on mortality but it may reduce invasive mechanical ventilation requirements and may improve time to symptom resolution. However, overall certainty of the evidence is low and further research is needed to confirm these findings. In patients with recent onset mild COVID-19 remdesivir may reduce hospitalizations; however, the certainty of the evidence is low because of imprecision. Further research is needed.

• **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. Seven studies with low risk of bias that assessed hydroxychloroquine in exposed individuals showed a modest reduction in symptomatic infections but certainty of the evidence was low because of imprecision and inconsistency. Further research is needed to confirm these findings.

• **Antibiotics**: The body of evidence on azithromycin and doxycycline shows no significant benefits in patients with mild to moderate or severe to critical COVID-19.

• **Convalescent plasma:** The results of 32 RCTs assessing convalescent plasma in COVID-19, including the RECOVERY trial with 11,558 hospitalized patients, showed no mortality reduction, significant mechanical ventilation requirement reduction or time to symptom resolution improvement with moderate to high certainty of the evidence. In mild patients, convalescent plasma probably does not have an important effect hospitalization with moderate certainty. Convalescent plasma may not increase severe adverse events with low certainty. No significant differences were observed between patients treated early (< 4 days since symptom onset) or with more advanced disease in a subgroup analysis from the RECOVERY trial.

• **Tocilizumab:** The results of 28 RCTs assessing tocilizumab show that, in patients with severe or critical disease, tocilizumab reduces mortality and mechanical ventilation requirements without significantly increasing severe adverse events.

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

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

• **Tofacitinib:** The results of two RCT assessing tofacitinib in hospitalized patients with moderate to severe disease, suggest possible increase in symptom resolution or improvement and possible increase in severe adverse events with tofacitinib. Certainty of the evidence was low and further research is needed.

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

• **Ivermectin:** Although 35 RCTs assessed ivermectin in patients with COVID-19, only 15 of those studies reported on clinical important outcomes. Pooled estimates suggest mortality reduction with ivermectin, but the certainty of the evidence was very low because of methodological limitations and small number of events. Based on the results reported by the four RCTs classified as low risk of bias, ivermectin probably does not improve time to symptom resolution and may not have an important effect on hospitalizations. Further research is needed to confirm these findings.

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

• **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** Thirteen RCTs assessed sofosbuvir with or without daclatasvir, ledipasvir or velpatasvir against standard of care or other interventions. Subgroup analysis showed significant differences between low risk of bias and high risk of bias studies. The results of the two studies classified as low risk of bias suggest that sofosbuvir alone or in combination may not reduce mortality or mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

• **Baricitinib:** The results of three RCTs show that, in patients with moderate to critical disease, baricitinib reduces mortality and time to symptom resolution without increasing severe adverse events. The certainty of the evidence was moderate because of risk of bias.

• **REGEN-COV (casirivimab and imdevimab):** The results of ten RCTs suggest that, in patients with severe to critical disease, overall REGEN-COV may reduce mortality, mechanical ventilation or increase symptom resolution or improvement. However, the certainty of the evidence was low. A subgroup analysis suggests a differential effect on seronegative patients in which REGEN-COV probably reduces mortality and mechanical ventilation requirements and increases symptom resolution or improvement. In patients with recent onset mild COVID-19, REGEN-COV probably reduces hospitalizations and improves time to symptom resolution without increasing severe adverse events, and in exposed asymptomatic individuals REGEN-COV reduces symptomatic infections. The certainty of the evidence was high for symptomatic infections and low to moderate because of indirectness and imprecision for the remaining outcomes. One study that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab in non-severe patients with risk factors for severity, reported no important differences in hospitalizations.

• **Bamlinivimab +/- etesevimab:** The results of six RCTs suggest that bamlinivimab probably decreases hospitalizations in patients with COVID-19 and probably decreases symptomatic infection in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed. One study that compared bamlanivimab +/- etesevimab against REGEN-COV (casirivimab and imdevimab) in non-severe patients with risk factors for severity, reported no important differences in hospitalizations.

• **Sotrovimab:** The results of two RCT show that, in patients with recent onset mild COVID-19, sotrovimab probably reduces hospitalizations and improves time to symptom resolution without increasing severe adverse events. The certainty of the evidence was moderate because of imprecision but with evidence of equipoise between sotrovimab and REGEN-COV.

• **Regdanvimab:** The results of two RCT show that, in patients with mild to moderate disease, regdanvimab may improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision. Its effects on other important outcomes are uncertain. Further research is needed to confirm or discard these findings.

• **Proxalutamide:** The results of four RCTs suggest that proxalutamide may result in important benefits. However, the certainty of the evidence was very low because of very serious risk of bias, imprecision, and indirectness. Further research is needed to confirm or discard these findings.

• **Dapagliflozin:** The results of one RCT suggest that, in patients with cardiometabolic risk factors hospitalized with moderate COVID-19, dapagliflozin may reduce mortality, but probably does not increase symptom resolution. However, the certainty of the evidence was low because of imprecision. Further research is needed to confirm or discard these findings.

• **Mesenchymal stem-cell transplantation:** The results of five RCTs show that, in patients with severe to critical, mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence was low because of imprecision. Further research is needed to confirm or discard these findings.

• **Inhaled corticosteroids:** The results of six RCTs show that inhaled corticosteroids probably improve time to symptom resolution. However, its effects on other relevant outcomes are uncertain. Further research is needed.

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

• **Lenzilumab:** The results of one RCT suggest that lenzilumab may reduce mortality and invasive mechanical ventilation requirements in severe patients. However, the certainty of the evidence was low because of imprecision. Further research is needed.

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

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

• **Anticoagulants:** Thromboembolic complications in patients infected with COVID-19 are relatively frequent. As for hospitalized patients with severe medical conditions current guidelines recommend thromboprophylactic measures to be adopted for inpatients with COVID-19 infection. Regarding the best thromboprophylactic scheme, excluding three studies classified as with high risk of bias, the results of eight RCTs that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day) showed no differences in mortality with low certainty (imprecision and inconsistency). Results of three RCTs inform that aspirin probably does not reduce mortality, nor mechanical ventilation and probably does not increase symptom resolution or improvement. In mild ambulatory patients two RCTs suggest that rivaroxaban in prophylactic dose may not importantly improve time to symptom resolution.

• **NSAIDS:** No association between NSAID exposure and increased mortality was observed. However, certainty of the evidence is very low and further research is needed to confirm these findings.

• **ACEIs or ARBs:** The results of five low-risk of bias RCTs suggest that initiating or continuing ACEIs or ARBs in patients with COVID-19 may increase mortality. However, certainty of the evidence is low because of imprecision and further research is needed to confirm these findings.

• **Molnupiravir:** The results of five RCTs show that molnupiravir probably reduces hospitalizations in patients with recent onset mild to moderate disease, and may not increase severe adverse events.

• **Nirmatrelvir-ritonavir:** The results of one RCT show that nirmatrelvir-ritonavir probably reduces hospitalizations in patients with recent onset mild to moderate disease, and probably does not increase severe adverse events.

• **Probiotics:** The results of four RCTs suggest that probiotics may improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

• **Mouthwash:** The results of twelve RCTs suggest that mouthwashes may improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

• **P2Y12 inhibitors:** The results of one RCT suggest that P2Y12 in combination with anticoagulants in full dose may increase mortality and may not improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

Changes since previous edition

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

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

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

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

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

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

• **Camostat mesylate:** New evidence included without significant changes.

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

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

• **Vitamin D:** New evidence included without significant changes.

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

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

• **Hyperimmune anti-COVID-19 intravenous immunoglobulin:** New evidence included without significant changes.

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

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

• **REGEN-COV (casirivimab e imdevimab):** New evidence included without significant changes.

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

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

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

Concluding remarks

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

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

• The safety of the patient suffering from COVID-19 is a key priority to improve the quality of care in the provision of health services.

• There remains an urgent need for additional high-quality randomized controlled trials that include patients with COVID-19 before most therapeutic options can be administered with any confidence. Adequately designed and reported clinical trials are crucial for the practice of evidence-based medicine. Most of the research to date on COVID-19 has very poor methodology that is hidden and very difficult to validate. Greater transparency and better designed studies are urgently needed.

Hallazgos clave

Opciones terapéuticas: Según el portal de búsqueda de la Plataforma de Registros Internacionales de Ensayos Clínicos (ICTRP) de la Organización Mundial de la Salud (OMS), se están investigando cientos de posibles tratamientos o sus combinaciones en más de 10.000 ensayos clínicos y estudios observacionales. En esta revisión, examinamos 178 opciones terapéuticas potenciales.

• **Corticosteroides:** El conjunto de evidencia sobre los corticoesteroides incluye 21 ensayos clínicos controlados aleatorizados (ECCA) y muestra que la administración de dosis bajas y moderadas (la dosis utilizada en el estudio RECOVERY fue dexametasona 6 mg diarios por vía oral o intravenosa durante 10 días) probablemente reduce la mortalidad en pacientes con infección grave por SARS-CoV-2. Los resultados se mantuvieron uniformes tras agregar al análisis estudios en los que pacientes con síndrome de dificultad respiratoria aguda (SDRA) de otras etiologías recibieron corticosteroides o manejo estándar de forma aleatoria. Esquemas con dosis más altas (por ejemplo, dexametasona 12 mg por día) podrían no resultar más efectivos que los esquemas habituales (por ejemplo dexametasona 6 mg por día).

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

• **Hidroxicloroquina, interferón beta 1-a y lopinavir-ritonavir:** El conjunto de evidencia sobre la hidroxicloroquina, el interferón beta 1-a y el lopinavir-ritonavir, incluidos los resultados preliminares de los estudios RECOVERY y Solidaridad, no muestra beneficios en la reducción de la mortalidad, la necesidad de ventilación mecánica invasiva o el plazo necesario para la mejoría clínica. Incluso la evidencia sobre hidroxicloroquina sugiere que su utilización probablemente genere un incremento en la mortalidad. Siete estudios con bajo riesgo de sesgo que evaluaron la hidroxicloroquina en personas expuestas a la COVID-19 sugieren una modesta reducción en el riesgo de infección, pero la certeza en la evidencia es baja por inconsistencia e imprecisión. Se necesita más información para confirmar estas conclusiones.

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

• **Plasma de convalecientes:** Los resultados de 32 ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19, incluido el estudio RECOVERY que incorpora 11.558 pacientes, mostraron ausencia de reducción de la mortalidad, ausencia de reducción en la necesidad de ventilación mecánica invasiva y ausencia de mejoría en el tiempo de resolución de los síntomas con certeza moderada. En pacientes leves, el plasma de convalecientes probablemente no tenga un efecto importante sobre las hospitalizaciones con certeza moderada. El plasma de convalecientes podría no asociarse a un aumento en los eventos adversos graves con certeza baja. En un análisis de subgrupo del estudio RECOVERY, no se observó un efecto diferencial entre aquellos pacientes tratados rápidamente (menos de 4 días desde el inicio de los síntomas) y aquellos con enfermedad más avanzada al iniciar dicho tratamiento.

• **Tocilizumab:** Los resultados de 28 ECCA muestran que el tocilizumab reduce la mortalidad y la necesidad de ventilación invasiva sin un incremento importante en los efectos adversos graves en pacientes con enfermedad grave o crítica.

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

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

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

• **Colchicina:** Los resultados de diez ECCA, entre los que se encuentra el estudio COLCORONA, que incluyó 4488 pacientes con diagnóstico reciente de COVID-19 y factores de riesgo para enfermedad grave y el estudio RECOVERY que incorpora 11.340 pacientes hospitalizados muestran que colchicina probablemente no reduce la mortalidad, la necesidad de ventilación mecánica, mejora la velocidad de resolución de los síntomas o reduce las hospitalizaciones en pacientes con enfermedad leve de reciente comienzo. Estos resultados están fundamentalmente sustentados en el estudio RECOVERY. El estudio COLCORONA, que incluyó pacientes ambulatorios con enfermedad leve, apunta una posible reducción en las hospitalizaciones, la necesidad de ventilación mecánica y la mortalidad en este subgrupo. Sin embargo, la certeza en la evidencia es baja por imprecisión muy grave, ya que el número de eventos fue bajo.

• **Ivermectina:** A pesar de que 35 ECCA evaluaron ivermectina en pacientes con COVID-19, solo 15 de estos estudios notificaron desenlaces clínicamente importantes. Los resultados combinados de estos estudios indican una reducción en la mortalidad con la ivermectina. Sin embargo, la

certeza en la evidencia es muy baja por limitaciones metodológicas y un número reducido de eventos. Con base en la información facilitada por los cuatro estudios con riesgo bajo de sesgo, probablemente no se asocie a una mejoría en la velocidad de resolución de los síntomas ni tenga un efecto importante sobre las hospitalizaciones. Se necesita más información para confirmar estas conclusiones.

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

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

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

• **REGEN-COV (casirivimab e imdevimab):** Los resultados de diez ECCA muestran que, en pacientes con enfermedad grave o crítica, el REGEN-COV podría reducir la mortalidad, la necesidad de ventilación invasiva y mejorar la velocidad de resolución de los síntomas de forma significativa. Sin embargo, la certeza en la evidencia es baja. Un análisis de subgrupo mostró un efecto diferencial en pacientes con anticuerpos negativos. En este subgrupo, el REGEN-COV probablemente reduzca la mortalidad, la necesidad de ventilación mecánica e incremente la resolución de síntomas. En pacientes con enfermedad leve de comienzo reciente, el REGEN-COV probablemente reduce las hospitalizaciones y mejora el tiempo de resolución de los síntomas sin aumentar el riesgo de eventos adversos graves; y en personas asintomáticas, expuestas a SARS-CoV-2, el REGEN-COV reduce las infecciones sintomáticas. La certeza en la evidencia es alta para infecciones sintomáticas y de baja a moderada por información indirecta e imprecisión para los restantes desenlaces. Un estudio que comparó el REGEN-COV (casirivimab e imdevimab) con el bamlanivimab con o sin etesevimab en pacientes con síntomas leves y factores de riesgo para enfermedad grave notificó ausencia de diferencias importantes en las hospitalizaciones.

• **Bamlinivimab con o sin etesevimab:** Los resultados de seis ECCA indican que el bamlanivimab probablemente reduce las hospitalizaciones en pacientes con COVID-19 y probablemente

disminuye las infecciones sintomáticas en personas expuestas. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información. Un estudio que comparó el bamlanivimab con o sin etesevimab con el REGEN-COV (casirivimab e imdevimab) en pacientes con síntomas leves y factores de riesgo para enfermedad grave notificó ausencia de diferencias importantes en las hospitalizaciones.

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

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

• **Proxalutamide:** Los resultados de cuatro ECCA sugieren un efecto favorable asociado a la proxalutamida. Sin embargo, la certeza en la evidencia es muy baja por riesgo de sesgo muy grave, imprecisión e información indirecta. Se necesita más información para confirmar o descartar estas conclusiones.

• **Dapagliflozina:** Los resultados de un ECCA muestran que, en pacientes con factores de riesgo cardiometabólicos hospitalizados por COVID-19 moderada, la dapagliflozina podría reducir la mortalidad, pero probablemente no mejora la resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.

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

• **Corticosteroides inhalados:** Los resultados de seis ECCA muestran que los corticosteroides inhalados probablemente mejoran el tiempo de resolución de los síntomas. Sin embargo, sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

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

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

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

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

• **Anticoagulantes:** Las complicaciones tromboembólicas en pacientes con COVID-19 son frecuentes. Al igual que en pacientes hospitalizados por afecciones médicas graves, las directrices vigentes indican que los pacientes hospitalizados por COVID-19 sean tratados con medidas tromboprofilácticas. En relación con el esquema tromboprofiláctico, excluyendo tres estudios clasificados con riesgo alto de sesgo, los resultados de ocho ECCA que compararon los anticoagulantes en dosis intermedias (p. ej., enoxaparina 1 mg/kg por día) o dosis completas (p. ej., enoxaparina 1 mg/kg cada 12 h por día) frente a dosis profilácticas (p. ej., enoxaparina 40 mg por día) mostraron ausencia de diferencias en la mortalidad con certeza baja (imprecisión e inconsistencia). Los resultados de tres ECCA informan que la indicación de aspirina probablemente tampoco se asocia a una reducción en la mortalidad o la necesidad de ventilación mecánica ni a la mejoría en la velocidad de resolución de los síntomas. Los resultados de dos ECCA sugieren que, en pacientes ambulatorios con enfermedad leve, el rivaroxaban en dosis profilácticas podría no mejorar el tiempo de resolución de los síntomas de forma considerable.

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

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

• **Molnupiravir:** Los resultados de cinco ECCA muestran que el tratamiento con molnupiravir indicado a pacientes con enfermedad leve a moderada de reciente comienzo y con factores de riesgo para enfermedad grave probablemente reduzca las hospitalizaciones y podría no aumentar los eventos adversos graves.

• **Nirmatrelvir-ritonavir:** Los resultados de un ECCA muestra que el tratamiento con nirmatrelvir-ritonavir indicado a pacientes con enfermedad leve a moderada de reciente comienzo y con factores de riesgo para enfermedad grave probablemente reduzca las hospitalizaciones y probablemente no aumente los eventos adversos graves.

• **Probióticos:** Los resultados de cuatro ECCA sugieren que el tratamiento con probióticos podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Enjuague bucal:** Los resultados de doce ECCA sugieren que el tratamiento con enjuagues bucales podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Inhibidores P2Y12:** Los resultados de un ECCA sugieren que el tratamiento con P2Y12 agregado a anticoagulantes en dosis completas podría aumentar la mortalidad y podría no mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

Cambios respecto a la versión anterior

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

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

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

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

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

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

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

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

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

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

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

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

• **Inmunoglobulina intravenosa hiperinmune anti-COVID-19:** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

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

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

• **REGEN-COV (casirivimab e imdevimab):** La evidencia nueva incluida no modifica la interpretación de los resultados ni la certeza de la evidencia.

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

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

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

Conclusiones

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

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

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

• Sigue siendo apremiante la necesidad de elaborar ensayos clínicos aleatorizados de alta calidad que incluyan pacientes con COVID-19 a fin de poder desarrollar estrategias de manejo confiables. La importancia de los ensayos clínicos controlados aleatorizados con un diseño adecuado es fundamental en la toma de decisiones basadas en la evidencia. Hasta el momento, la mayoría de la investigación en el campo de la COVID-19 tiene muy baja calidad metodológica, lo que dificulta su identificación y validación. Urge incrementar la transparencia y plantear estudios de más calidad.

Systematic review of therapeutic options for treatment of COVID-19

Background

The vast amount of data generated by clinical studies of potential therapeutic options for COVID-19 presents important challenges. This new information must be interpreted quickly so that prescribers can make optimal treatment decisions with as little harm to patients as possible, and so that medicines manufacturers can scale-up production rapidly and bolster their supply chains. Interpreting new data quickly will save lives by ensuring that reportedly successful drugs can be administered to as many patients as possible as quickly as possible. Moreover, if evidence indicates that a medication is not effective, then ongoing clinical trials could change focus and pivot to more promising alternatives. Since many physicians are currently using treatments that rely on compassionate-use exemptions or off-label indications to treat patients with COVID-19,[1] it is crucial that they have access to the most up-to-date research evidence to inform their treatment decisions.

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

Methods

We used the Living OVerview of Evidence (L·OVE; https://iloveevidence.com) platform to identify studies for inclusion in this review. This platform is a system that maps PICO (Patient–Intervention–Comparison–Outcome) questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in electronic databases, preprint servers, trial registries, and other resources relevant to COVID-19. The 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. It was last checked for this review on 22 February 2022. The

searches covered the period from the inception date of each database, and no study design, publication status or language restriction was applied.

Study selection

The results of the searches in the individual sources were de-duplicated by an algorithm that compares unique identifiers (database identification number, digital object identifier (DOI), trial registry identification number), and citation details (i.e., author names, journal, year of publication, volume, number, pages, article title, and article abstract). Then, the information matching the search strategy was sent in real-time to the L·OVE platform where at least two authors independently screened the titles and abstracts yielded against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis and then decided about their inclusion.

Inclusion criteria

We aimed to find all available RCTs for potential therapeutic pharmacological interventions for COVID-19 with study designs that included head-to-head comparisons, or control groups with no intervention or a placebo. Target patient populations included both adults and children exposed to or with confirmed or suspected COVID-19. We focused on comparative effectiveness studies that provide evidence on outcomes of crucial importance to patients (mortality, invasive mechanical ventilation, symptom resolution or improvement, infection [prophylaxis studies] and severe adverse events).[3] In addition to RCTs, we included comparative non-RCTs that report on effects of NSAID consumption on mortality. We only incorporated non-RCTs that included at least 100 patients. We presented results of RCTs and non-RCTs separately.[4]

Living evidence synthesis

An artificial intelligence algorithm deployed in the Coronavirus/COVID-19 topic of the L·OVE platform provides instant notification of articles with a high likelihood of being eligible. The authors review them, decide upon inclusion, and update the living web version of the review accordingly. If meta-analytical pooling is possible from retrieved evidence, we will do this to derive more precise estimates of effect and derive additional statistical power.

The focus has been on RCTs studies for all included therapeutic pharmacological interventions (adults and children). Adults and children exposed to or with confirmed or suspected COVID-19 were and will be included. Trials that compare interventions head-to-head or against no intervention or placebo is the focus. We have focused on comparative effectiveness studies that provide evidence on patient-important outcomes (mortality, invasive mechanical ventilation, symptom resolution or improvement, infection (prophylaxis studies), hospitalization (studies that included patients with non-severe disease) and severe adverse events).[3] For studies that assessed thromboprophylactic interventions we also assessed venous thromboembolic events and major bleeding. For the outcome “hospitalization” we included information from studies reporting the

number of hospitalizations or the number of hospitalizations combined with the number of deaths without hospitalization. We did not include information from studies reporting a combination of hospitalizations and medical consultations. No electronic database search restrictions were imposed.

For any meta-analytical pooling, if and when data allow, we pool all studies and present the combined analysis with relative and absolute effect sizes. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). We extracted mortality and invasive mechanical ventilation baseline risks from the ISARIC cohort as of 18 December 2020.[5,6] For baseline infection risk in exposed to COVID-19 we used estimates from a SR on physical distancing and mask utilization,[7] and for adverse events and symptom resolution/improvement we used the mean risk in the control groups from included RCTs until 18 December 2020. For venous thromboembolic events and major bleeding baseline risk we used the mean risk in the control groups from included RCTs until 25 March 2021. For hospitalization baseline risk we used the median risk in the control groups from included RCTs until 23 December 2021. We continuously monitor baseline risks by assessing the mean risk of every outcome in the control groups of included RCTs. When substantial changes to baseline risks are detected, we update the estimates used for absolute effects calculations. For mortality, there were some drug instances whereby we provide systematic-review (meta-analysis) evidence indirectly related to patients with COVID-19, e.g., corticosteroids in patients with ARDS.

For result interpretations and imprecision assessment we used a minimally contextualized approach which considers whether the 95%CI includes the null effect, or, when the point estimate is close to the null effect, whether the 95%CI lies within the boundaries of small but important benefit and harm that corresponds to every outcome assessed.[8,9]
We used the following thresholds to define important benefits and harms: Mortality, +/- 1%; Mechanical ventilation, +/- 2%; Symptom resolution or improvement, +/- 5%; Symptomatic infection in exposed individuals, +/- 5%; Hospitalization in patients with mild recent COVID-19, +/- 2%; Severe adverse events, +/- 3%.

For some interventions when we found significant heterogeneity, we performed subgroup analysis considering: 1) risk of bias (high/moderate vs low risk of bias); 2) disease severity (mild, moderate, severe, or critical); and 3) intervention's characteristics (i.e., different doses or administration schemes). When we observed significant differences between subgroups, we presented individual subgroup's estimates of effect and certainty of the evidence assessment.

A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect (Table 4).[10] For non-RCTs, potential residual confounding was assumed in all cases and certainty of the evidence was downgraded twice for risk of bias. The GRADE approach was used to assess the certainty on the body of evidence for every comparison on an outcome basis (Table 5).[11] Risk of bias judgments were compared against other similar projects (Drug treatments for covid-19: living systematic

review and network meta-analysis and The COVID-NMA initiative). Significant discrepancies were discussed until a final decision was reached.

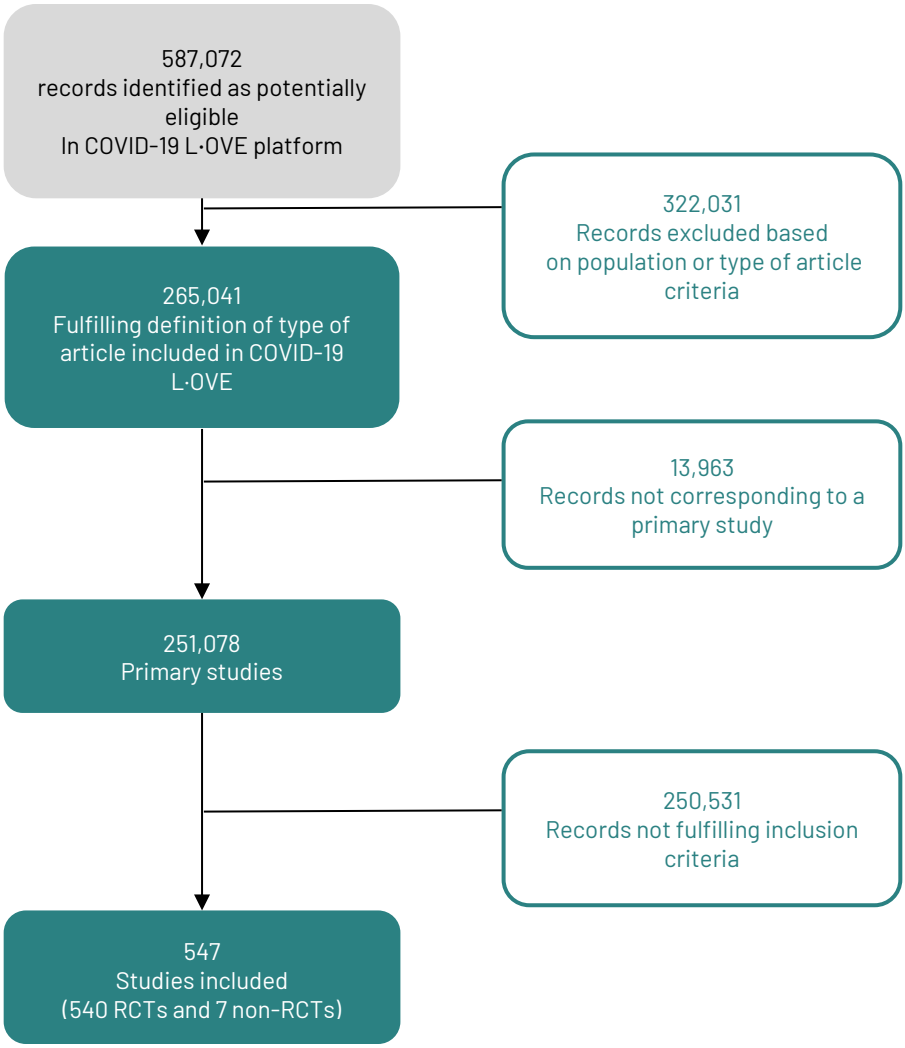
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in Figure 1. A total of 547 studies were selected for inclusion, 540 RCTs and 7 non-RCTs. A list of excluded studies is available upon request.

Figure 1. Study identification and selection process



Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs resulted in high risk of bias due to suboptimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal. For the observational studies, we had concerns with the representativeness of study groups (selection bias)

and imbalance of the known and unknown prognostic factors (confounding). Many studies are also at risk of being confounded by indication. Most are not prospective in nature and the outcome measures are mainly heterogeneous with wide variation in reporting across the included studies. In general, follow-up was short and as mentioned, confounded potentially by the severity of disease, comorbidities, and previous or concomitant COVID-19 treatment. The risk of bias assessment of each RCT is presented in Table 4.

Table 4. Risk of bias of included RCTs

Study	Risk-of-bias arising from randomization process	Risk-of-bias due to deviations from the intended interventions	Risk-of-bias due to 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 - Dexa	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
RECOVERY - Hydroxychloroquine	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
BCN PEP CoV-2	Low	Some Concerns	Some Concerns	Some Concerns	Low		Some Concerns
ACTT-1	Low	Low	Low	Some Concerns	Low	Low	Low
COVID-19 PEP	Low	Low	High	Low	Low		High
Cavalcanti et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kamran SM et al	High	Some Concerns	Low	High	Low		High
COVID-19 PET	Low	Low	Low	Low	Low	Low	Low
SIMPLE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BCN PEP CoV-2	High	Some Concerns	Low	High	Low		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		High
Chen, Zeng et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Chuan Li C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zheng et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ELACOI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CONCOVID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
GLUCOCOVID	High	Some Concerns	Low	Low	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
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	High	High	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
CARDEA	Low	Low	Low	Low	Low	Low	Low
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
Shouman et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahmani H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ConPlas-19	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
DEXA-COVID19							
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Steroids-SARI							
COVID STEROID							
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
Chowdhury et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLACID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
Gharebaghi N et al	High	Low	Low	Low	Low	Some Concerns	Some Concerns
TX-COVID19	High	Some Concerns	Low	Some Concerns	Low	High	High
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 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
Mahmud et al	Low	Low	Low	Low	Low	Low	Low
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
Yethindra V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shi L et al	Low	Low	Low	Low	Low	Low	Low
RCT-TCZ-COVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BACC Bay Tocilizumab Trial	Low	Low	Low	Low	Low	Low	Low
SARITA-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
Ghaderkhani S et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PEP (University of Washington)	Low	Low	Low	Low	Low	NA	Low
Hashim HA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ILBS-COVID-02	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
PROBIOZOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Padmanabhan U et al (Medical Education and Drugs Departmen	High	Low	Low	Low	Low	High	High
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khamis F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BLAZE-1	High	Low	Low	Low	Low	High	High
PETAL	Low	Low	Low	Low	Low	Low	Low
Lanzoni G et al	High	Low	Low	Low	Low	High	High
Ruzhentsova T et al (R-Pharm)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Lenze E et al	Low	Low	Low	Low	Low	Low	Low
Monk P et al	Low	Low	Low	Low	Low	Low	Low
SHADE trial	High	Some Concerns	Low	Some Concerns	Low	High	High
Yakoot M et al (Pharco Corporate)	High	Some Concerns	Low	Some Concerns	Low	High	High
Ghandehari S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HAHPS	Low	High	Low	Some Concerns	Low	High	High
Elgazzar et al (mild)	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgazzar et al (severe)	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgazzar et al (prophylaxis)	High	Some Concerns	Low	Some Concerns	Low	High	High
Tabarsi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAV052020 (Promomed, LLC)	High	Some Concerns	Low	Some Concerns	Low	High	High
Murai IH et al (University of Sao Paulo)	Low	Low	Low	Low	Low	Low	Low
Udwadia ZF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-TOCI 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EMPACTA	Low	Low	Low	Low	Low	Low	Low
HYCOVID	Low	Low	Low	Low	Low	Low	Low
Krolewiecki et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ILIAD	Low	Low	Low	Low	Low	Low	Low
AB-DRUG-SARS-004	High	Low	Low	Low	Low	High	High
Q-PROTECT	Low	Low	Low	Low	Low	Low	Low
Hassan M et al	High	Low	Low	Low	Low	High	High
FundacionINFANT-Plasma	Low	Low	Low	Low	Low	Low	Low
COVID-Lambda	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Niaee et al	Some Concerns	Some Concerns	Low	Some Concerns	Low	High	High
PICP19	High	Some Concerns	Low	Some Concerns	Low	High	High
Mukhtar K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ahmed et al	High	Low	Low	Low	Low	High	High
ITOLI-C19-02-I-00	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Prolectin-M	High	Some Concerns	Low	Some Concerns	Low	High	High
Maldonado V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
GARGLES	High	Some Concerns	Low	Some Concerns	Low	High	High
ERSul	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
Chaccour et al	Low	Low	Low	Low	Low	Low	Low
ACTT-2	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
RECOVERY	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
EIDD-2801-1001	Low	Low	Low	Low	Low	Low	Low
Weinreich	Low	Low	Low	Low	Low	Low	Low
Roozbeh F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTIV-3/TICO	Low	Low	Some Concerns	Low	Low	Low	High
Chachar et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Balykova LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Babalola et al	Low	Low	Low	Low	Low	Low	Low
REMAP-CAP - tocilizumab	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Abdelmaksoud AA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kirti et al	Low	Low	Low	Low	Low	Low	Low
Kumari P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FK/FAV00A-CoV/2020	High	Low	Low	Low	Low	High	High
Chahla et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIFERON	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY-Plasma	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Interferon in COVID (Alavi Darazam I et al)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AB-DRUG-SARS-004 (Cadegiani FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
JamaliMoghadamSiahkali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedighiyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Roostaei A et al	High	Low	Low	Low	Low	High	High
Bee-Covid	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEOT	High	Some Concerns	Low	Some Concerns	Low	High	High
Mohan et al	Low	Low	Low	Low	Low	Low	Low
Shahbaznejad et al	Low	Low	Low	Low	Low	Low	Low
Spoorthi et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Samaha et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Bukhari el al	High	Some Concerns	Low	Some Concerns	Low	High	High
Okumus et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Veiga	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Gottlieb	Low	Low	Low	Low	Low	Low	Low
BRACE CORONA	Low	Some Concerns	Some Concerns	Low	Low	Low	High
CORIMUNO-ANA-1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Thakar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Onal H et al	High	High	Low	Some Concerns	Low	High	High
Tang X et al	Low	Some Concerns	Low	Low	Low	Low	Low
COLCORONA	Low	Some Concerns	Low	Low	Low	Low	Low
Lopardo	Low	Low	Low	Low	Low	Low	Low
Dabbous HM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ATTRACT	Low	Some Concerns	Low	Low	Low	Low	Low
Ranjbar K et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
EAT-DUTA AndroCoV	Low	Low	High	Low	Low	High	High
Farnoosh G et al	Some Concerns	Some Concerns	High	Some Concerns	Low	High	High
Khalili H et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Baklaushev VP et al	High	Some Concerns	Low	Some Concerns	Low	High	High
KILLER	High	Some Concerns	Low	Some Concerns	Low	High	High
HYDRA	Low	Some Concerns	Low	Low	Low	Low	Low
Sali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
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
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
ZINC COVID	Low	Some Concerns	Low	Low	Low	Low	Low
PATCH 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AB-DRUG-SARS-004-2	High	Some Concerns	Low	Some Concerns	Low	High	High
Nouri-Vaskeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopez-Medina et al	Low	Low	Low	Low	Low	Low	Low
Lakkireddy M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Silva	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High
Bermejo Galan et al	Low	Low	Low	Low	Low	Low	Low
Pott-Junior et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mikhaylov	Low	Some Concerns	Low	Some Concerns	Low	Low	High
2GAMMACOVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
AAAS9924	Low	Low	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Tolouian et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ElZein R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PEGI.20.002	High	Some Concerns	Low	Some Concerns	Low	High	High
MASH-COVID	Low	Some Concerns	Low	Low	Low	Low	Low
INSPIRATION	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Zarychanski	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Santos PSS et al	Low	Some Concerns	Low	Low	Low	Low	Low
Solaymani-Dodaran M et al	Low	Some Concerns	Low	Low	Low	Low	Low
TD-0903-0188	High	Some Concerns	Low	Some Concerns	Low	High	High
DISCOVER	Low	Some Concerns	Low	Low	Low	Low	Low
SURG-2020-28683	Low	Some Concerns	Low	Low	Low	Low	Low
Alavi-Moghaddam M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CT-P59 3.2	Low	Some Concerns	Low	Low	Low	Low	Low
Yadollahzadeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BBCovid	Low	Some Concerns	Low	Low	Low	Low	Low
Hanna Huang Y et al	High	Some Concerns	Low	Some Concerns	Low	High	High
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
RESIST	High	Some Concerns	Low	Some Concerns	Low	High	High
CARR-COV-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Seet	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SBU-COVID19-ConvalescentPlasma	Low	Some Concerns	Low	Low	Low	Low	Low
TOGETHER	Low	Some Concerns	Low	Low	Low	Low	Low
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
OSCAR	Low	Some Concerns	Low	Low	Low	Low	Low
POLYCOR	Low	Some Concerns	Low	Low	Low	Low	Low
Vanguard	Low	Some Concerns	Low	Low	Low	Low	Low
Samimagham HR et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CamoCO-19	Low	Some Concerns	Low	Low	Low	Low	Low
BCR-PNB-001	High	Some Concerns	Low	Some Concerns	Low	High	High
ATOMIC2	Low	Some Concerns	Low	Some Concerns	Low	Low	High

Siami Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CLOROTRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High
PROBCO	High	Some Concerns	Low	Some Concerns	Low	High	High
Nesari TM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PISCO	High	Some Concerns	Low	Some Concerns	Low	High	High
HNS-COVID-PK	Low	Some Concerns	Low	Low	Low	Low	Low
Rashad A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Moni M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
FACCT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COV-BARRIER	Low	Some Concerns	Low	Low	Low	Low	Low
LIVE-AIR	Low	Some Concerns	Low	Low	Low	Low	Low
PreToVid	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mahmoudi M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
AGILE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hamdy Salman O et al	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-RT-01	Low	Some Concerns	Low	Low	Low	Low	Low
COVID-ARB	High	Some Concerns	Low	Some Concerns	Low	High	High
Perepu U et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zarychanski-Non-critical	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Sarilumab-COVID19 Study	Low	Some Concerns	Low	Low	Low	Low	Low
CAPSID	High	Some Concerns	Low	Some Concerns	Low	High	High
CHEER	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - Colchicine	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Silvia Mendez-Flores S et al	High	Low	Low	Low	Low	High	High
SAVE-MORE	Low	Some Concerns	Low	Low	Low	Low	Low
Winchester S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgohary MAS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ARMY-1	Low	Some Concerns	Low	Low	Low	Low	Low
Hamidi-Alamdari D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zarehoseinzade E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Biber et al	Low	Low	Some Concerns	Low	Low	Low	Low
Faisal et al	High	Some Concerns	Low	Some Concerns	Low	High	High
SOVECOD	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTION	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
BLAZE-2	Low	Low	Low	Low	Low	Low	Low
ProPAC-COVID	Low	Low	Low	Low	Low	Low	Low
Tian F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RECOVERY - ASA	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
HONEST	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COMET-ICE	Low	Low	Low	Low	Low	Low	Low
ISMMSCCOVID19	Low	Low	Low	Low	Low	Low	Low
SENTAD-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEV-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
CATALYST	High	Some Concerns	Low	Some Concerns	Low	High	High
Ali S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY - REGEN-COV	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Taher A et al	High	Low	Low	Low	Low	High	High
ACEI-COVID	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Covid-19 Phase 3 Prevention Trial	Low	Low	Low	Low	Low	Low	Low
EIDD-2801-2003	Low	Low	Low	Low	Low	Low	Low
REMAP-CAP	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
STOP-COVID	Low	Low	Low	Low	Low	Low	Low
Vallejos et al	Low	Low	Low	Low	Low	Low	Low
CONCOR-1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ALBERTA HOPE-Covid19	Low	Low	Low	Low	Low	Low	Low
Hamed DM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COUNTER-COVID	Low	Low	Low	Low	Low	Low	Low
Abdulamir AS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
KP-DRUG-SARS-003	High	Low	Low	Low	Low	High	High
Aref ZF et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Di Pierro F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
AR0-CORONA	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ARCHITECTS	Low	Low	Low	Low	Low	Low	Low
CORIMUNO-TOCI ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COV-AID	Low	Low	Low	Low	Low	Low	Low
COVIDOSE-2	Low	Low	Low	Low	Low	Low	Low
COVIDSTORM	Low	Low	Low	Low	Low	Low	Low
COVITOZ-01	Low	Low	Low	Low	Low	Low	Low
HMO-0224-20	High	Low	Low	Low	Low	High	High
REMDACTA	Low	Low	Low	Low	Low	Low	Low
ImmCoVA	Low	Low	Low	Low	Low	Low	Low
Davoudian N et al	Low	Low	Low	Low	Low	Low	Low
TOCOVID	Low	Low	Low	Low	Low	Low	Low
COVINTOC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-SARI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-SARI ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SARCOVID	Low	Low	Low	Low	Low	Low	Low
SARICOR	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SARTRE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COV-AID-2	Low	Low	Low	Low	Low	Low	Low
REGENERON Sari P3	Low	Some Concerns	Low	Low	Low	Low	Low
COPEP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RAPID	Low	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns
Wang Q et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Hosseinzadeh A et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BLAZE-1	Low	Low	Low	Low	Low	Low	Low
Najmeddin F et al	Low	Low	Low	Low	Low	Low	Low
CAN-COVID	Low	Low	Low	Low	Low	Low	Low
Eduardo FP et al	Low	Low	Low	Low	Low	Low	Low
AB-DRUG-SARS-005	High	Low	Low	Low	Low	High	High
COVID STEROID 2	Low	Low	Low	Low	Low	Low	Low

ACTION	Low	Low	High	Low	Low	Some Concerns	Some Concerns
Gaitan-Duarte HG et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Sabico S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PLACOVID	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
UAIIC	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BISHOP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Asadipooya K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ravichandran et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DARE-19	Low	Low	Low	Low	Low	Low	Low
DOXYCOV	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PRINCIPLE	Low	Low	Low	Low	Low	Low	Low
Parikh D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Covid-19 Phase 3 Prevention Trial - Exposed	Low	Low	Low	Low	Low	Low	Low
Three C	Low	Low	Low	Low	Low	Low	Low
COVIDIT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
KUMC-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Abbass S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
C3PO	Low	Low	Low	Low	Low	Low	Low
Kosak et al	High	Some Concerns	Low	Some Concerns	Low	High	High
TOGHETER-Fluvoxamine	Low	Low	Low	Low	Low	Low	Low
TOCIDEX	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Fakharian A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HERO-HCQ	Low	Low	Low	Low	Low	Low	Low
Alizadeh Z et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Bhushan S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
VASCEPA COVID-19 CARDIOLINK-9	High	Some Concerns	Low	Some Concerns	Low	High	High
Shinkai M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rodrigues C et al	Low	Low	Low	Low	Low	Low	Low
Mousavi SA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Strich	Low	Low	Low	Low	Low	Low	Low
MADRID-COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
J2W-MC-PYAA	Low	Low	Low	Low	Low	Low	Low
DAWn-Plasma	Low	Some Concerns	Low	Some Concerns	Low	Some Concerns	High
OPTIMISE-C19	Low	Low	Low	Low	Low	Low	Low
Coppola	High	Low	Low	Low	Low	High	High
ALV-020-001	Low	Low	Low	Low	Low	Low	Low
Gates MRI RESPOND-1	Low	Low	Low	Low	Low	Low	Low
ACTIV-2	High	Some Concerns	Low	Some Concerns	Low	Low	Low
CARVIN	Low	Low	Low	Low	Low	Low	Low
Buonfrate et al	Low	Low	Low	Low	Low	Low	Low
McCreary M et al	Low	Low	Low	Low	Low	Low	Low
Ghanei M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Maskin et al	Low	Low	Low	Low	Low	Low	Low
COL-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE - Colchicine	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hassaniazad M et al	High	Low	Low	Low	Low	High	High
Ramachandran R et al	Low	Low	Low	Low	Low	Low	Low
CPI-006-002	High	Low	Low	Low	Low	High	High
Di-Domênico MB et al	High	Low	Some Concerns	Low	Low	High	High
CT-P59 1.2	Low	Low	Low	Low	Low	Low	Low
ABC-110	Low	Low	Low	Low	Low	Low	Low
CORONA	Low	Low	Low	Low	Low	Low	Low
STARS	High	Some Concerns	Low	Some Concerns	Low	High	High
ARTAN-C19	High	Low	High	Low	Low	High	High
Babalola OE et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESPERIDIN	Low	Low	Low	Low	Low	Low	Low
Reszinate	Low	Low	Low	Low	Low	Low	Low
Azizi H et al	High	Low	High	Low	Low	High	High
FIGHT-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
CANDIDATE	Low	Low	Low	Low	Low	Low	Low
BEMICOP	High	Some Concerns	Low	Some Concerns	Low	High	High
HEP-COVID	Low	Low	Low	Low	Low	Some Concerns	Some Concerns
ACTIV-4B	Low	Low	Low	Low	Low	Low	Low
COV-BARRIER-IMV	Low	Low	Low	Low	Low	Low	Low
DEFINE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEV-COVID	High	Some Concerns	Low	Some Concerns	Low	High	High
SARPAC	High	Some Concerns	Low	Some Concerns	Low	High	High
Elamir YM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PROCOV-19-2020	High	Some Concerns	Low	Some Concerns	Low	High	High
Haghighi S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
RUXCOVID	Low	Low	Low	Low	Low	Low	Low
ACTT-3	Low	Low	Low	Low	Low	Low	Low
Ameri A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Maghbooli Z et al	High	Low	Low	Low	Low	High	High
INTEREST	Low	Low	Low	Low	Low	Low	Low
Oliynyk O et al	High	Some Concerns	Low	Some Concerns	Low	High	High
EB-P12-01	Low	Low	Low	Low	Low	Low	Low
Mobarak S et al	Low	Low	Low	Low	Low	Low	Low
Leal F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Zhu R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CONTAIN	Low	Low	Low	Low	Low	Low	Low
COV-AID-3	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Somersan-Karakaya	Low	Low	Low	Low	Low	Low	Low
COVID-19-MCS	High	Low	Low	Low	Low	High	High
Yildiz E et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CYTOCOV-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Algahtani FD et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ALPS-COVID	Low	Low	Low	Low	Low	Low	Low
R10933-10987-COV-20145	Low	Low	Low	Low	Low	Low	Low
VCACS	High	Some Concerns	Low	Some Concerns	Low	High	High
CVD-04-CD-001	Low	Low	Low	Low	Low	Low	Low

PennCCP2	High	Some Concerns	Low	Some Concerns	Low	High	High
Toroghi N et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Isa F et al	Low	Low	Low	Low	Low	Low	Low
MOVe-OUT	Low	Low	Low	Low	Low	Low	Low
Weinreich_2	Low	Low	Low	Low	Low	Low	Low
Beigmohammadi MT et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sarhan RM et al	High	Some Concerns	Low	Some Concerns	Low	High	High
AP-014	High	Some Concerns	Low	Some Concerns	Low	High	High
Asgardoon M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Kharazmi AB et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COMBAT-COVID	Low	Low	Low	Low	Low	Low	Low
ACPREGCOV	Low	Low	Low	Low	Low	Low	Low
X-Covid 19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Holubar M et al	Low	Low	Low	Low	Low	Low	Low
Malaysian Favipiravir Study	Low	Some Concerns	Low	Some Concerns	Low	Low	High
George C et al	Low	Low	Low	Low	Low	Low	Low
TSUNAMI	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COnV-ert & CoV-Early	Low	Low	Low	Low	Low	Low	Low
Raghavan K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shohan et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CSSC-004	Low	Low	Low	Low	Low	Low	Low
Cannellotto M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
CRITICAL	Low	Low	Low	Low	Low	Low	Low
Regkirona_Part2							
PINETREE	Low	Low	Low	Low	Low	Low	Low
BUCOSARS	Low	Low	Low	Low	Low	Low	Low
BK-CLV-201	High	Some Concerns	Low	Some Concerns	Low	High	High
HIGHLOWDEXA	High	Some Concerns	Low	Some Concerns	Low	High	High
DEFINE	High	Some Concerns	Low	Some Concerns	Low	High	High
Ahmad B et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Pushkala et al.	High	Some Concerns	Low	Some Concerns	Low	High	High
Baxter AL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAVI-COV-US201	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kazempour et al.	High	Some Concerns	Low	Some Concerns	Low	High	High
Kerget B et al	High	Some Concerns	Low	Some Concerns	Low	High	High
WINCOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Poleti ML et al	Low	Low	High	Low	Low	High	High
COP20	Low	Some Concerns	Low	Some Concerns	Low	Low	High
WHIP COVID-19	Low	Low	Low	Low	Low	Low	Low
TOGETHER 2	Low	Low	Low	Low	Low	Low	Low
CONTAIN COVID-19	Low	Low	Low	Low	Low	Low	Low
COVIDENZA	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COLCOVID	Low	Low	Low	Low	Low	Low	Low
Alsultan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
OPTIMISE-C19	Low	Low	Low	Low	Low	Low	Low
COVID-Omega-F	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Majidi N et al	High	Low	Low	Low	Low	High	High
ICU-VR	High	Some Concerns	Low	Some Concerns	Low	High	High
ALLIANCE	High	Some Concerns	Low	Some Concerns	Low	High	High
PROTECT-EHC	Low	Low	Low	Low	Low	Low	Low
UNAB-003	High	Some Concerns	Low	Some Concerns	Low	High	High
Tolouian R et al	Low	Low	Low	Low	Low	Low	Low
INSPIRATION/INSPIRATION-S	Low	Low	Low	Low	Low	Low	Low
Abuhasira R et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hu Q et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Avi-Mild	Low	Low	Low	Low	Low	Low	Low
APLICOV-PC	Low	Low	Low	Low	Low	Low	Low
MARIPOSA	Low	Some Concerns	Low	Some Concerns	Low	Low	High
IMPACT	High	Some Concerns	Low	Some Concerns	Low	High	High
Covid19DPP4i	High	Some Concerns	Low	Some Concerns	Low	High	High
ABB-COVID19	Low	Low	Low	Low	Low	Low	Low
COVID MED	Low	Low	Low	Low	Low	Low	Low
Naik NB et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV-4a	Low	Low	Low	Low	Low	Low	Low
CATCO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
MEFECOVID-19	Low	Low	Low	Low	Low	Low	Low
Rondanelli M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
De Santis GC et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Murugesan H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Manomaipiboon A et al	Low	Low	Low	Low	Low	Low	Low
DOXPREVENT.ICU	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pourdowlat G et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Chupp G et al	Low	Low	Low	Low	Low	Low	Low
NACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
MEDIC-LAUMC	High	Low	Low	Low	Low	High	High
REsCue	Low	Low	Low	Low	Low	Low	Low
ITAC	Low	Low	Low	Low	Low	Low	Low
EPIC-HR	Low	Low	Low	Low	Low	Low	Low
I-TECH	Low	Some Concerns	Low	Some Concerns	Low	Low	High
FORCE	Low	Low	Low	Low	Low	Low	Low
Caims DM et al	Low	Low	Low	Low	Low	Low	Low
PHYDRA	Low	Low	Low	Low	Low	Low	Low

Main findings

Corticosteroids

See Summary of findings Table 1, Appendix 1

We identified 15 RCTs including 8,404 participants in which systemic corticosteroids (dexamethasone, methylprednisolone, or hydrocortisone) were compared against standard of care or other treatments. Thirteen of these trials provided information on mortality for the corticosteroids against standard of care comparison. The RECOVERY trial was the biggest with 2,104 patients assigned to dexamethasone and 4,321 to standard of care. All 15 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. In addition, we identified five studies including 1499 patients in which different corticosteroid dosage schemes were compared and one study including 41 patients in which high dose corticosteroids was compared to tocilizimab. Our results showed:

- Corticosteroids probably reduce mortality, RR 0.90 (95%CI 0.80 to 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate certainty ⊕⊕⊕◯ (Figure 2)
- Corticosteroids probably reduce invasive mechanical ventilation requirement, RR 0.87 (95%CI 0.73 to 1.04); RD -2.2% (95%CI -4.7% to 0.7%); Moderate certainty ⊕⊕⊕◯
- Corticosteroids may improve time-to-symptom resolution, RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⊕⊕◯◯
- Corticosteroids may not significantly increase the risk of severe adverse events, RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕◯◯
- Results were consistent with trials in which corticosteroids were used to treat non COVID-19 patients with ARDS. No significant differences between subgroups of studies using different corticosteroids were observed. (Figures 3 and 4)
- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) may not reduce mortality compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.95 (95%CI 0.67 to 1.34); RD -0.8% (95%CI -5.3% to 5.4%); Low certainty ⊕⊕◯◯ (Figure 5)
- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) may not increase severe adverse events compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.85 (95%CI 0.61 to 1.19); RD -1.5% (95%CI -4% to 1.9%); Low certainty ⊕⊕◯◯

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

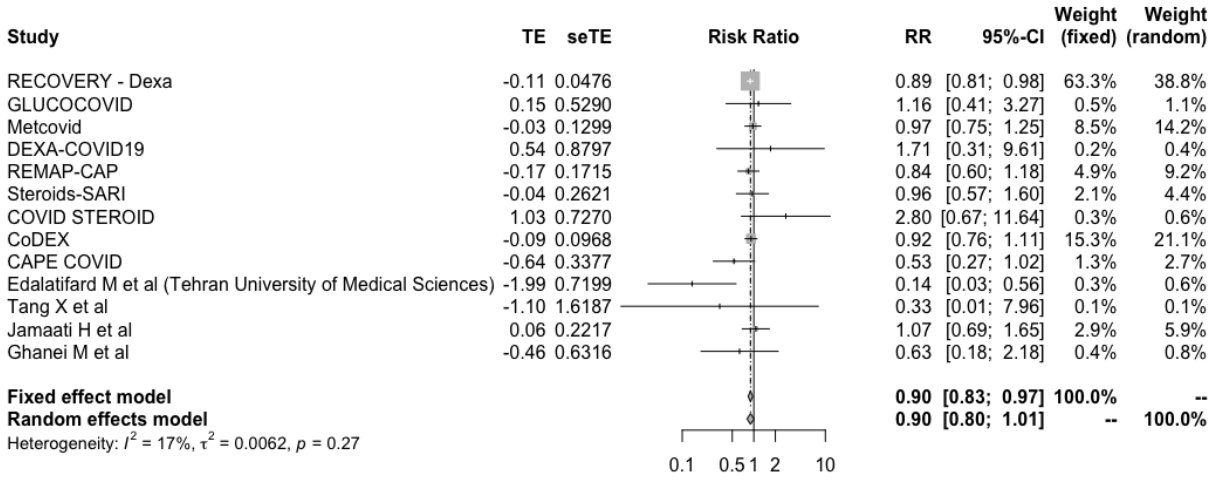


Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

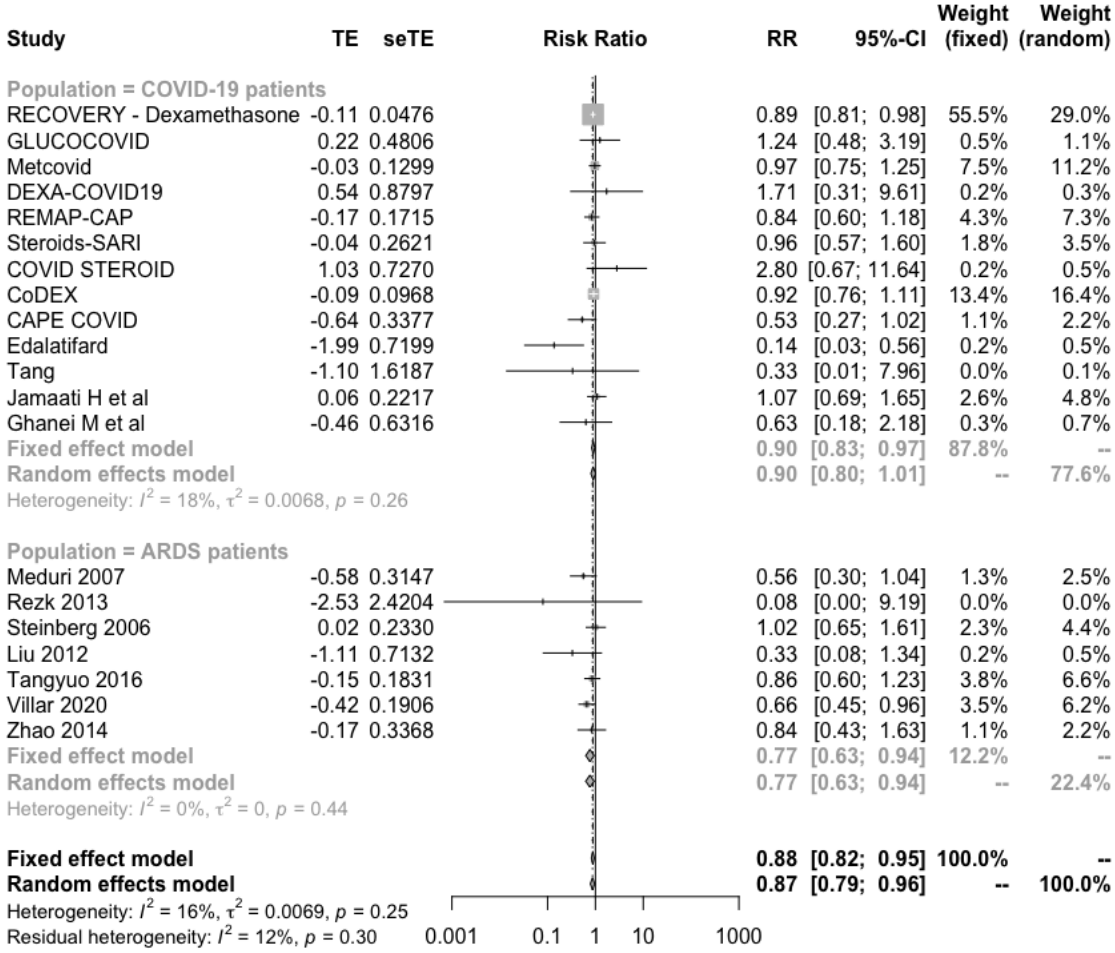

Study
TE
seTE
Risk Ratio
RR
95%-CI
Weight (fixed)
Weight (random)
Population = COVID-19 patients
RECOVERY - Dexamethasone -0.11 0.0476 0.89 [0.81; 0.98] 55.5% 29.0%
GLUCOCOVID 0.22 0.4806 1.24 [0.48; 3.19] 0.5% 1.1%
Metcovid -0.03 0.1299 0.97 [0.75; 1.25] 7.5% 11.2%
DEXA-COVID19 0.54 0.8797 1.71 [0.31; 9.61] 0.2% 0.3%
REMAP-CAP -0.17 0.1715 0.84 [0.60; 1.18] 4.3% 7.3%
Steroids-SARI -0.04 0.2621 0.96 [0.57; 1.60] 1.8% 3.5%
COVID STEROID 1.03 0.7270 2.80 [0.67; 11.64] 0.2% 0.5%
CoDEX -0.09 0.0968 0.92 [0.76; 1.11] 13.4% 16.4%
CAPE COVID -0.64 0.3377 0.53 [0.27; 1.02] 1.1% 2.2%
Edalatifard -1.99 0.7199 0.14 [0.03; 0.56] 0.2% 0.5%
Tang -1.10 1.6187 0.33 [0.01; 7.96] 0.0% 0.1%
Jamaati H et al 0.06 0.2217 1.07 [0.69; 1.65] 2.6% 4.8%
Ghanei M et al -0.46 0.6316 0.63 [0.18; 2.18] 0.3% 0.7%
Fixed effect model 0.90 [0.83; 0.97] 87.8% --
Random effects model 0.90 [0.80; 1.01] -- 77.6%
Heterogeneity: I^2 = 18%, τ^2 = 0.0068, p = 0.26
Population = ARDS patients
Meduri 2007 -0.58 0.3147 0.56 [0.30; 1.04] 1.3% 2.5%
Rezk 2013 -2.53 2.4204 0.08 [0.00; 9.19] 0.0% 0.0%
Steinberg 2006 0.02 0.2330 1.02 [0.65; 1.61] 2.3% 4.4%
Liu 2012 -1.11 0.7132 0.33 [0.08; 1.34] 0.2% 0.5%
Tangyuo 2016 -0.15 0.1831 0.86 [0.60; 1.23] 3.8% 6.6%
Villar 2020 -0.42 0.1906 0.66 [0.45; 0.96] 3.5% 6.2%
Zhao 2014 -0.17 0.3368 0.84 [0.43; 1.63] 1.1% 2.2%
Fixed effect model 0.77 [0.63; 0.94] 12.2% --
Random effects model 0.77 [0.63; 0.94] -- 22.4%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.44
Fixed effect model 0.88 [0.82; 0.95] 100.0% --
Random effects model 0.87 [0.79; 0.96] -- 100.0%
Heterogeneity: I^2 = 16%, τ^2 = 0.0069, p = 0.25
Residual heterogeneity: I^2 = 12%, p = 0.30
0.001
0.1
1
10
1000

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

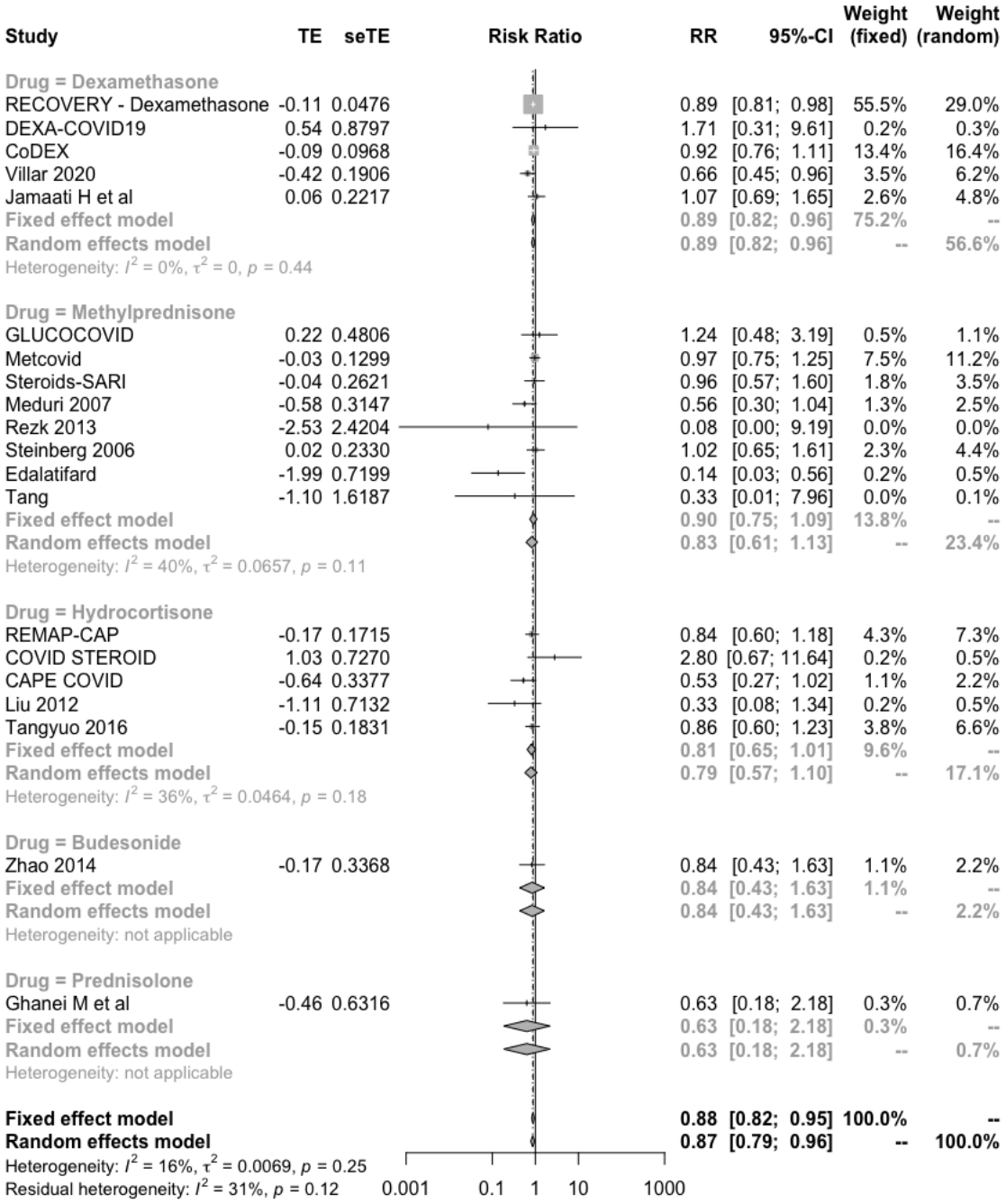
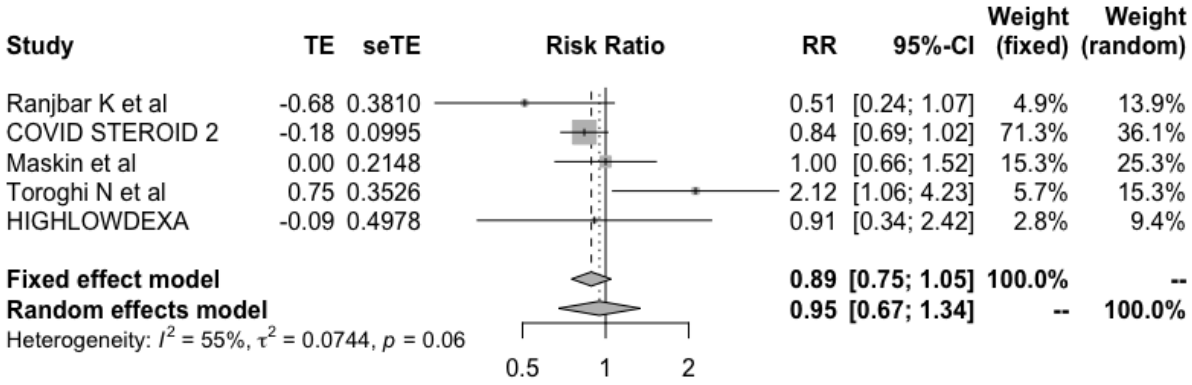


Figure 5. All-cause mortality in RCTs comparing high-dose corticosteroids (i.e., dexamethasone 12 mg a day) with standard-dose corticosteroids (i.e., dexamethasone 6 mg a day) in patients with COVID-19



In addition, one study that compared high dose corticosteroids (dexamethasone 20mg a day) to tocilizumab reported higher mortality in patients treated with high dose corticosteroids.

Remdesivir

See Summary of findings Table 2, Appendix 1

We identified ten RCTs including 8,990 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 three studies included non-severe patients with 2% o less mortality in the control arm. Our results showed:

- Remdesivir may not reduce mortality, RR 0.97 (95%CI 0.85 to 1.10); RD -0.5% (95%CI -2.4% to 1.6%); Low certainty ⊕⊕◯◯ (Figure 6)
- Remdesivir may reduce invasive mechanical ventilation requirement, RR 0.79 (95%CI 0.55 to 1.14); RD -3.6% (95%CI -7.8% to 2.4%); Low certainty ⊕⊕◯◯ (Figure 7)
- Remdesivir may improve time to symptom resolution, RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low certainty ⊕⊕◯◯ (Figure 8)
- Remdesivir may reduce hospitalizations in patients with recent onset mild, RR 0.28 (95%CI 0.11 to 0.75); RD -3.4% (95%CI -4.3% to -1.2%); Low certainty ⊕⊕◯◯
- Remdesivir may not increase the risk of severe adverse events, RR 0.77 (95%CI 0.46 to 1.29); RD -2.3% (95%CI -5.5% to 3%); Low certainty ⊕⊕◯◯

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

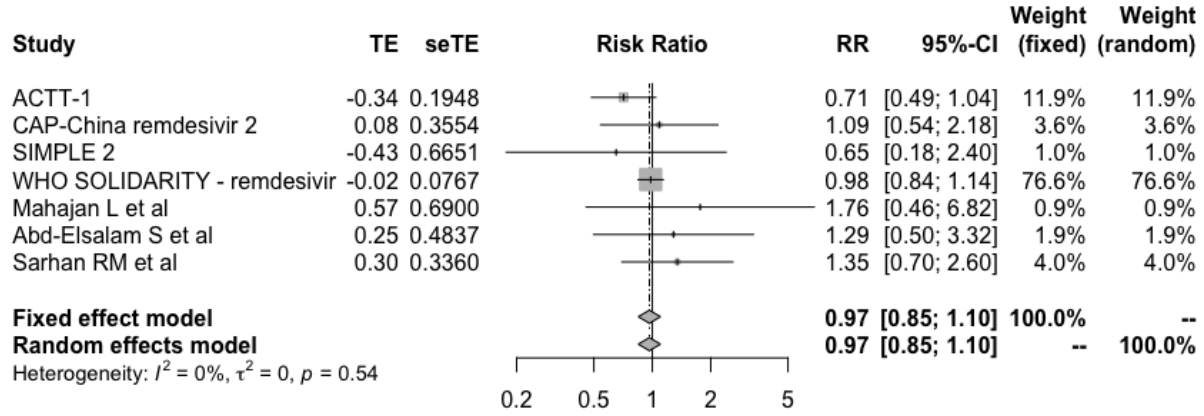


Figure 7. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

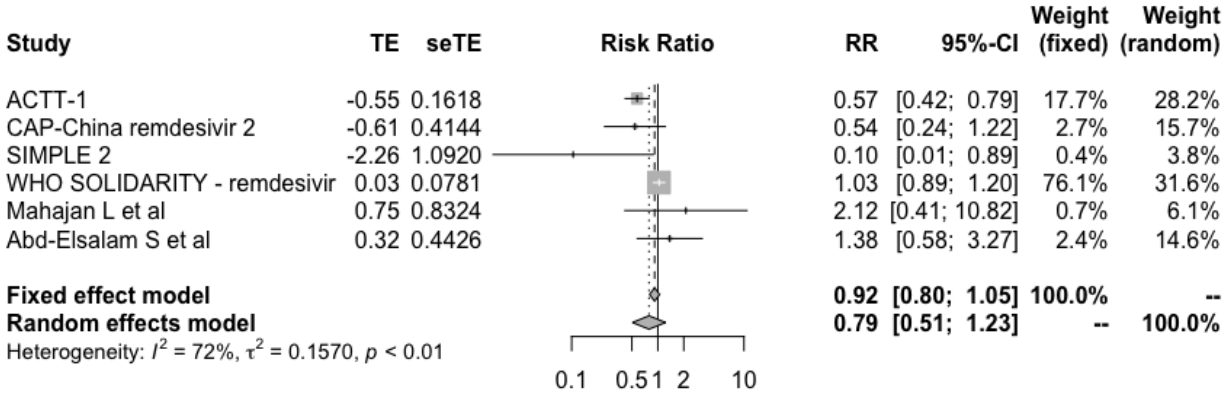
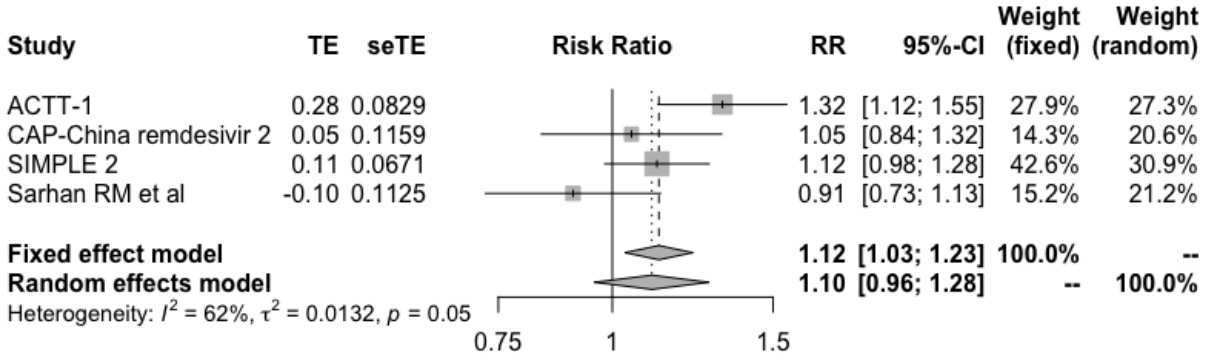


Figure 8. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 54 RCTs including 23,151 patients in which hydroxychloroquine or chloroquine were compared against standard of care or other treatments. The RECOVERY trial was the biggest with 1,561 patients assigned to dexamethasone and 3,155 to standard of care. In both the RECOVERY and SOLIDARITY trials, patients had severe disease as shown by the high mortality risk in control arms (24.9% and 9.2%, respectively). The remaining studies included patients with non-severe disease, as shown by the lower mortality risk in control arms, ranging from 0 to 5.2%. Additionally, we identified nine studies in which hydroxychloroquine was used in healthy persons to prevent COVID-19 infection. Our results showed:

- Hydroxychloroquine or chloroquine probably increase mortality, RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕◯ (Figure 9)
- Hydroxychloroquine or chloroquine probably does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.93 to 1.24); RD 1.2% (95%CI -1.2% to 4.2%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine probably does not improve time to symptom resolution, RR 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% to 6.1%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine may reduce COVID-19 symptomatic infection in exposed individuals, RR 0.87 (95%CI 0.65 to 1.15); RD -2.2% (95%CI -6.1% to 2.7%); Low certainty ⊕⊕◯◯ (Figure 10) (based on low risk of bias studies)
- Hydroxychloroquine or chloroquine may not significantly increase the risk of severe adverse events, RR 0.94 (95%CI 0.66 to 1.34); RD -0.6% (95%CI -3.5% to 3.5%); Low certainty ⊕⊕◯◯
- It is uncertain if hydroxychloroquine or chloroquine affects hospitalizations in patients with mild COVID-19, RR 0.91 (95%CI 0.56 to 1.47); RD -0.4% (95%CI -2.1% to 2.3%); Very low certainty ⊕◯◯◯

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

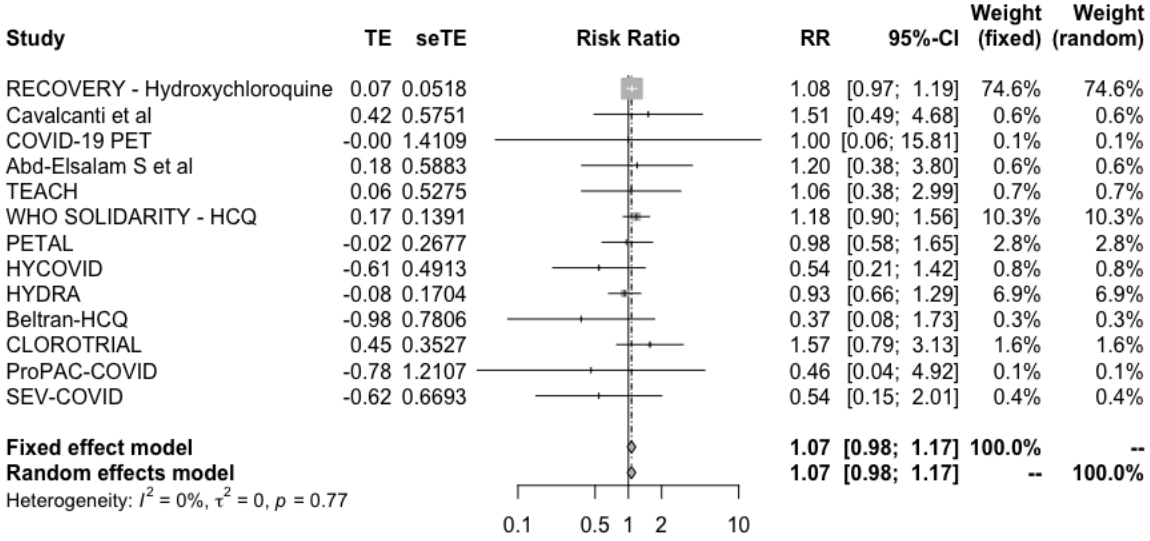
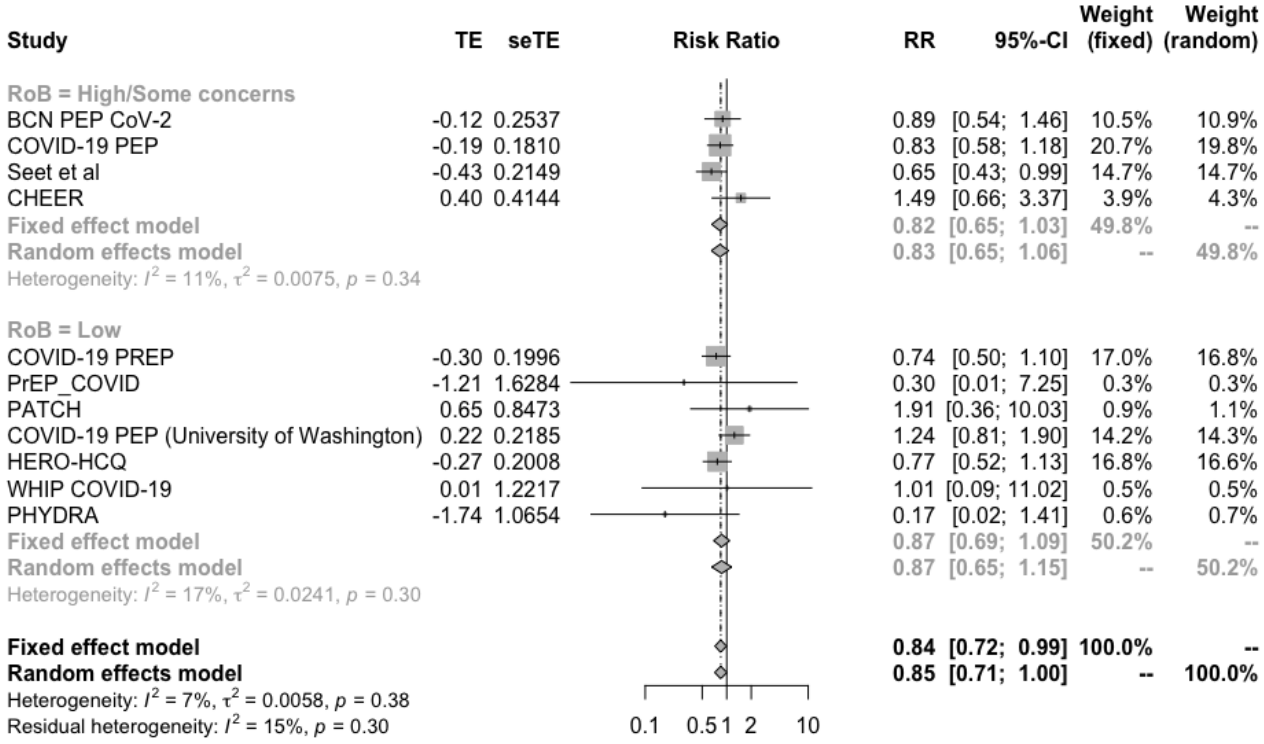


Figure 10. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



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

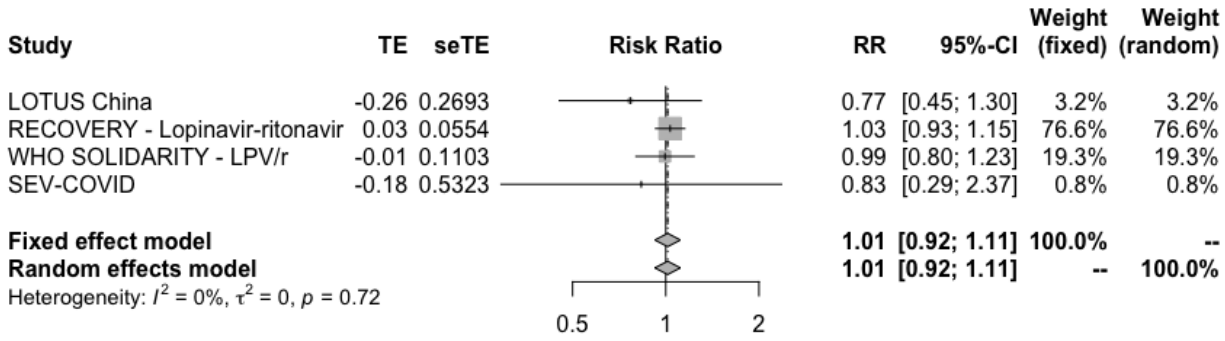
Lopinavir-ritonavir

See Summary of findings Table 4, Appendix 1

We identified 17 RCTs including 10,327 patients in which lopinavir-ritonavir was compared against standard of care or other treatments. The RECOVERY trial was the biggest with 1,616 patients assigned to dexamethasone and 3,424 to standard of care. Three studies provided information on mortality outcome, all of which included patients with severe disease, as shown by the mortality risk in control arms, which ranged from 10.6% to 25%. Our results showed:

- Lopinavir-ritonavir probably does not reduce mortality, RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -1.3% to 1.8%); Moderate certainty ⊕⊕⊕◯ (Figure 11)
- Lopinavir-ritonavir does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕
- Lopinavir-ritonavir probably does not improve symptom resolution or improvement; RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯
- Lopinavir-ritonavir may not increase the risk of severe adverse events, RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -6.5% to -0.2%); Low certainty ⊕⊕◯◯
- It is uncertain if lopinavir-ritonavir increases or decreases symptomatic infections in exposed individuals, RR 1.40 (95%CI 0.78 to 2.54); RD 1.8% (95%CI -3.8% to -26.8%); Very low certainty ⊕◯◯◯
- It is uncertain if lopinavir-ritonavir increases or decreases hospitalizations, RR 1.24 (95%CI 0.6 to 2.56); RD 1.2% (95%CI -1.9% to -7.5%); Very low certainty ⊕◯◯◯

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



Convalescent plasma

See summary of findings Table 5 in appendix 1

We identified 32 RCTs including 21,665 patients in which convalescent plasma was compared against standard of care or other treatments. RECOVERY was the largest study including

11,588 patients. Most studies (27/32) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 7.9% to 53%. The remaining studies included patients with recent onset symptoms and reported a control-arm mortality rate of 0.4% to 6.6%. Convalescent plasma was administered in one to three infusions to symptomatic patients in all cases. Our results showed:

- Convalescent plasma does not reduce mortality, RR 0.99 (95%CI 0.94 to 1.05); RD 0% (95%CI -0.2% to 0.8%); RD 0% (95%CI -1% to 0.8%); High certainty ⊕⊕⊕⊕ (Figure 12) (based on low risk of bias studies)
- Convalescent plasma does not significantly reduce invasive mechanical ventilation requirements, RR 1.05 (95% CI 0.96 to 1.14); RD 0.8% (95%CI -0.7% to 2.4%); High certainty ⊕⊕⊕⊕ (based on low risk of bias studies)
- Convalescent plasma probably does not improve symptom resolution or improvement, RR 0.99 (95% CI 0.95 to 1.03); RD -0.6% (95%CI -3% to 1.8%); Moderate certainty ⊕⊕⊕◯
- Convalescent plasma may not increase severe adverse events, RR 1.03 (95% CI 0.85 to 1.26); RD 0.3% (95%CI -1.5% to 2.6%); Low certainty ⊕⊕◯◯ (Figure 13)
- Convalescent plasma probably has no important effect on hospitalizations, RR 0.78 (95% CI 0.57 to 1.06); RD -1.1% (95%CI -2.1% to 3%); Moderate certainty ⊕⊕⊕◯ (Figure 13). The observed effect would probably be considered important in patients with very high hospitalization risk.

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

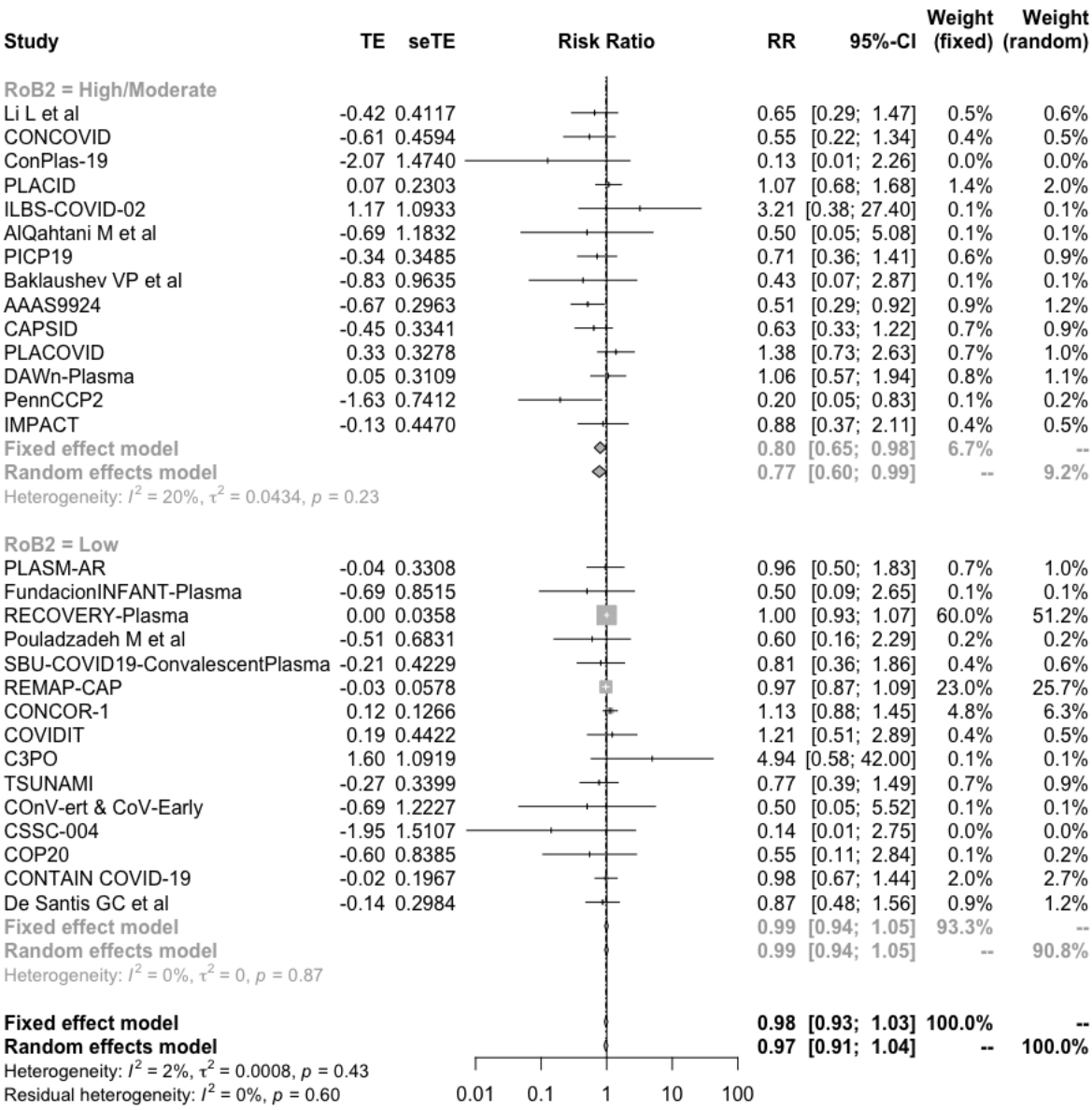
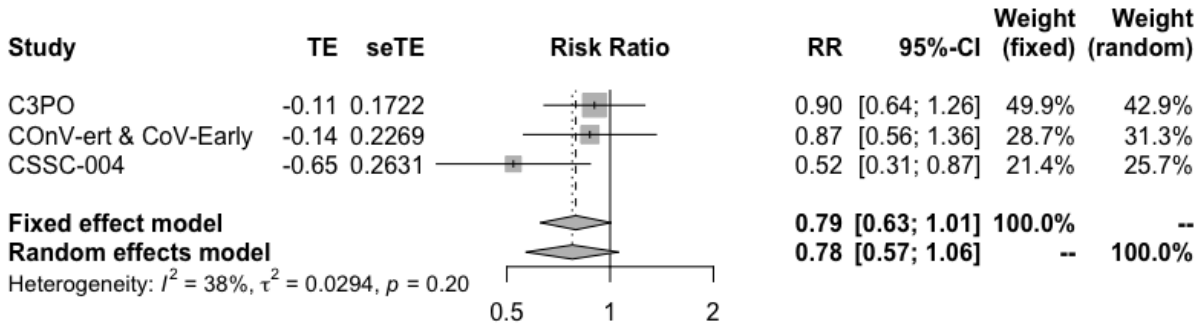

Study
TE
seTE
Risk Ratio
RR
95%-CI
Weight (fixed)
Weight (random)
RoB2 = High/Moderate
Li L et al -0.42 0.4117 0.65 [0.29; 1.47] 0.5% 0.6%
CONCOVID -0.61 0.4594 0.55 [0.22; 1.34] 0.4% 0.5%
ConPlas-19 -2.07 1.4740 0.13 [0.01; 2.26] 0.0% 0.0%
PLACID 0.07 0.2303 1.07 [0.68; 1.68] 1.4% 2.0%
ILBS-COVID-02 1.17 1.0933 3.21 [0.38; 27.40] 0.1% 0.1%
AlQahtani M et al -0.69 1.1832 0.50 [0.05; 5.08] 0.1% 0.1%
PICP19 -0.34 0.3485 0.71 [0.36; 1.41] 0.6% 0.9%
Baklaushev VP et al -0.83 0.9635 0.43 [0.07; 2.87] 0.1% 0.1%
AAAS9924 -0.67 0.2963 0.51 [0.29; 0.92] 0.9% 1.2%
CAPSID -0.45 0.3341 0.63 [0.33; 1.22] 0.7% 0.9%
PLACOVID 0.33 0.3278 1.38 [0.73; 2.63] 0.7% 1.0%
DAWn-Plasma 0.05 0.3109 1.06 [0.57; 1.94] 0.8% 1.1%
PennCCP2 -1.63 0.7412 0.20 [0.05; 0.83] 0.1% 0.2%
IMPACT -0.13 0.4470 0.88 [0.37; 2.11] 0.4% 0.5%
Fixed effect model 0.80 [0.65; 0.98] 6.7% --
Random effects model 0.77 [0.60; 0.99] -- 9.2%
Heterogeneity: I^2 = 20%, τ^2 = 0.0434, p = 0.23
RoB2 = Low
PLASM-AR -0.04 0.3308 0.96 [0.50; 1.83] 0.7% 1.0%
FundacionINFANT-Plasma -0.69 0.8515 0.50 [0.09; 2.65] 0.1% 0.1%
RECOVERY-Plasma 0.00 0.0358 1.00 [0.93; 1.07] 60.0% 51.2%
Pouladzadeh M et al -0.51 0.6831 0.60 [0.16; 2.29] 0.2% 0.2%
SBU-COVID19-ConvalescentPlasma -0.21 0.4229 0.81 [0.36; 1.86] 0.4% 0.6%
REMAP-CAP -0.03 0.0578 0.97 [0.87; 1.09] 23.0% 25.7%
CONCOR-1 0.12 0.1266 1.13 [0.88; 1.45] 4.8% 6.3%
COVIDIT 0.19 0.4422 1.21 [0.51; 2.89] 0.4% 0.5%
C3PO 1.60 1.0919 4.94 [0.58; 42.00] 0.1% 0.1%
TSUNAMI -0.27 0.3399 0.77 [0.39; 1.49] 0.7% 0.9%
COnV-ert & CoV-Early -0.69 1.2227 0.50 [0.05; 5.52] 0.1% 0.1%
CSSC-004 -1.95 1.5107 0.14 [0.01; 2.75] 0.0% 0.0%
COP20 -0.60 0.8385 0.55 [0.11; 2.84] 0.1% 0.2%
CONTAIN COVID-19 -0.02 0.1967 0.98 [0.67; 1.44] 2.0% 2.7%
De Santis GC et al -0.14 0.2984 0.87 [0.48; 1.56] 0.9% 1.2%
Fixed effect model 0.99 [0.94; 1.05] 93.3% --
Random effects model 0.99 [0.94; 1.05] -- 90.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87
Fixed effect model 0.98 [0.93; 1.03] 100.0% --
Random effects model 0.97 [0.91; 1.04] -- 100.0%
Heterogeneity: I^2 = 2%, τ^2 = 0.0008, p = 0.43
Residual heterogeneity: I^2 = 0%, p = 0.60
0.01
0.1
1
10
100

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



In one of the studies, 58 patients were randomized to early administration of convalescent plasma (at the time they were randomized) or late administration (only if clinical deterioration was observed). All patients in the early arm received the treatment, while just 43.3% of patients received it in the late arm. Results showed no mortality reduction (OR 4.22, 95%CI 0.33 to 53.57) 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 29 RCTs including 9,265 patients in which tocilizumab was compared against standard of care or other interventions. Twenty studies reported on the mortality outcome, including the RECOVERY study that recruited 4,116 patients. All studies included severe patients, but some excluded critical patients. The proportion of critical patients in those studies that included them was 16.5% to 47.5%. Our results showed:

- Tocilizumab reduces mortality, RR 0.85 (95%CI 0.79 to 93); RD -2.4% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕ (Figure 14)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.83 (95%CI 0.78 to 0.90); RD -2.9% (95%CI -3.8% to -1.7%); High certainty ⊕⊕⊕⊕ (Figure 15)
- Tocilizumab may improve time to symptom resolution, RR 1.07 (95%CI 1.01 to 1.13); RD 4.6% (95%CI 0.6% to 7.9%); Low certainty ⊕⊕◯◯
- Tocilizumab probably does not significantly increase severe adverse events at 28-30 days, RR 0.95 (95%CI 0.86 to 1.04); RD -0.5% (95%CI -1.4% to 0.4%); Moderate certainty ⊕⊕⊕◯

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

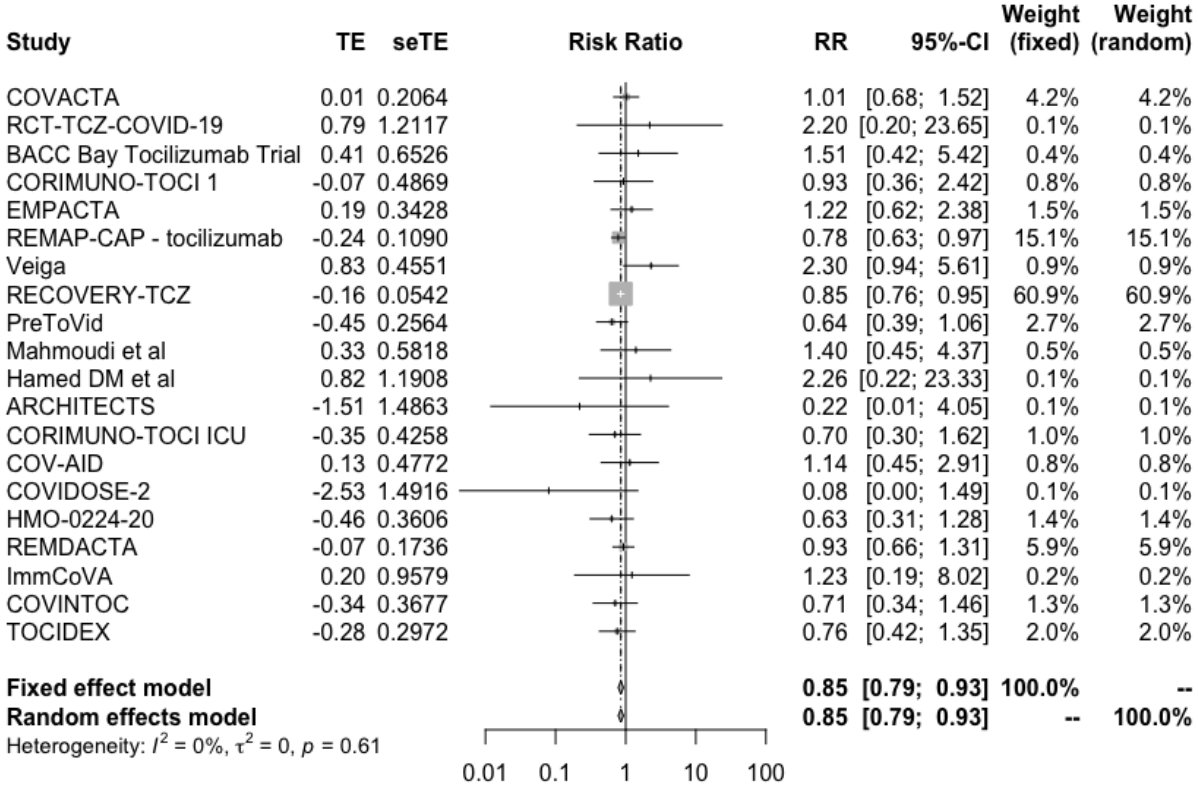
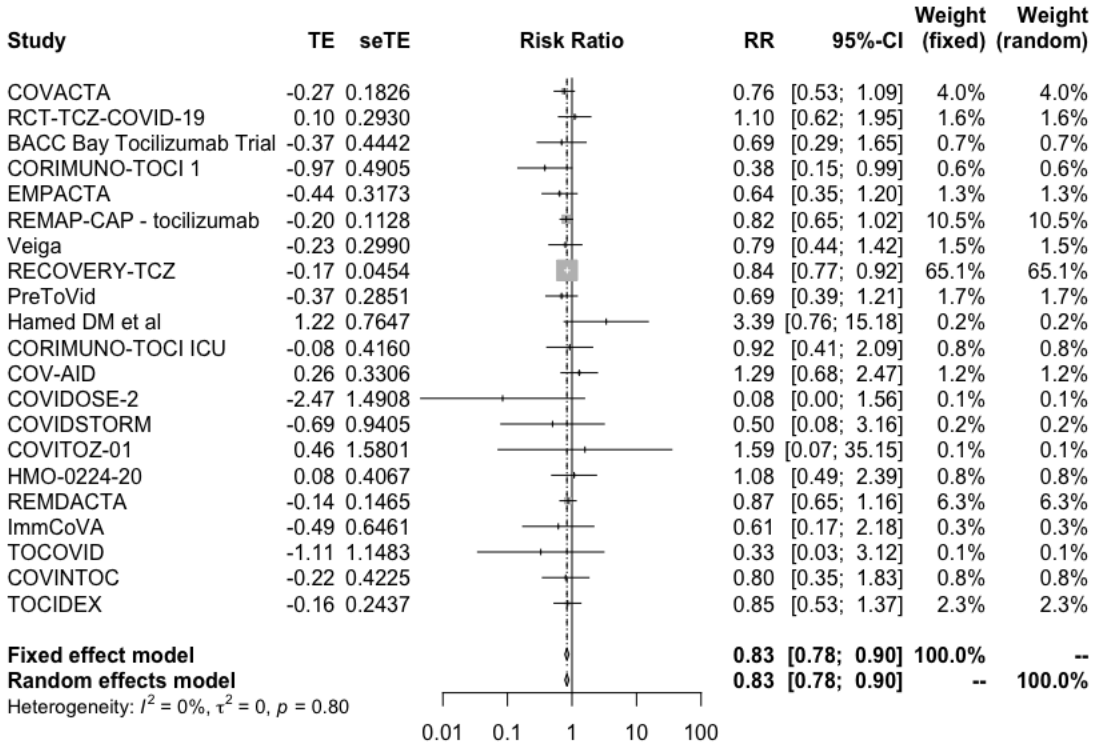


Figure 15. Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



A subgroup analysis, performed in the RECOVERY trial, comparing the effect of tocilizumab in severe and critical patients, did not suggest a subgroup modification effect according to baseline disease severity (p=0.52).
In addition, one study that compared standard dose (4 mg/kg) versus high dose (8 mg/kg) found no significant differences, however the certainty of the evidence was low because of imprecision.

Anticoagulants

See Summary of findings Table 7, Appendix 1

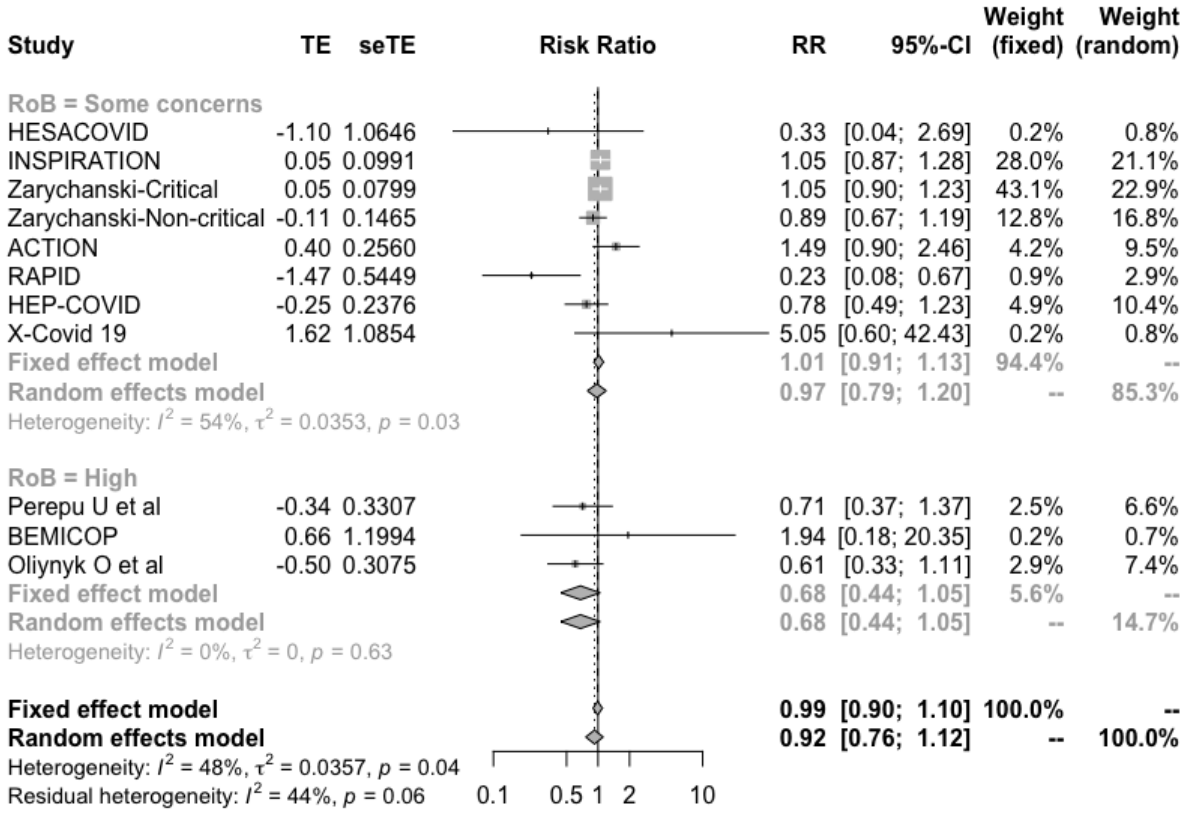
Thromboembolic complications in patients infected with COVID-19 are relatively frequent.[13] As for hospitalized patients with severe medical conditions, current guidelines recommend thromboprophylaxis measures should be used for inpatients with COVID-19 infection.[14] Regarding the best thromboprophylactic scheme, we identified thirteen RCTs including 6,637 patients that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day), or anticoagulants versus standard of care in patients with mild ambulatory disease. All studies included hospitalized patients with COVID-19. Our results showed:

- In moderate to critical patients, anticoagulants in intermediate dose or full dose may not reduce mortality in comparison with prophylactic dose, RR 0.97 (95%CI 0.79 to 1.2); RD

-0.5% (95%CI -3.4% to 3.2%); Low certainty ⊕⊕◯◯ (excluding high risk of bias studies) (Figure 16)

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

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



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

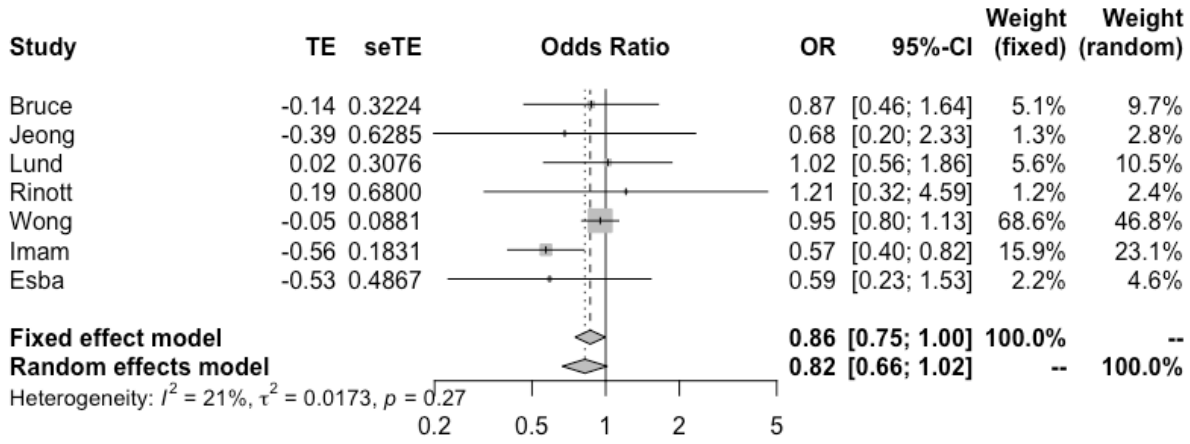
NSAIDs

See Summary of findings Table 8, Appendix 1

We identified seven non-RCTs including at least 100 patients in which COVID-19 mortality risk was compared between groups of patients exposed to NSAIDs and those that were not. Populations varied between studies. For example, Wong et al. included individuals exposed to COVID-19 (living in a region affected by the pandemic) while other studies included only patients with confirmed COVID-19 infection. Our results showed:

- No association between NSAID exposure and mortality, OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕◯◯◯ (Figure 17)

Figure 17. All-cause mortality in non-RCTs comparing exposure to NSAIDs with no exposure in individuals exposed to or infected with COVID-19



Interferon Beta-1a

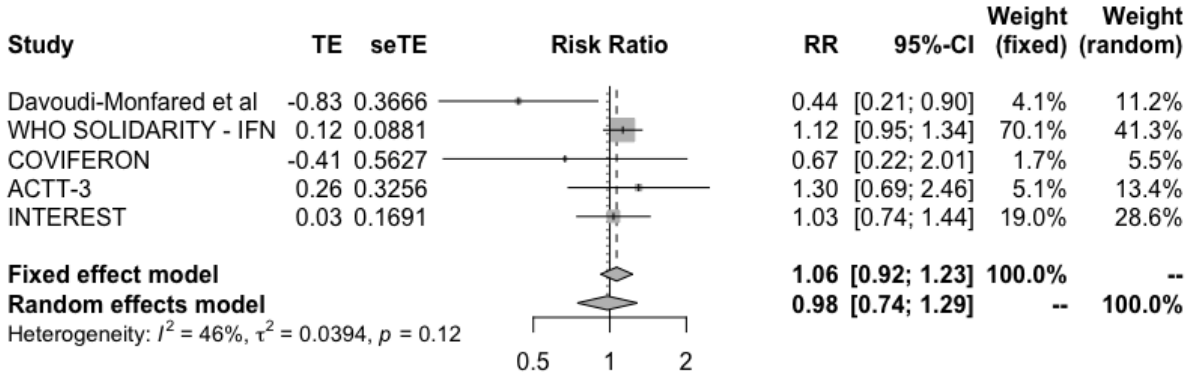
See Summary of findings Table 9, Appendix 1

We identified six RCTs including 5,752 patients in which interferon beta-1a was compared against standard of care or other treatments and informed on mortality outcome. The WHO SOLIDARITY trial was the biggest, with 2,050 patients assigned to intervention and 2,050 to control. The studies

included severe patients, as shown by the fact that mortality in the control arms ranged from 10.5% to 45%. Our results showed:

- Interferon beta-1a (subcutaneous) probably does not reduce mortality, RR 0.98 (95%CI 0.74 to 1.29); RD -0.3% (95%CI -4.2% to 4.6%); Moderate certainty ⊕⊕⊕◯ (Figure 18)
- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 0.97 (95%CI 0.83 to 1.14); RD -0.5% (95%CI -2.9% to 2.4%); Moderate certainty ⊕⊕⊕◯
- Interferon beta-1a (subcutaneous) probably does not increase symptom resolution or improvement; RR 0.96 (95%CI 0.92 to 0.99); RD -2.6% (95%CI -4.8% to -3.2%); Moderate certainty ⊕⊕⊕◯
- Interferon beta-1a probably does not increase severe adverse events, RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕◯
- Interferon beta-1a (inhaled) may improve time to symptom resolution, HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯

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



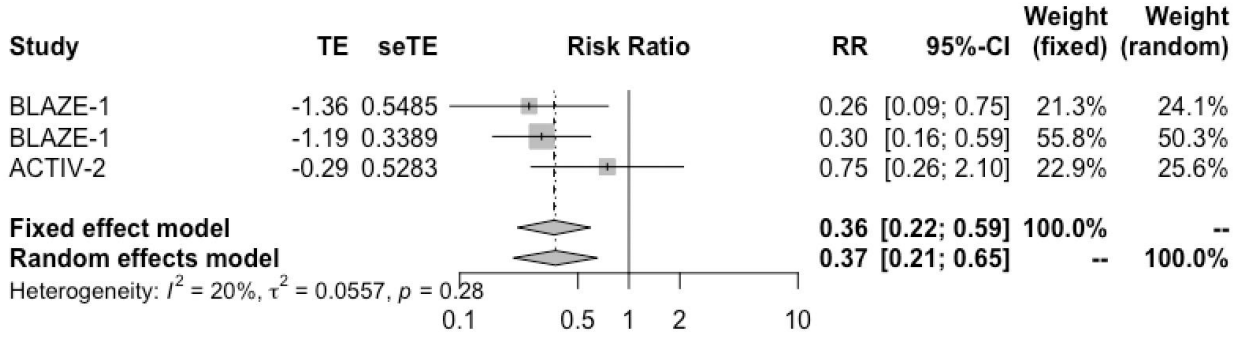
Bamlanivimab +/- etesevimab (monoclonal antibody)

See Summary of findings Table 10, Appendix 1

We identified eight RCTs including 5,464 patients in which bamlanivimab was compared against standard of care. Three studies included patients with mild to moderate COVID-19 and one included exposed individuals and assessed bamlanivimab as a prophylactic intervention. Our results showed:

- It is uncertain if bamlanivimab reduces mortality or mechanical ventilation requirements; RR 0.68 (95%CI 0.17 to 2.8); RD -5.1% (95%CI -13.2% to 2.8%); Very low certainty ⊕◯◯◯
- Bamlanivimab probably does not significantly improve time to symptom resolution, RR 1.02 (95%CI 0.99 to 1.06); RD 1.2% (95%CI 3.6% to 5.4%); Moderate certainty ⊕⊕⊕◯
- Bamlanivimab probably decreases symptomatic infection in exposed individuals, RR 0.56 (95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Moderate certainty ⊕⊕⊕◯
- Bamlanivimab may increase severe adverse events; RR 1.12 (95%CI 0.75 to 1.66); RD 1.2% (95%CI -2.5% to -6.7%); Low certainty ⊕⊕◯◯
- Bamlanivimab probably reduces hospitalizations in patients with non-severe disease; RR 0.37 (95%CI 0.21 to 0.65); RD -3% (95%CI -3.8% to -1.7%); Moderate certainty ⊕⊕⊕◯ (Figure 19)

Figure 19. Hospitalizations with bamanivimab vs. standard of care in randomized studies including COVID-19 patients



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

Favipiravir

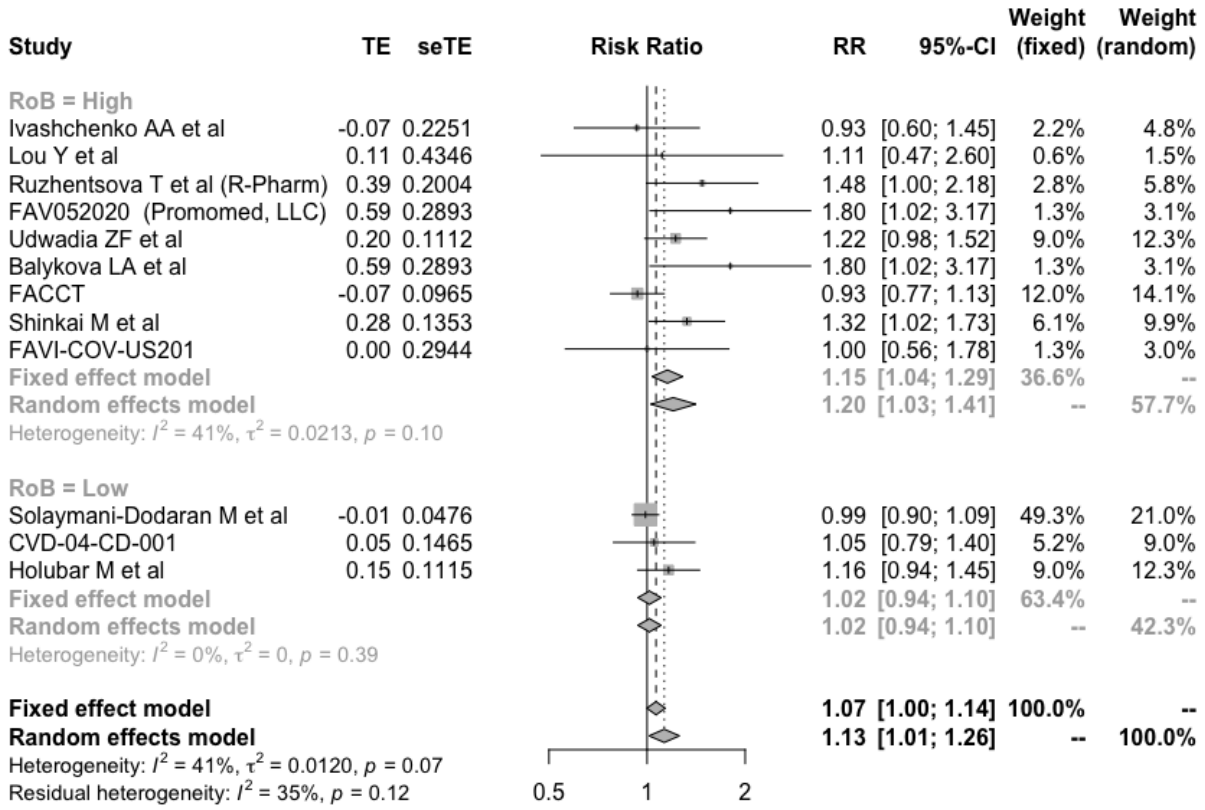
See Summary of findings Table 11, Appendix 1

We identified 21 RCTs including 3,754 patients in which favipiravir was compared against standard of care or other treatments. Nine studies reported on favipiravir with or without HCQ versus standard of care, two studies reported on favipiravir vs HCQ or CQ, one study reported on favipiravir vs lopinavir ritonavir and the remaining studies compared favipiravir against other active interventions. As there is moderate to high certainty that HCQ and lopinavir-ritonavir are not related to significant benefits, we assumed those interventions as equivalent to standard of care. Our results showed:

- Favipiravir may increase mortality; RR 1.18 (95%CI 0.83 to 1.69); RD 2.9% (95%CI -2.7% to 11%); Low certainty ⊕⊕◯◯

- Favipiravir may increase mechanical ventilation requirements; RR 1.27 (95%CI 0.91 to 1.76); RD 4.7% (95%CI -1.6% to 13.1%); Low certainty ⊕⊕◯◯
- Favipiravir probably does not increase symptom resolution or improvement, RR 1.02 (95%CI 0.94 to 1.1); RD 1.2% (95%CI -3.6% to 6%); Moderate certainty ⊕⊕⊕◯ (Figure 20) (based on low risk of bias studies)
- It is uncertain if favipiravir increases the risk of severe adverse events; RR 0.80 (95%CI 0.46 to 1.41); RD -2% (95%CI -5.5% to 4.2%); Very low certainty ⊕◯◯◯
- It is uncertain if favipiravir affects hospitalizations in patients with non-severe disease; RR 0.89 (95%CI 0.16 to 5.05); RD -0.5% (95%CI -4% to 19.4%); Very low certainty ⊕◯◯◯

Figure 20. Symptom resolution at 7-15 days in randomized studies comparing favipiravir with standard of care in patient with COVID-19



Ivermectin

See Summary of findings Table 12, Appendix 1

We identified 35 RCTs including 6,347 patients in which ivermectin was compared against standard of care or other treatments. Studies included patients with mild to severe disease, as shown by the mortality rates in the control arms, which ranged from 0% to 21.7%. Most studies did not report on clinical important outcomes and most of the ones that did have important

methodological limitations including inappropriate randomization process and lack or unclear report of allocation concealment. Our results showed:

- It is uncertain if ivermectin affects mortality, RR 0.81 (95%CI 0.5 to 1.33); RD -3% (95%CI -8% to 5.2%); Very Low certainty ⊕◯◯◯ (Figure 21) (based on low risk of bias studies)
- It is uncertain if ivermectin affects mechanical ventilation, RR 0.9 (95%CI 0.57 to 1.42); RD -1.7% (95%CI -7.4% to 7.3%); Very Low certainty ⊕◯◯◯
- Ivermectin probably does not improve symptom resolution or improvement, RR 1.03 (95%CI 0.96 to 1.1); RD 1.8% (95%CI -2.4% to 6.1%); Moderate certainty ⊕⊕⊕◯ (Figure 22) (based on low risk of bias studies)
- It is uncertain if ivermectin affects symptomatic infection, RR 0.22 (95%CI 0.09 to 0.53); RD -13.6% (95%CI -15.8% to -8.2%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects severe adverse events, RR 1.63 (95%CI 0.62 to 4.32); RD 6.4% (95%CI -3.9% to 33.8%); Very low certainty ⊕◯◯◯
- Ivermectin may not have an important effect on hospitalizations in non-severe patients, RR 0.67 (95%CI 0.39 to 1.14); RD -1.6% (95%CI -2.9% to 0.7%); Low certainty ⊕⊕◯◯. The observed effect would probably be considered important in patients with very high hospitalization risk.

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

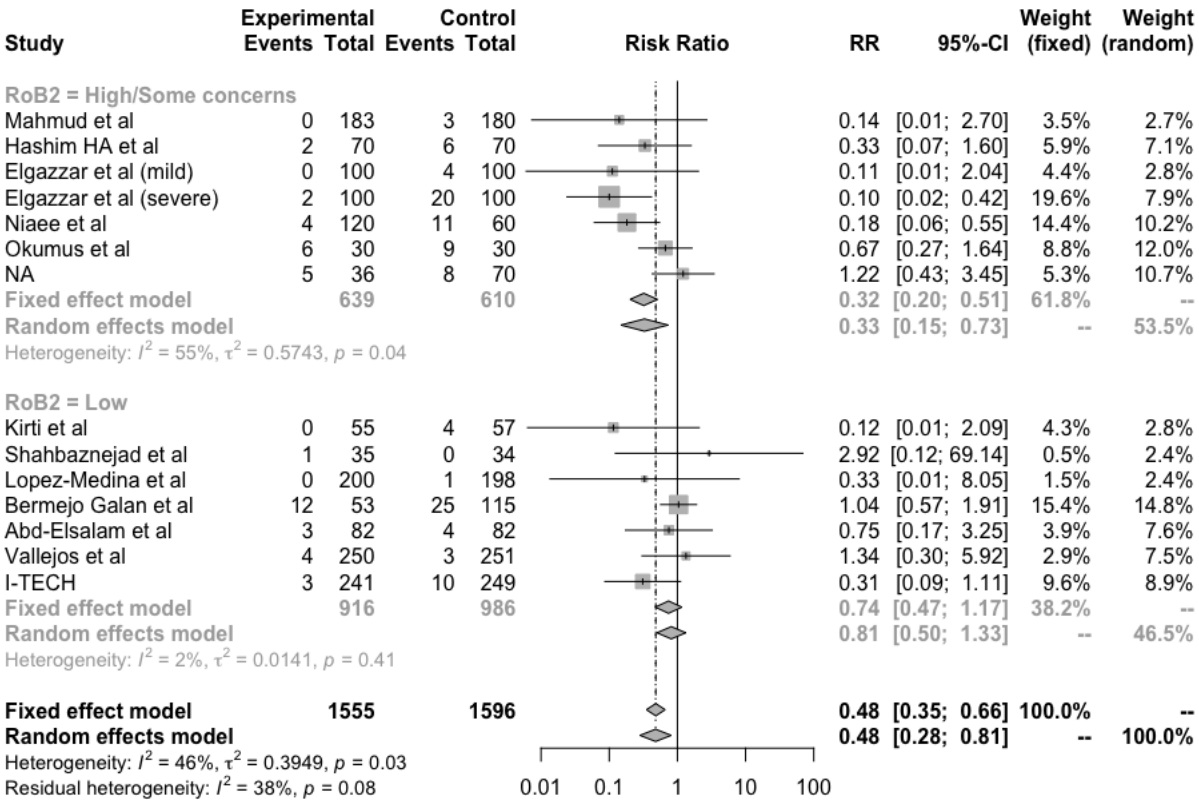
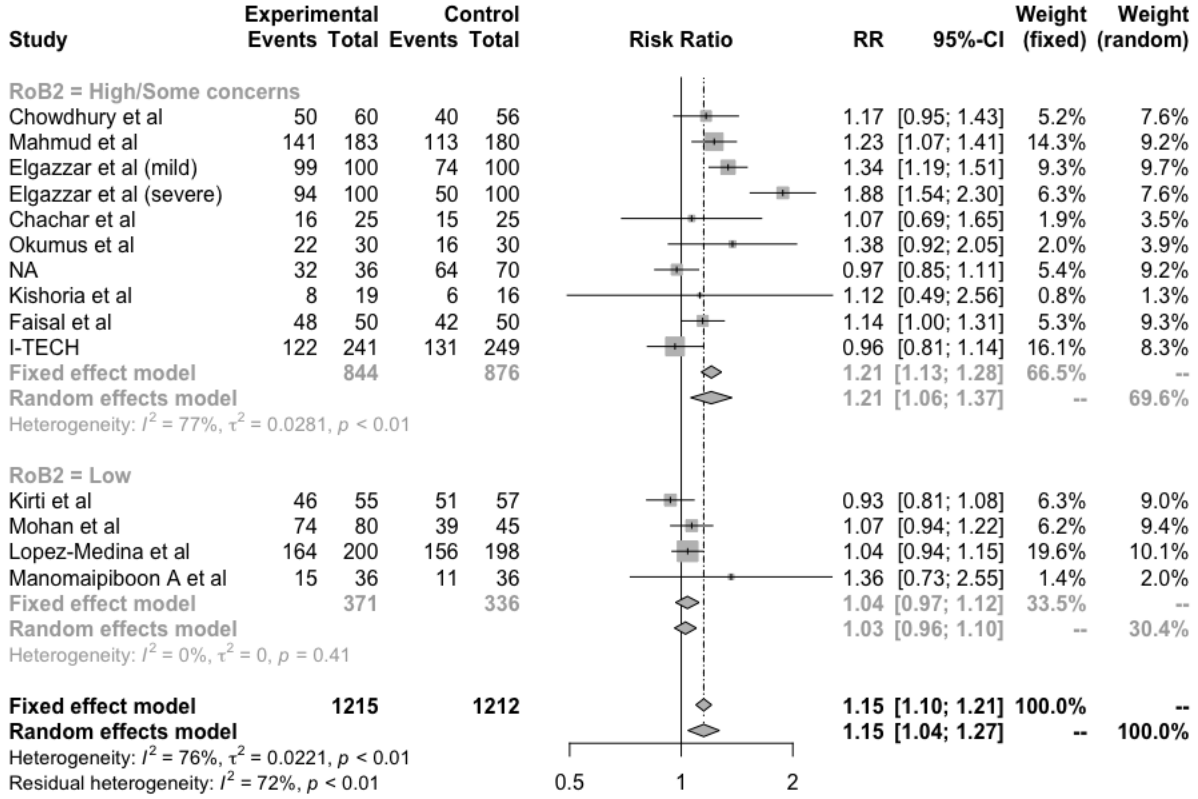

Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI
Weight (fixed)
Weight (random)
RoB2 = High/Some concerns
Mahmud et al 0 183 3 180 0.14 [0.01; 2.70] 3.5% 2.7%
Hashim HA et al 2 70 6 70 0.33 [0.07; 1.60] 5.9% 7.1%
Elgazzar et al (mild) 0 100 4 100 0.11 [0.01; 2.04] 4.4% 2.8%
Elgazzar et al (severe) 2 100 20 100 0.10 [0.02; 0.42] 19.6% 7.9%
Niaee et al 4 120 11 60 0.18 [0.06; 0.55] 14.4% 10.2%
Okumus et al 6 30 9 30 0.67 [0.27; 1.64] 8.8% 12.0%
NA 5 36 8 70 1.22 [0.43; 3.45] 5.3% 10.7%
Fixed effect model 639 610 0.32 [0.20; 0.51] 61.8% --
Random effects model 0.33 [0.15; 0.73] -- 53.5%
Heterogeneity: I^2 = 55%, τ^2 = 0.5743, p = 0.04
RoB2 = Low
Kirti et al 0 55 4 57 0.12 [0.01; 2.09] 4.3% 2.8%
Shahbaznejad et al 1 35 0 34 2.92 [0.12; 69.14] 0.5% 2.4%
Lopez-Medina et al 0 200 1 198 0.33 [0.01; 8.05] 1.5% 2.4%
Bermejo Galan et al 12 53 25 115 1.04 [0.57; 1.91] 15.4% 14.8%
Abd-Elsalam et al 3 82 4 82 0.75 [0.17; 3.25] 3.9% 7.6%
Vallejos et al 4 250 3 251 1.34 [0.30; 5.92] 2.9% 7.5%
I-TECH 3 241 10 249 0.31 [0.09; 1.11] 9.6% 8.9%
Fixed effect model 916 986 0.74 [0.47; 1.17] 38.2% --
Random effects model 0.81 [0.50; 1.33] -- 46.5%
Heterogeneity: I^2 = 2%, τ^2 = 0.0141, p = 0.41
Fixed effect model 1555 1596 0.48 [0.35; 0.66] 100.0% --
Random effects model 0.48 [0.28; 0.81] -- 100.0%
Heterogeneity: I^2 = 46%, τ^2 = 0.3949, p = 0.03
Residual heterogeneity: I^2 = 38%, p = 0.08
0.01
0.1
1
10
100

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



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

Baricitinib

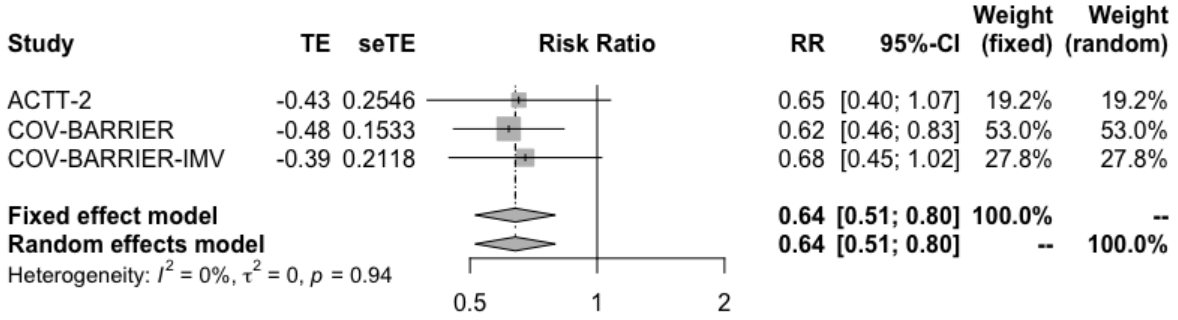
See Summary of findings Table 13, Appendix 1

We identified three RCTs including 2,659 patients in which baricitinib was compared against standard of care. Both studies included moderate to severe hospitalized patients. Critical patients were excluded. Our results showed:

- Baricitinib reduces mortality, RR 0.64 (95%CI 0.51 to 0.8); RD -5.7% (95%CI -7.8% to -3.2%); High certainty ⊕⊕⊕◯ (Figure 23)
- Baricitinib may reduce mechanical ventilation, RR 0.66 (95%CI 0.46 to 0.93); RD -5.9% (95%CI -9.2% to -1.2%); Low certainty ⊕⊕◯◯

- Baricitinib probably improves time to symptom resolution, RR 1.27 (95%CI 1.13 to 1.42); RD 16.3% (95%CI 7.9% to 25.5%); High certainty ⊕⊕⊕◯
- Baricitinib probably does not increase severe adverse events, RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⊕⊕⊕◯

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



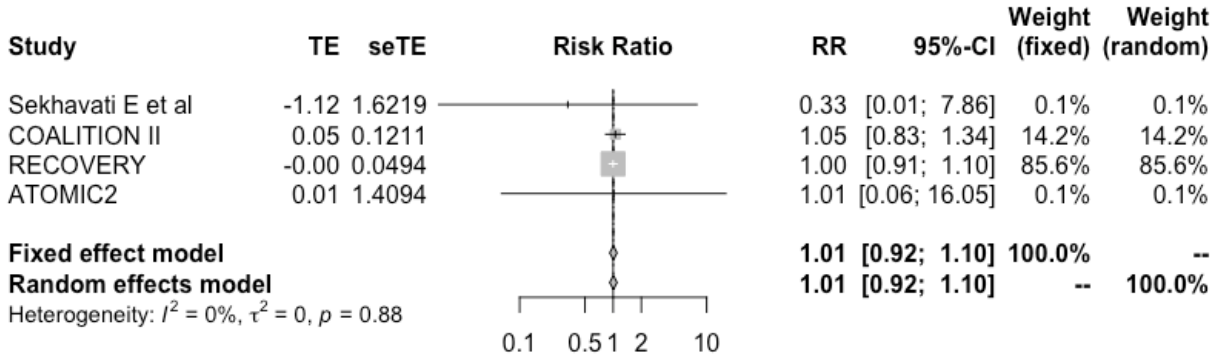
Azithromycin

See Summary of findings Table 14, Appendix 1

We identified ten RCTs including 10,429 patients in which azithromycin was compared against standard of care or other treatments. RECOVERY trial was the biggest study including 7,762 patients with severe disease (mortality in the control arm 19%). Our results showed:

- Azithromycin probably does not reduce mortality, RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ (Figure 24)
- Azithromycin probably does not reduce mechanical ventilation requirements, RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⊕⊕⊕◯
- Azithromycin does not improve time to symptom resolution, RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕
- It is uncertain if azithromycin increases severe adverse events, RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯
- Azithromycin may not reduce hospitalizations, RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -2.3% to 4.1%); Low certainty ⊕⊕◯◯

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

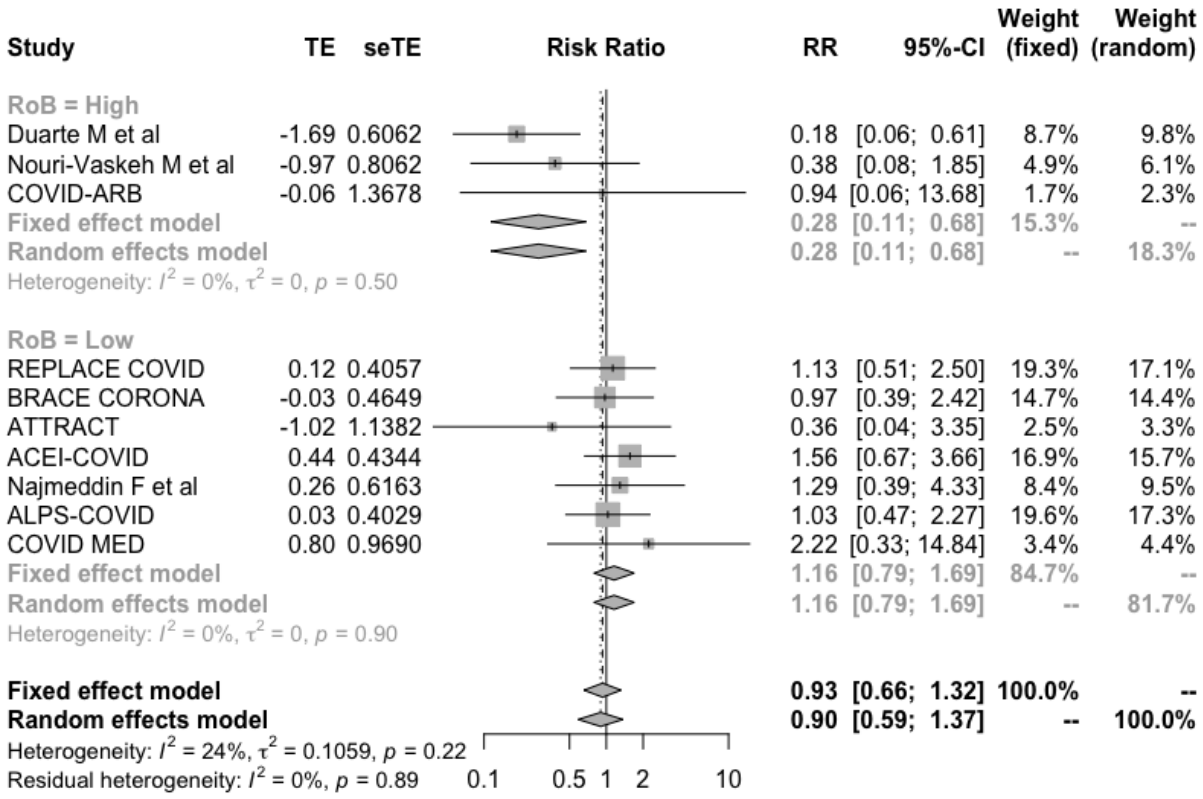


ACEI/ARB initiation or continuation

We identified eleven RCTs including 1,766 patients in which patients with COVID-19 were randomized to initiate or continue ACEI/ARB treatment and compared to standard of care or discontinue ACEI/ARB. Our results showed:

- ACEI/ARB initiation or continuation may increase mortality, RR 1.16 (95%CI 0.79 to 1.69); RD 2.6% (95%CI -3.4% to 11%); Low certainty ⊕⊕◯◯ (Figure 25) (based on low risk of bias studies)
- ACEI/ARB discontinuation may reduce mechanical ventilation requirements, RR 0.89 (95%CI 0.66 to 1.22); RD -1.9% (95%CI -5.9% to 3.8%); Low certainty ⊕⊕◯◯

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



Colchicine

See Summary of findings Table 15, Appendix 1

We identified ten RCTs including 17,963 patients in which colchicine was compared against standard of care or other treatments. The COLCORONA trial was the biggest including mild ambulatory patients, with 2,235 patients assigned to intervention and 2,253 to control, and the RECOVERY trial was the biggest including moderate to critical hospitalized patients, with 5,610 patients assigned to intervention and 5,730 assigned to control. Our results showed:

- Colchicine probably does not reduce mortality, RR 0.99 (95%CI 0.93 to 1.06); RD -0.2% (95%CI -1.1% to 1%); Moderate certainty ⊕⊕⊕◯ (Figure 26)
- Colchicine probably does not reduce mechanical ventilation requirements, RR 0.98 (95%CI 0.89 to 1.08); RD -0.3% (95%CI -1.9% to 1.4%); Moderate certainty ⊕⊕⊕◯ (Figure 27)
- Colchicine does not increase symptom resolution or improvement, RR 1.01 (95%CI 0.96 to 1.06); RD 0.6% (95%CI -2.4% to 3.6%); High certainty ⊕⊕⊕⊕

- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕
- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕◯◯◯
- Colchicine probably has no important effect on hospitalizations in patients with recent onset disease, RR 0.81 (95%CI 0.63 to 1.04); RD -0.9% (95%CI -1.8% to 0.2%); Moderate certainty ⊕⊕⊕◯

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

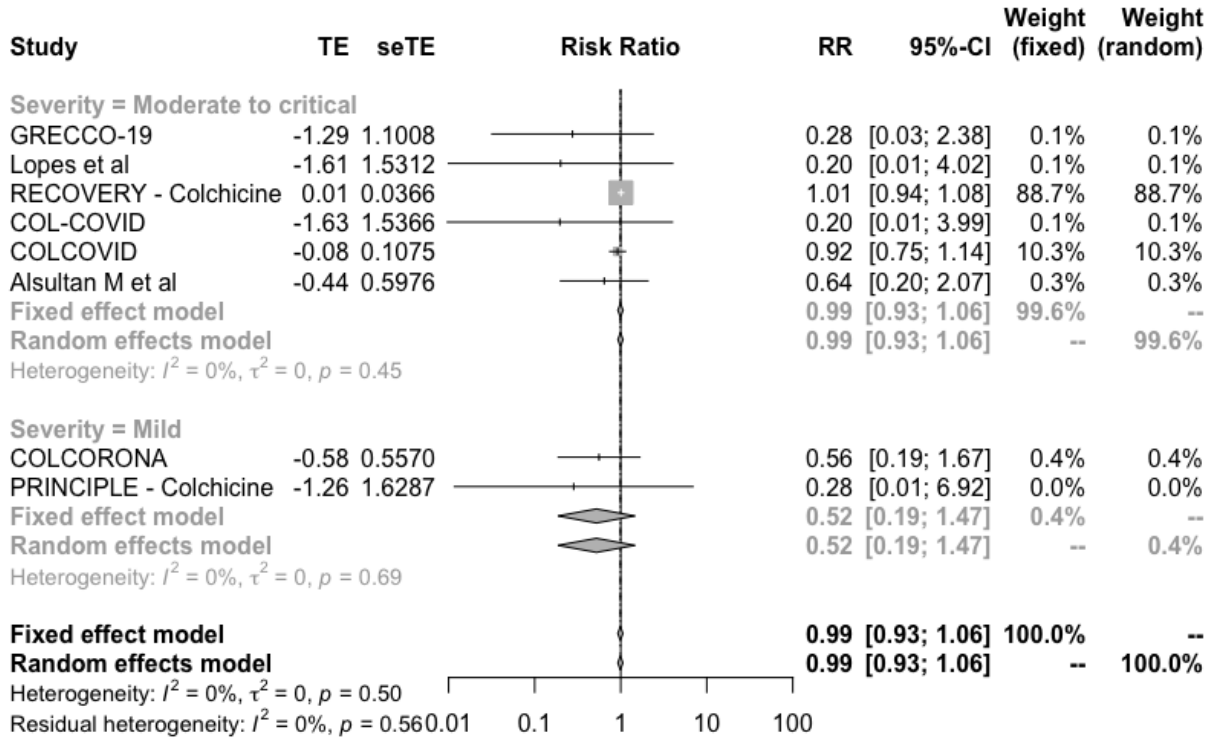
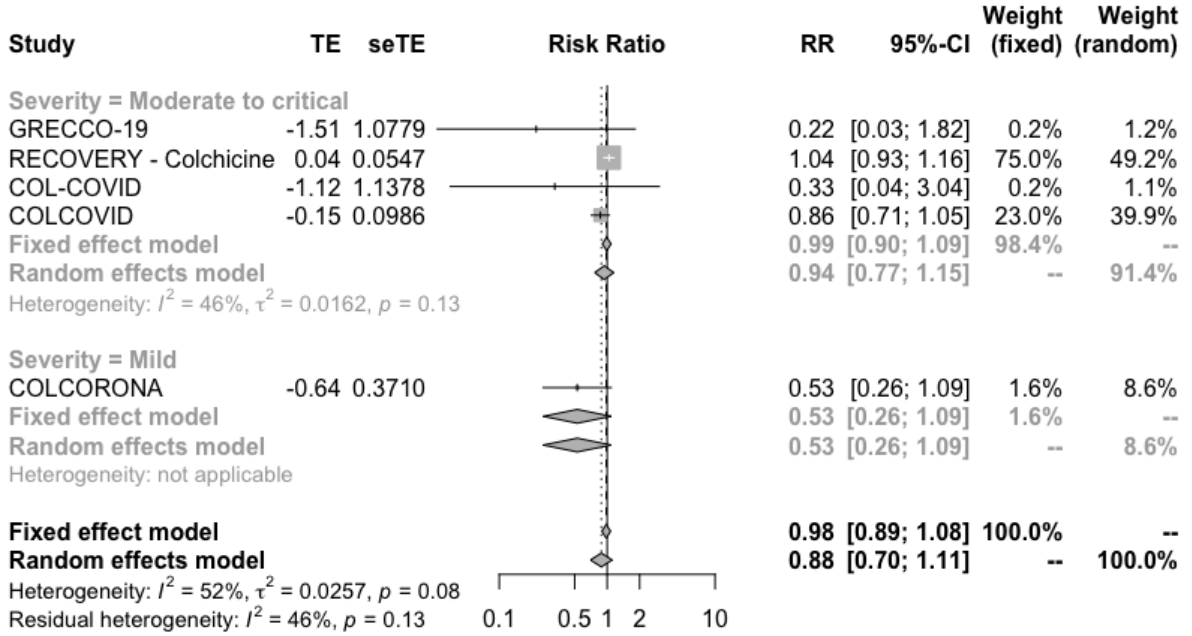


Figure 27. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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

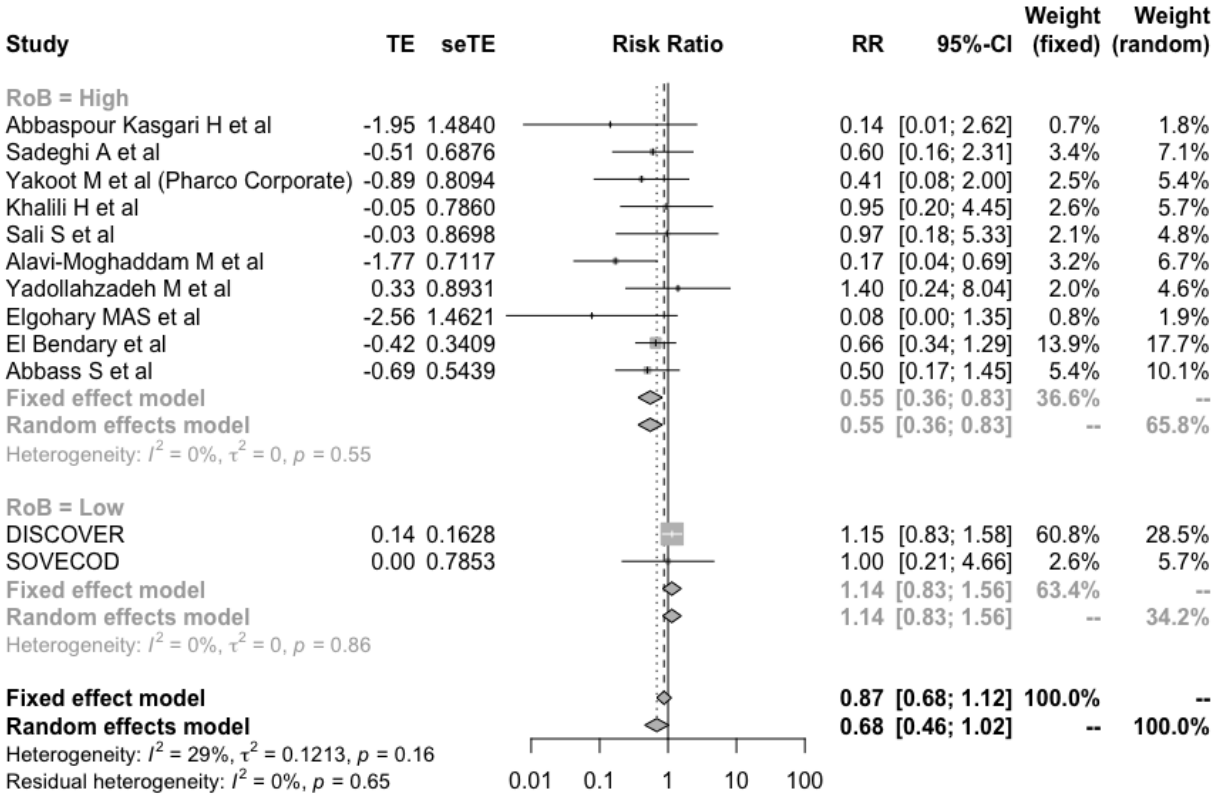
Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir

See Summary of findings Table 16, Appendix 1

We identified 13 RCTs including 2,270 patients in which sofosbuvir alone or in combination with daclatasvir or ledipasvir was compared against standard of care or other treatments. One study compared sofosbuvir alone vs. standard of care, one study compared sofosbuvir + ravidasvir vs. standard of care, one study compared sofosbuvir alone vs. lopinavir-ritonavir, four studies compared sofosbuvir + daclatasvir vs. standard of care, two studies compared sofosbuvir + daclatasvir vs. lopinavir-ritonavir, and two studies compared sofosbuvir + ledipasvir vs. standard of care. As there is moderate to high certainty that lopinavir-ritonavir is not related to significant benefits, we assumed that intervention as equivalent to standard of care. The DISCOVER trial was the biggest, with 1,083 patients and the only one categorized as with low risk of bias. Studies included patients with mild to severe disease. Our results showed:

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

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



REGEN-COV (casirivimab and imdevimab)

See Summary of findings Table 17, Appendix 1

We identified ten RCTs including 24,659 patients in which REGEN-COV (casirivimab and imdevimab) was compared against standard of care in patients with recent onset COVID-19. RECOVERY trial was the biggest, included severe to critical patients and reported differential

effect in seronegative patients at baseline. Eight of the other nine studies included mild patients with recent onset disease or exposed individuals with negative PCR. Our results showed:

- Overall REGEN-COV may decrease mortality, RR 0.83 (95%CI 0.64 to 1.07); RD -2.7% (95%CI -5.8% to 1.1%); Low certainty ⊕⊕◯◯
- In seronegative patients REGEN-COV probably decreases mortality, RR 0.79 (95%CI 0.71 to 0.89); RD -3.4% (95%CI -4.6% to -1.8%); Moderate certainty ⊕⊕⊕◯ (Figure 29)
- Overall REGEN-COV may decrease mechanical ventilation, RR 0.79 (95%CI 0.54 to 1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕◯◯
- In seronegative patients REGEN-COV probably reduces mechanical ventilation, RR 0.82 (95%CI 0.74 to 0.9); RD -3.1% (95%CI -4.5% to -1.7%); Moderate certainty ⊕⊕⊕◯
- Overall REGEN-COV may increase symptom resolution, RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕⊕◯
- In seronegative patients REGEN-COV probably increases symptom resolution, RR 1.1 (95%CI 1.06 to 1.14); RD 6% (95%CI 3.6% to 8.5%); Moderate certainty ⊕⊕⊕◯
- REGEN-COV reduces symptomatic infections in exposed individuals, RR 0.43 (95%CI 0.31 to 0.59); RD -9.9% (95%CI -12% to -7.1%); High certainty ⊕⊕⊕⊕
- REGEN-COV probably does not increase severe adverse events, RR 0.54 (95%CI 0.27 to 1.07); RD -4.7% (95%CI -7.4% to 0.7%); Moderate certainty ⊕⊕⊕◯
- REGEN-COV probably reduces hospitalization, RR 0.30 (95%CI 0.20 to 0.46); RD -3.4% (95%CI -3.8% to -2.6%); Moderate certainty ⊕⊕⊕◯ (Figure 30)

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

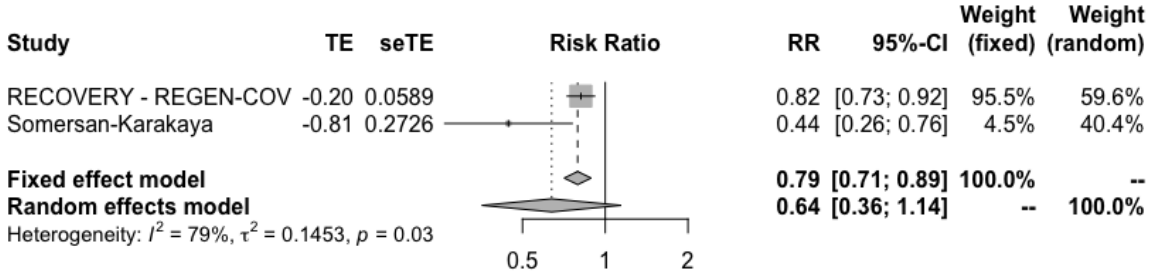
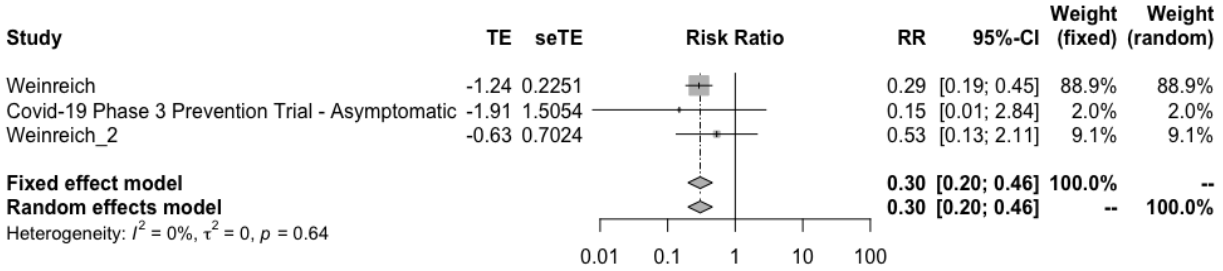


Figure 30. Hospitalization in randomized studies comparing REGEN-COV vs standard of care in patients with COVID-19



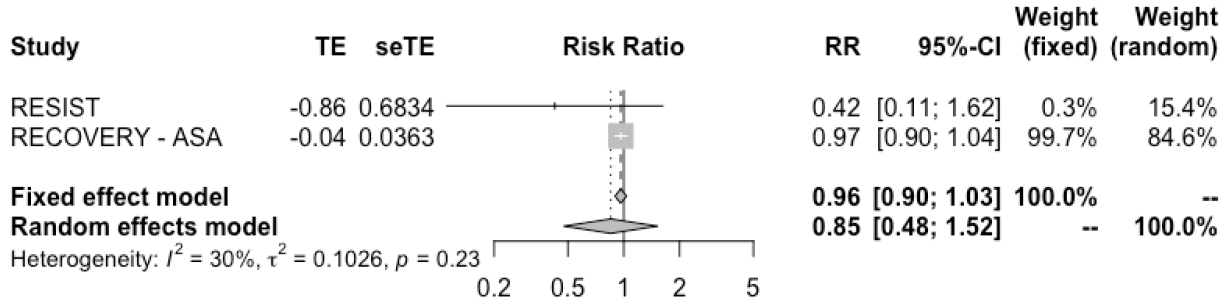
In addition, two studies that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab and sotrovimab in non-severe patients with risk factors for severity reported no important differences in hospitalizations.

Aspirin

We identified three RCTs including 15,612 patients in which aspirin was compared against standard of care in patients with COVID-19. Our results showed:

- Aspirin probably does not reduce mortality, RR 0.96 (95%CI 0.90 to 1.03); RD -0.6% (95%CI -1.6% to 0.5%); Moderate certainty ⊕⊕⊕◯ (Figure 31)
- Aspirin probably does not reduce mechanical ventilation, RR 0.95 (95%CI 0.87 to 1.05); RD -0.8% (95%CI -2.2% to 0.9%); Moderate certainty ⊕⊕⊕◯
- Aspirin probably does not increase symptom resolution or improvement, RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕◯

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



Sotrovimab

We identified two RCT including 4141 patients with recent onset mild COVID-19 and risk factors for severe disease, in which sotrovimab was compared against standard of care. Our results showed:

- Sotrovimab probably reduces hospitalizations, RR 0.14 (95%CI 0.04 to 0.48); RD -4.1% (95%CI -4.6% to -2.5%); Moderate certainty ⊕⊕⊕◯ (certainty upgraded because of evidence of equipoise of sotrovimab and REGEN-COV)
- Severe adverse events, RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⊕⊕◯◯

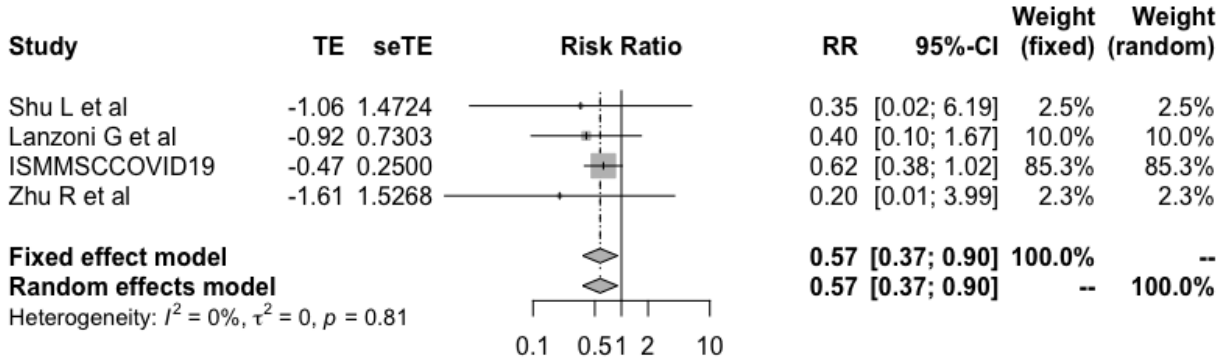
One study that compared REGEN-COV and sotrovimab in mild to moderate patients showed similar hospitalization rates (RR 0.93 95%CI, 0.77 to 1.13)

Mesenchymal stem-cell transplantation

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

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

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

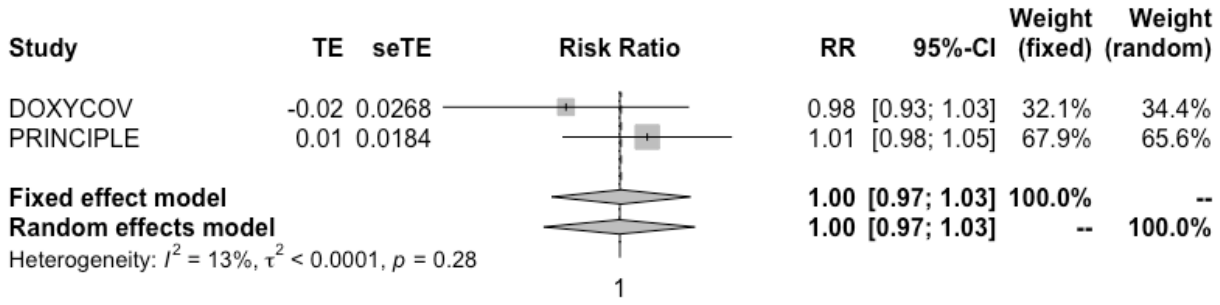


Doxycycline

We identified three RCTs including 2,302 patients with mild COVID-19, in which doxycycline was compared against standard of care. Our results showed:

- It is uncertain if doxycycline reduce or increase mortality, RR 1.10 (95%CI 0.63 to 1.93); RD 1.6% (95%CI -5.9% to 14.9%); Very low certainty ⊕◯◯◯
- Doxycycline does not increase symptom resolution or improvement, RR 1 (95%CI 0.97 to 1.03); RD -0% (95%CI -91.8% to -1.8%); High certainty ⊕⊕⊕⊕ (Figure 33)
- Doxycycline may not reduce hospitalizations, RR 1.13 (95%CI 0.73 to 1.74); RD 0.6% (95%CI -1.3% to 3.6%); Low certainty ⊕⊕◯◯

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



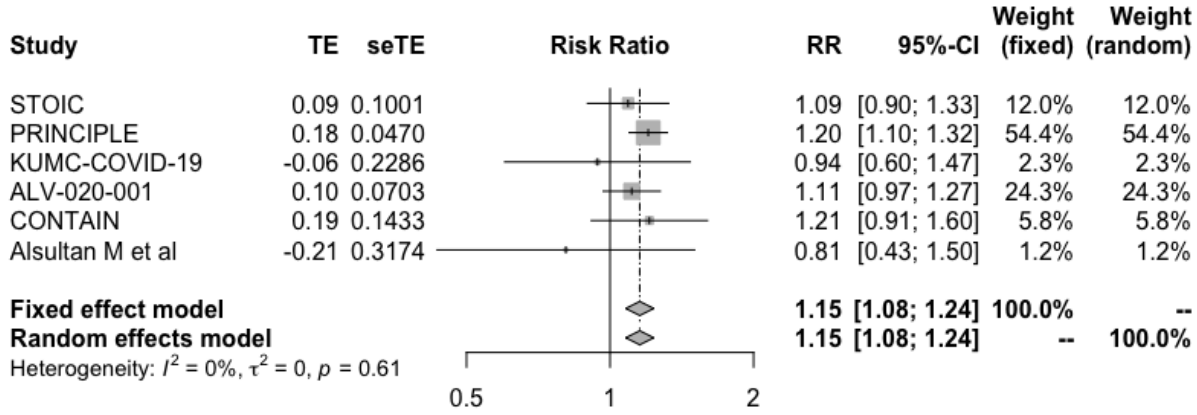
Inhaled corticosteroids

See Summary of findings Table 18, Appendix 1

We identified six RCTs including 2,695 patients with mild COVID-19, in which inhaled coticosteroids were compared against standard of care. Our results showed:

- It is uncertain if inhaled corticosteroids reduce or increase mortality, RR 0.90 (95%CI 0.46 to 1.77); RD -1.6% (95%CI -8.6% to 12.3%); Very low certainty ⊕◯◯◯
- It is uncertain if inhaled corticosteroids reduce or increase mechanical ventilation, RR 0.94 (95%CI 0.44 to 1.98); RD -1% (95%CI -9.6% to 17%); Very low certainty ⊕◯◯◯
- Inhaled corticosteroids probably increase symptom resolution or improvement, RR 1.15 (95%CI 1.08 to 1.24); RD 9.1% (95%CI 4.8% to 14.5%); Moderate certainty ⊕⊕⊕◯ (Figure 34)
- It is uncertain if inhaled corticosteroids reduce or increase hospitalizations, RR 0.85 (95%CI 0.58 to 1.26); RD -0.7% (95%CI -2% to 1.2%); Very low certainty ⊕◯◯◯

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



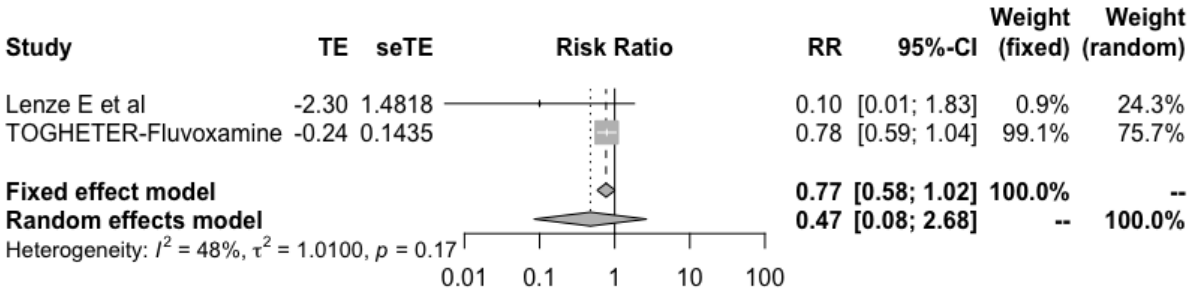
Fluvoxamine

See Summary of findings Table 19, Appendix 1

We identified two RCTs including 1,649 patients with COVID-19, in which fluvoxamine was compared against standard of care. Our results showed:

- It is uncertain if fluvoxamine reduces or increase mortality, RR 0.69 (95%CI 0.36 to 1.27); RD -5% (95%CI -10.2% to 4.3%); Very low certainty ⊕◯◯◯
- It is uncertain if fluvoxamine reduces or increase mechanical ventilation, RR 0.77 (95%CI 0.45 to 1.3); RD -3.7% (95%CI -8.8% to 4.8%); Very low certainty ⊕◯◯◯
- Fluvoxamine probably does not have an important effect on hospitalizations in patients with recent onset disease, RR 0.77 (95%CI 0.58 to 1.02); RD -1.1% (95%CI -2% to 0.1%); Moderate certainty ⊕⊕⊕◯ (Figure 35). The observed effect would probably be considered important in patients with very high hospitalization risk.
- Fluvoxamine may not increase severe adverse events, RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕◯◯

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



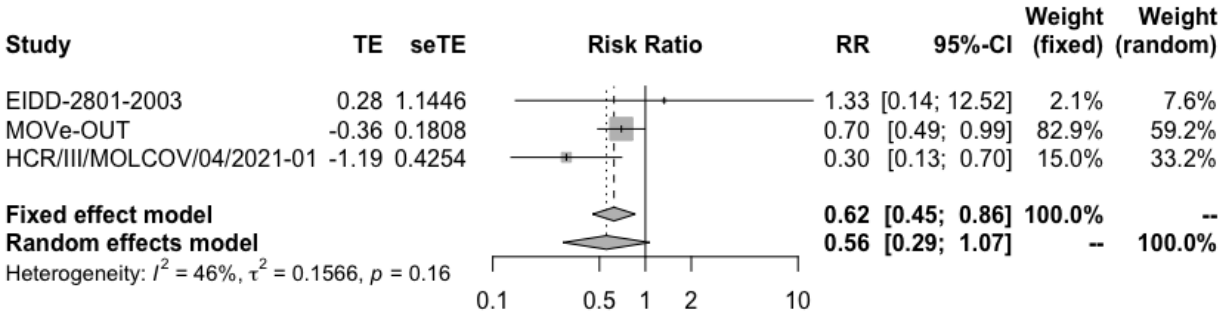
Molnupiravir

See Summary of findings Table 20, Appendix 1

We identified five RCTs including 2,433 patients with COVID-19, in which molnupiravir was compared against standard of care. Our results showed:

- It is uncertain if molnupiravir reduces or increase mortality, RR 0.13 (95%CI 0.02 to 0.77); RD -13.9% (95%CI -15.7% to -3.6%); Very low certainty ⊕◯◯◯
- Molnupiravir probably does not have an important effect on hospitalizations in patients with recent onset disease, RR 0.56 (95%CI 0.29 to 1.07); RD -2.1% (95%CI -3.3% to 0.3%); Moderate certainty ⊕⊕⊕◯ (Figure 36). The observed effect would probably be considered important in patients with very high hospitalization risk.
- Molnupiravir may not increase severe adverse events, RR 0.49 (95%CI 0.23 to 1.05); RD -5.2% (95%CI -7.8% to 0.5%); Low certainty ⊕⊕◯◯

Figure 36. Hospitalizations in randomized studies comparing molnupiravir vs standard of care in patients with COVID-19



Nirmatrelvir-ribavirin

See Summary of findings Table 21, Appendix 1

We identified one RCTs including 2085 patients with COVID-19, in which nirmatrelvir-ritonavir was compared against standard of care. Our results showed:

- It is uncertain if nirmatrelvir-ritonavir reduces or increase mortality, RR 0.04 (95%CI 0.002 to 0.68); RD -15.3% (95%CI -15.9% to -5.1%); Very low certainty ⊕◯◯◯
- Nirmatrelvir-ritonavir probably reduces hospitalizations in patients with recent onset disease, RR 0.12 (95%CI 0.06 to 0.25); RD -5.2% (95%CI -7.1% to -2%); Moderate certainty ⊕⊕⊕◯
- Nirmatrelvir-ritonavir probably does not increase severe adverse events, RR 0.49 (95%CI 0.30 to 0.80); RD -5.2% (95%CI -7.8% to 0.5%); Moderate certainty ⊕⊕⊕◯

Full description of included studies

Table 5, below, lists all the identified studies that were included in this systematic review by intervention. The treatments are arranged in alphabetical order. Study or author names, publication status, patient populations, interventions, sources of bias, outcomes, effect sizes and certainty are listed for each study.

Table 5. Description of included studies and interventions effects

99mTc-MDP Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Yuan et al;[15] preprint; 2020	Patients with mild COVID-19 infection. 10 assigned to 99mTc-MDP 5/ml once a day for 7 days and 11 assigned to standard of care.	Median age 61 ± 20, male 42.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Adalimumab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Fakharian A et al trial;[16] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 34 assigned to adalimumab 40 mg once and 34 assigned to SOC	Mean age 54.6 ± 12, male 58.8%, hypertension 29.4%, diabetes 27.9%, COPD 1.5%, CHD 4.4%, CKD 1.5%, cancer 1.5%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ammonium chloride Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Siami et al;[17] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 60 assigned to ammonium chloride 125 mg and 60 assigned to SOC	NR	Corticosteroids 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** Very low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
AMP5A (inhaled) Uncertainty in potential benefits and harms. Further research is needed.					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
AP-014 trial;[18] Roshon et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to AMP5A (inhaled) four nebulization a day for 5 days and 21 assigned to SOC	Mean age 64 ± 15, male 62.5%	Corticosteroids 78%, remdesivir 40%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁⨁◯◯ **Hospitalization:** No information

Anakinra It is uncertain if anakinra improves clinical important outcomes. Further research is needed to confirm or discard these findings					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CORIMUNO-ANA-1 trial;[19] Bureau et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 59 assigned to anakinra 400 mg a day for 3 days followed by 200 mg for 1 day followed by 100 mg for 1 day and 55 assigned to SOC	Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD 31.6%, cancer 9.6%,	Corticosteroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%, tocilizumab 0.8%, azithromycin 24.6%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
SAVE-MORE trial;[20] Kyriazopoulou et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 405 assigned to anakinra 100 mg SC a day for 7 to 10 days and 189 assigned to SOC	Mean age 61.9 ± 12.1, male 57.9%, diabetes 15.8%, COPD 4%, asthma %, CHD 3%, CKD 1.7%	Corticosteroids 86.2%, remdesivir 71.9%, azithromycin 18.7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COV-AID-3 trial;[21] Declercq et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 112 assigned to anakinra 100mg a day for 28 days and 230 assigned to SOC	Mean age 65.5, male 77.4%, hypertension 46.4%, diabetes 27.7%, COPD %, CHD 20.5%, CKD 10.8%	Corticosteroids 62.3%, remdesivir 5%, hydroxychloroquine 11.7%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Kharazmi et al;[22] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 15 assigned to anakinra 100mg a day for up to 14 days and 15 assigned to SOC	Mean age 54.1, male 63.3%, hypertension 33.3%, diabetes 36.6%, CHD 26.6%	Corticosteroids 63.3%, remdesivir 20%, lopinavir-ritonavir 63.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
REPLACE COVID trial;[23] Cohen et al; Peer reviewed; 2020	Patients with mild to severe COVID-19 previously treated with ACEI/ARB. 75 assigned to continuation of ACEI/ARB and 77 assigned to discontinuation of ACEI/ARB	Mean age 62 ± 12, male 55.5%, hypertension 100%, diabetes 37%, COPD 17%, asthma %, CHD 12%,	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.16 (95%CI 0.79 to 1.69); RD 2.6% (95%CI -3.4% to 11%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.89 (95%CI 0.66 to 1.22); RD -1.9% (95%CI -5.9% to 3.8%); Low certainty ⨁⨁◯◯ **Symptom**

BRACE CORONA trial;[24] Lopes et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB	Median age 55.5 ± 19, male 59.6%, hypertension 100%, diabetes 31.9%, COPD %, asthma 3.9%, CHD 4.6%, CKD 1.4%, cancer 1.5%,	Corticosteroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.	**resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
ACEI-COVID trial;[25] Bauer et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 100 assigned to continuation of ACEI/ARB and 104 assigned to discontinuation of ACEI/ARB	Mean age 72 ± 11, male 63%, hypertension 98%, diabetes 33%, CHD 22%	Remdesivir 6.8%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ATTRACT trial;[26] Tornling et al; peer reviewed; 2020	Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200 mg a day for 7 days and 55 assigned to SOC	Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%	Corticosteroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Nouri-Vaskeh et al;[27] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan	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	

	50 mg a day for 14 days and 39 assigned to Amlodipine 5 mg a day for 14 days			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
SURG-2020-28683 trial;[28] Puskarich et al; Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to losartan 25 mg a day for 10 days and 59 assigned to SOC	Age (35-54) 46%, male 51.4%, hypertension 7.7%, diabetes 6%, COPD %, asthma 10.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
COVID-ARB trial;[29] Geriak et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 16 assigned to losartan 25 mg a day for 10 days and 15 assigned to SOC	Median age 53, male %, hypertension 38.7%, diabetes 25.8%, CHD 3.2%, obesity 41.9%	Corticosteroids 22.6%, remdesivir 29%, hydroxychloroquine 9.7%, , azithromycin 16.1%, convalescent plasma 6.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Duarte et al;[30] peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 71 assigned to Telmisartan 80 mg twice daily and 70 assigned to SOC	Mean age 66 ± 17, male 53.2%, hypertension 44.3%, diabetes 19%, chronic lung disease 11.4%, asthma 1.3%, CHD NR%, CKD 3.2%, cerebrovascular disease 6.9%, obesity 15.2%	Corticosteroids 50.6%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. Significant number of exclusions post randomization. Stop early for benefit in the context of multiple interim analysis.	
Najmeddin et al;[31] peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to continuation of	Mean age 66.3 ± 9.9, male 46.9%, diabetes 50%, COPD 1.6%, CHD 25%, CKD 1.6%,	Corticosteroids 42.2%, remdesivir 10.9%, , azithromycin 9.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection,	

	ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB	cancer 4.7%,		and adverse events Notes: 10.9% lost to follow-up	
ALPS-COVID trial;[32] Puskarich et al; preprint; 2021	Patients with moderate COVID-19 infection. 101 assigned to ACEI/ARB losartan 100 mg a day and 104 assigned to SOC	Mean age 55, male 60%, hypertension 42%, diabetes 22.9%, COPD 11.7%, asthma 13.2%, CHD 7.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
COVID MED trial;[33] Freilich et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 9 assigned to losartan 25 mg and 5 assigned to SOC	Mean age 63, male 64.2%, diabetes 7.1%, COPD 42.9%, asthma %, CHD 42.9%, CKD 0%, immunosuppression 35.7%, obesity 14.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Anticoagulants

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
HESACOVID trial;[34] Bertoldi Lemos et al; peer reviewed; 2020	Patients with critical COVID-19. Ten assigned to low molecular weight heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and 10 assigned to prophylactic dose (i.e., enoxaparin 40 mg a day)	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, coronary heart disease 10%, immuno-suppression 5%	Corticosteroids 70%, hydroxy-chloroquine 25%, azithromycin 90%	Some concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse	**Mortality:** RR 0.97 (95%CI 0.79 to 1.2); RD -0.5% (95%CI -3.4% to 3.2%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** No information **Symptom**

				events outcomes results.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Venous thromboembolic events (intermediate dose):** RR 0.82 (95%CI 0.33 to 2); RD -1.2% (95%CI -4.7% to 7%); Low ⨁⨁◯◯ **Venous thromboembolic events (therapeutic dose):** RR 0.56 (95%CI 0.44 to 0.72); RD -3.1% (95%CI -3.9% to -1.9%); Moderate ⨁⨁⨁◯ **Major bleeding:** RR 1.76 (95%CI 1.19 to 2.62); RD 1.4% (95%CI 0.4% to 3.1%); Moderate ⨁⨁⨁◯ **Hospitalization:** No information
REMAP-CAP, ACTIV-4a, ATTACC trial;[35] Zarychanski et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 534 assigned low molecular weight heparin therapeutic dose (i.e., enoxaparin 1 mg/kg twice a day) and 564 assigned to prophylactic dose (i.e., enoxaparin 40 mg a day)	Mean age 61 ± 12.5, male 70%, diabetes 32.7%, COPD 24.1%, CHD 6.9%, CKD 9.6%,	Corticosteroids 79.3%, remdesivir 30.8%, tocilizumab 1.8%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
INSPIRATION trial;[36] Sadeghipour et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 276 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 286 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 62 ± 21, male 57.8%, hypertension 44.3%, diabetes 27.7%, COPD 6.9%, CHD 13.9%, CKD %, cerebrovascular disease 3%	Corticosteroids 93.2%, remdesivir 60.1%, lopinavir-ritonavir 1%, tocilizumab 13.2%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
Perepu et al;[37] preprint; 2021	Patients with severe to critical COVID-19 infection. 87 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 86 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 64 ± 62, male 56%, hypertension 60%, diabetes 37%, COPD 23%, CHD 31%, cancer 12%, obesity 49%	Corticosteroids 75%, remdesivir 61%, azithromycin 21%, convalescent plasma 27%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP, ACTIV-4a,	Patients with moderate to severe	Mean age 59 ± 14, male 58.7%, hypertension	Corticosteroids 61.7%, remdesivir 36.4%,	Some concerns for mortality and	

ATTACC trial;[38] Zarychanski et al; preprint; 2021	COVID-19 infection. 1171 assigned to enoxaparin 1 mg/kg twice a day and 1048 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	51.8%, diabetes 29.7%, COPD 21.7%, CHD 10.6%, CKD 6.9%, immunosuppressive therapy 9.7%	tocilizumab 0.6%,	mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
ACTION trial;[39] Lopes et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 311 assigned to enoxaparin 1 mg/kg twice a day or rivaroxaban 20 mg a day and 304 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 56.6 ± 14.3, male 60%, hypertension 49.1%, diabetes 24.4%, COPD 3.1%, asthma 4.7%, CHD 4.6%, cancer 2.6%,	Corticosteroids 83%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Although patients and careers were aware of the intervention arm assigned, outcome assessors were blinded.	
RAPID trial;[40] Sholzberg et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 228 assigned to therapeutic anticoagulation (i.e., enoxaparin 1 mg/kg) twice a day and 237 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 60 ± 14.5, male 56.8%, hypertension 43.8%, diabetes 34.4%, COPD 13.5%, asthma %, CHD 7.3%, CKD 7.1%, cerebrovascular disease 4.1%, cancer 6.9%,	Corticosteroids 69.4%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Open-label study but outcome assessors were blinded.	
HEP-COVID trial;[41] Spyropoulos et al; peer reviewed;	Patients with severe to critical COVID-19 infection. 129 assigned	Mean age 66.7 ± 14, male 53.8%, hypertension 59.9%,	Corticosteroids 81%, remdesivir 70.6%,	Some concerns for mortality and mechanical ventilation;	

2021	to enoxaparin 1mg/kg twice a day and 124 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	diabetes 37.3%, COPD 6.7%, CHD 8.7%, CKD 3.6%, cerebrovascular disease 3.2%, cancer 2%		some concerns for symptom resolution, infection, and adverse events	
BEMICOP trial;[42] Marcos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 33 assigned to bemiparin 115 IU/Kg once daily and 32 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	Mean age 62.7 ± 13, male 63.1%, hypertension 33.8%, diabetes 7.7%, COPD 16.9%, asthma %, CHD 6.2%, cancer 3.1%,	Corticosteroids 95.4%, remdesivir 13.8%, tocilizumab 23.1%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Oliynyk et al;[43] peer reviewed; 2021	Patients with severe COVID-19 infection. 84 assigned to enoxaparin 100 anti-Xa IU/kg twice a day or unfractionated heparin 80 U/kg/h intravenously, followed by a maintenance dose of 18 U/kg/h and 42 assigned to enoxaparin enoxaparin 50 anti-Xa IU/kg a day	Mean age 70.6, male 60.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
X-Covid 19 trial;[44] Morici et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection.	Mean age 59 ± 21, male 62.8%, hypertension 36.1%, diabetes 13.7%,	Corticosteroids 45.9%, remdesivir 21.8%, tocilizumab 1.1%	Low for mortality and mechanical ventilation; high for symptom	

	91 assigned to enoxaparin 40 mg twice a day and 92 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose	COPD 5.5%, CKD 1.6%, cerebrovascular disease 2.7%		resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTIV-4B trial;[45] Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 278 assigned to apixaban 2.5 to 5mg twice a day and 136 assigned to SOC	Median age 54 ± 13, male 40.9%, hypertension 35.3%, diabetes 18.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.08 (95%CI 0.92 to 1.27); RD 4.8% (95%CI -4.8% to 16.4%); Low ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** No information **Venous thromboembolic events (intermediate dose):** No information **Clinically important bleeding:** Very low certainty ⨁◯◯◯
Gates MRI RESPOND-1 trial;[46] Ananworanich et al; peer reviewed; 2021	Patients with mild covid-19 and risk factors for severity. 222 assigned to rivaroxaban 10mg a day and 222 assigned to SOC	Median age 49, male 39.3%, hypertension 51.8%, diabetes 27.7%, COPD 6.1%, immunosuppressive therapy 3.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

					Hospitalization: Very low certainty ⊕◯◯◯
Aprepitant **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Mehboob et al;[47] preprint; 2020	Patients with mild to critical COVID-19 infection. 10 assigned to aprepitant 80 mg once a day for 3-5 days and 8 assigned to standard of care	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
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;[48] Tieu et al; Preprint; 2020	Patients with mild to moderate COVID-19. 39 assigned to artemisinin 500 mg for 5 days and 21 assigned to SOC	Mean age 43.3 ± 11.9, male 63.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Aspirin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
RESIST trial;[49] Ghati et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 221 assigned to aspirin 75 mg once a day for 10 days and 219	Mean age 53.1 ± 9.2, male 73.3%, hypertension 28.6%, diabetes 27.7%, CHD 1.1%, CKD 2.4%	Corticosteroids 27.3%, remdesivir 20.6%, hydroxychloroquine 9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	**Mortality:** RR 0.96 (95%CI 0.90 to 1.03); RD -0.6% (95%CI -1.6% to 0.5%); Moderate certainty ⨁⨁⨁◯

	assigned to SOC			Notes: Blinding and concealment probably inappropriate.	**Invasive mechanical ventilation:** RR 0.95 (95%CI 0.87 to 1.05); RD -0.8% (95%CI -2.2% to 0.9%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 1.0 to 1.04); RD 1% (95%CI -0.1% to 2.2%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
RECOVERY - ASA trial;[50] Horby et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 7351 assigned to aspirin 150 mg a day and 7541 assigned to SOC	Median age 59.2 ± 14.2, male 61.5%, diabetes 22%, COPD 19%, asthma %, CHD 10.5%, CKD 3%,	Corticosteroids 94%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTIV-4B trial;[45] Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 144 assigned to aspirin 81mg a day and 136 assigned to SOC	Median age 54 ± 13, male 40.9%, hypertension 35.3%, diabetes 18.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Auxora

Auxora may reduce mortality 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 (standard of care) and GRADE certainty of the evidence
RCT					
CARDEA trial;[51] Bruen et al; Preprint; 2020	Patients with severe COVID-19 infection. 130 assigned to Auxora initial dose 2.0	Mean age 60, male 67.4%, hypertension 62.8%, diabetes 41.8%	Steroids 100%, remdesivir 77.6%, tocilizumab 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	**Mortality:** RR 0.68 (95%CI 0.39 to 1.17); RD -5.1% (95%CI -9.8% to 2.7%); Low

	mg/kg (max 250 mg), followed by 1.6 mg/kg (max 200 mg) at 24 and 48 h and 131 assigned to SOC			adverse events	certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.07 (95%CI 0.94 to 1.22); RD 4.2% (95%CI -3.6% to 13.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.69 (95%CI 0.48 to 1); RD -3.2% (95%CI -5.3% to 0%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information

Avdoralimab

Avdoralimab may increase mortality and 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					
FORCE trial;[52] Carvelli et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 103 assigned to avdoralimab 500 mg	Mean age 63.6, male 71%, hypertension 51%, diabetes 36%, obesity 45%	Corticosteroids 85%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	**Mortality:** RR 1.68 (95%CI 0.87 to 3.26); RD 10.9% (95%CI -2.1% to 36.2%); Low

	once followed by 200 mg every 48 hours and 104 assigned to SOC			adverse events	certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.15 (95%CI 0.85 to 1.55); RD 1.5% (95%CI -1.5% to 5.6%); Low certainty ⊕⊕◯◯ **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[53] Jihad et al; preprint (now retracted); 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	Mean age 61 ± NR, male 69%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information

	SOC			concealment probably inappropriate.	**Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Azelastine (inhaled) **Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CARVIN trial;[54] Klussmann et al; preprint; 2021	Patients with mild COVID-19 infection. 56 assigned to azelastine (inhaled) 0.02 to 0.1% twice a day for 11 days and 28 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis**

					studies): No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Azithromycin **Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Sekhavati et al;[55] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to azithromycin 500 mg twice daily and 55 assigned to standard of care	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⨁⨁⨁⨁
Guvenmez et al;[56] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

COALITION II trial;[57] Furtado et al; peer-reviewed; 2020	Patients with severe COVID-19. 214 assigned to azithromycin 500 mg once a day for 10 days and 183 assigned to standard of care	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, coronary heart disease 5.8%, chronic kidney disease 11%, cerebrovascular disease 3.8%, immunosuppression %, cancer 3.5%, obesity %	Corticosteroids 18.1%, lopinavir-ritonavir 1%, oseltamivir 46%, ATB 85%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⨁◯◯◯ **Hospitalization:** RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -2.3% to 4.1%); Low certainty ⨁⨁◯◯
RECOVERY trial[58] Horby et al; preprint; 2020	Patients with moderate to critical COVID-19. 2582 assigned to azithromycin 500 mg a day for 10 days and 5182 assigned to standard of care	Mean age 65.3 ± 15.6, male 62%, diabetes 27.5%, COPD 24.5%, asthma %, coronary heart disease 26.5%, chronic kidney disease 6%	Corticosteroids 61%,	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Rashad et al;[59] preprint ; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to Clarithromycin 1000 mg a day for 7 days and 99 assigned to SOC	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
PRINCIPLE trial;[60] Butler et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 500 assigned to azithromycin 500 mg a day for 3 days and 629 assigned to SOC	Mean age 60.7 ± 7.8, male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,	NR	Some concerns for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have	

				introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	
ATOMIC2 trial;[61] Hinks et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 145 assigned to azithromycin 500 mg a day for 14 days and 147 assigned to SOC	Mean age 45.9 ± 14.8, male 51.5%, hypertension 17.6%, diabetes 8.5%, COPD 4.1%, asthma 18%, CHD 4.1%, cancer 0.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTION trial;[62] Oldenburg et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 131 assigned to azithromycin 1.2 g once and 70 assigned to SOC	Median age 43, male 44%, hypertension 12.2%, diabetes 3.8%, COPD 1.5%, asthma 12%, CKD 1%, cerebrovascular disease 1%, cancer 0.4%,	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	
Ghanei et al;[63] peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to Lopinavir-Ritonavir 200/50mg twice a day for 7 days and 110 assigned to azithromycin 500mg once followed by 250mg a day for 5 days	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Azvudine

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

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

					certainty of the evidence
RCT					
Ren et al;[64] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 10 assigned to azvudine 5 mg once a day and 10 assigned to standard of care	Median age 52 ± 59, male 60%, hypertension 5%, diabetes 5%, coronary heart disease 5%	Antivirals 100%, antibiotics 40%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**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

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;[65] 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	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	**Mortality:** No information **Invasive mechanical ventilation:** No information

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

Bamlanivimab +/- etesevimab (monoclonal antibody)

Bamlanivimab may reduce hospitalizations and infections in exposed individuals. It is uncertain if it affects mortality, mechanical ventilation requirements. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
BLAZE-1 trial;[66] Chen et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700 mg, 2800 mg, or 7000 mg once and 143 assigned to standard of care	Mean age 45 ± 68, male 55%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.06); RD 1.2% (95%CI 3.6% to 5.4%); Moderate certainty ⊕⊕⊕◯
ACTIV-3/TICO trial;[67] Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000 mg once and 151	Median age 71 ± 22, male 66%, hypertension 49%, diabetes 29%, COPD %, asthma 9%, CHD 4%, CKD 11%, obesity 52%	Corticosteroids 49%, remdesivir 95%,	Low for mortality and adverse events; high for symptom resolution. Notes: Significant loss to follow-up for symptom	

	assigned to SOC			improvement/resolution outcome.	**Symptomatic infection (prophylaxis studies):** RR 0.56 (95%CI 0.39 to 0.81); RD -7.6% (95%CI -10.6% to -3.6%); Moderate certainty ⊕⊕⊕◯ **Adverse events:** RR 1.12 (95%CI 0.75 to 1.66); RD 1.2% (95%CI -2.5% to -6.7%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.37 (95%CI 0.21 to 0.65); RD -3% (95%CI -3.8% to -1.7%); Moderate certainty ⊕⊕⊕◯
Gottlieb et al;[68] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700-7000 mg once, 112 assigned to bamlanivimab + etesevimab and 156 assigned to SOC	Mean age 44.7 ± 15.7, male 45.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
BLAZE-2 trial;[69] Cohen et al; peer reviewed; 2021	Patients exposed to SARS-CoV2. 484 assigned to bamlanivimab 4200 mg once and 482 assigned to SOC	Median age 53	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
BLAZE-1 trial;[70] Dougan et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 518 assigned to bamlanivimab + etesevimab 2800/2800 mg and 517 assigned to SOC	Mean age 53.8 ± 16.8, hypertension 33.9%, diabetes 27.5%, COPD %, CHD 7.4%, CKD 3.5%, immunosuppressive therapy 4.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
J2W-MC-PYAA trial;[71] Chen et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 18 assigned to bamlanivimab 700 to 7000 mg once and 6 assigned to SOC	Mean age 53.9, male 54.2%, hypertension 33.3%, diabetes 25%, asthma 25%, CHD 12.5%, CKD 4%, obesity 8.3%	Corticosteroids 29.1%, remdesivir 50%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OPTIMISE-C19 trial;[72] McCreary et al; preprint; 2021	Patients with mild COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2 (Regeneron) and 1013 assigned to bamlanivimab +/- etesevimab	Mean age 56 ± 16, male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD 6.5%, immunosuppresive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

ACTIV-2 trial;[73] Chew et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 159 assigned to bamlanivimab 700 to 7000mg and 158 assigned to SOC	Mean age 46.2 ± , male 48.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OPTIMISE-C19 trial;[74] Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD 16%, CKD 4.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Baricitinib

Baricitinib reduces mortality and time to symptom resolution. Certainty of the evidence was moderate because of risk of bias. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
ACTT-2 trial;[75] Kalil et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 515 assigned to baricitinib + remdesivir 4 mg a day for 14 days + 200 mg once followed by 100 mg a day for 10 days and 518 assigned to remdesivir	Mean age 55.4 ± 15.7, male 63.1%, comorbidities 84.4%	Corticosteroids 11.9%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	**Mortality:** RR 0.64 (95%CI 0.51 to 0.8); RD -5.7% (95%CI -7.8% to -3.2%); High 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 1.27 (95%CI 1.13 to
COV-BARRIER trial;[76] Marconi et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 764 assigned to baricitinib 4 mg for 14 days and 761 assigned to SOC	Mean age 57.6 ± 14.1, male 63.1%, hypertension 47.9%, diabetes 30%, COPD 4.6%, obesity 33%	Corticosteroids 79.3%, remdesivir 18.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

COV-BARRIER-IMV trial;[77] Wesley et al; preprint; 2021	Patients with critical COVID-19 infection. 51 assigned to baricitinib 4 mg a day for 14 days and 50 assigned to SOC	Mean age 58.6 ± 13.8, male 54.5%, hypertension 54.5%, diabetes 35.6%, COPD 3%, obesity 56.4%	Corticosteroids 86.1%, remdesivir 2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	1.42); RD 16.3% (95%CI 7.9% to 25.5%); High certainty ⨁⨁⨁⨁ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⨁⨁⨁◯ **Hospitalization:** No information

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

					No information **Adverse events:** No information **Hospitalization:** No information
Beta glucans **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Raghavan et al;[79] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 16 assigned to beta glucans 3 to 13 gr a day and 8 assigned to SOC	Mean age 41.2	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Pushkala et al;[80] preprint; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to beta glucans 19 gr a day and assigned to SOC	Mean age 44 ± , male 65%, hypertension 10%, diabetes 37.5%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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;[81] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 32 assigned to bioven 0.8-1 g/kg once a day for 2 days and 34 assigned to SOC	NA	NA	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Bromhexine hydrochloride **Bromhexine may reduce symptomatic infections in exposed individuals. Further research 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;[82] peer-reviewed; 2020	Patients with severe to critical COVID-19. 12 assigned to bromhexine hydrochloride 32 mf three times a day for 14 days and 6 assigned	Median age 52 ± 15.5, male 77.8%, hypertension 33.3%, diabetes 11.1%	Corticosteroids 22.2%, interferon 77.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯

	to standard of care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** RR 0.38 (95%CI 0.13 to 1.09); RD -10.8% (95%CI -15.1% to 1.6%); Low certainty ⨁⨁◯◯ **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Ansarin et al;[83] peer-reviewed; 2020	Patients with mild to critical COVID-19. 39 assigned to bromhexine 8 mg three time a day for 14 days and 39 assigned to standard of care	Mean age 59.7 ± 14.9, male 55.1%, hypertension 50%, diabetes 33.3%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Mikhaylov et al;[84] Peer reviewed; 2021	Patients exposed to COVID-19 infection. 25 assigned to bromhexine 12 mg a day and 25 assigned to SOC	Mean age 40.6 ± 7.6, male 42%, comorbidity 6%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tolouian et al;[85] Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 48 assigned to bromhexine 32 mg a day for 14 days and 52 assigned to SOC	Mean age 52 ± 16, male 46%, hypertension 39%, diabetes 33%, COPD 7%, asthma 6%, CHD 9%, CKD 5%, cerebrovascular disease 2%, cancer 6%,	Lopinavir-ritonavir 100%, interferon 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tolouian et al;[86] preprint; 2021	Patients with exposed COVID-19 infection. 187 assigned to Bromhexine 24 mg a	Median age 40 , male 53.2%, hypertension 6.2%, diabetes 9.1%, COPD 0.5%, asthma	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	

	day for 14 days and 185 assigned to SOC	1.1%, CHD 8.3%, CKD 1.6%, immunocompromised 0.8%, cancer 0.5%,		adverse events	
Calcitriol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Elamir et al;[87] peer reviewed; 2022	Patients with moderate COVID-19 infection. 25 assigned to calcitriol 0.5 µg daily for 14 days and 25 assigned to SOC	Mean age 66.5, male 30%, hypertension 60%, diabetes 40%, COPD 16%, cancer 4%, obesity 20%	Corticosteroids 50%, remdesivir 52%, convalescent plasma 12%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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
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;[88] Gunst et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 137 assigned to camostat mesilate 200 mg a day for 5 days and 68 assigned to SOC	Median age 61 ± 23, male 60%, hypertension 34%, diabetes 17%, COPD 10%, asthma 13%, CHD 19%, cancer 14%, obesity 33%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯
Chupp et al;[89] preprint; 2021	Patients with mild COVID-19 infection. 35 assigned to camostat mesilate 800 mg a day for 7 days and 35 assigned to SOC	Mean age 44.1 ± 13.3, male 60%, hypertension 20%, diabetes 5.7%, CKD 2.9%, obesity 68.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Canakinumab

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

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

CAN-COVID trial;[90] Caricchio et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 223 assigned to canakinumab 450-750 mg/kg once and 223 assigned to SOC	Median age 59, male 58.8%, hypertension 55.7%, diabetes 36.1%, COPD 7.3%, asthma 7.7%, CHD 20.3%, CKD 8.8%, cerebrovascular disease 5.9%	Corticosteroids 36.3%, remdesivir 20.7%, hydroxychloroquine 13.2%, azithromycin 37.4%, convalescent plasma 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Three C trial;[91] Cremer et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 29 assigned to canakinumab 300 to 600 mg once and 16 assigned to SOC	Mean age 68.8 ± 13.2, male 73.3%, hypertension 71.1%, diabetes 46.7%, COPD 17.8% CHD 22.2%, CKD 33.3%, cerebrovascular disease 4.4%	Steroids 46.7%, remdesivir 46.7%, convalescent plasma 9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Cannabidiol

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
CANDIDATE trial;[92] Crippa et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 49 assigned to cannabidiol 300mg a day for 14 days and 42 assigned to SOC	Mean age 39.7, male 32.7%, hypertension 4.4%, diabetes 2.2%, COPD %, asthma 3.3%, cancer 1.1%, obesity 6.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**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 ⊕◯◯◯
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;[93] preprint; 2021	Patients with mild to moderate COVID-19 infection. 31 assigned to CERC-002 16 mg/kg once and 31 assigned to SOC	Mean age 58.5 ± 14, male 69.5%	Corticosteroids 91.5%, remdesivir 68.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Chloroquine nasal drops **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Thakar et al;[94] Peer reviewed; 2020	Patients with mild COVID-19. 30 assigned to chloroquine nasal drops 0.03% six times a day for 10 days and 30 assigned to SOC	Mean age 34.9 ± 10.35, male 78.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

CIGB-325 Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ATENEA-Co-300 trial;[95] Cruz et al; preprint; 2020	Patients with mild to moderate COVID-19. 10 assigned to CIGB-325 2.5 mg/kg/day during 5-consecutive days) and 10 assigned to standard of care	Mean age 45.3 ± 12, male 70%, hypertension 25%, diabetes 0%, cancer 5%, obesity 25%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Clarithromycin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Rashad et al;[59] preprint; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500 mg a day for 7 days, 99 assigned to clarithromycin 1000 mg a day for 7 days and 99 assigned to SOC	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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

BK-CLV-201 trial;[96] Song et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 41 assigned to clevudine 120 mg a day for 14 days and 20 assigned to SOC	Mean age 59.9 ± 12.8, male 49.2%, hypertension 45.9%, diabetes 26.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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

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;[97] 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
COVID-19-MCS trial;[98] Altay et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 229 assigned to Cofactors (L-Carnitine, N-Acetylcysteine, Nicotinamide, Serine) and 75 assigned to SOC	Mean age 36.3 , male 57.6%, hypertension 9.2%, diabetes 6.2%	Hydroxychloroquine 81.9%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Hu et al;[99] preprint; 2021	Patients with moderate to severe with diabetes COVID-19 infection. 12 assigned to nicotinamide 500 mg a day and 12 assigned to SOC	Mean age 69.5, male 45.8%, hypertension 33.3%, diabetes 16.6%, COPD 0%, CHD 8.3%, CKD 4.2%, cerebrovascular disease 8.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Colchicine **Colchicine probably does not reduce mortality and mechanical ventilation requirements nor improve time to symptom resolution; In mild ambulatory patients it may reduce hospitalizations but the certainty of the evidence is low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
GRECCO-19 trial;[100] 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 0.99 (95%CI 0.93 to 1.06); RD -0.2% (95%CI -1.1% to 1%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.89 to 1.08); RD -0.3% (95%CI -1.9% to 1.4%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.96 to 1.06); RD 0.6% (95%CI -2.4% to 3.6%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.61 to
Lopes et al;[101] preprint; 2020	Patients with moderate to severe COVID-19 infection. 19 assigned to colchicine 0.5 mg three times a day, for 5 days followed by 0.5 mg twice daily for 5 days and 19 assigned to standard of care	Median age 50.75 ± 26.2, male 40%, diabetes 31.4%, chronic lung disease 14.2%, coronary heart disease 40%	Corticosteroids 40%, hydroxychloroquine 100%, azithromycin 100%, heparin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Salehzadeh et al;[102] preprint; 2020	Patients with moderate to critical COVID-19. 50 assigned to colchicine 1 mg a day for 6 days and 50 assigned to standard of care	Mean age 56, male 41%, hypertension 11%, diabetes 11%, chronic lung disease 4%, coronary heart disease 15%, chronic kidney disease 5%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study. Concealment of allocation is probably inappropriate.	0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕ **Pulmonary embolism:** RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.81 (95%CI 0.63 to 1.04); RD -0.9% (95%CI -1.8% to 0.2%); Low certainty ⊕⊕◯◯
Tardif et al;[103] peer-reviewed; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe disease. 2235 assigned to colchicine 1 mg a day for 3 days followed by 0.5 mg for a total of 27 days and 2253 assigned to SOC	Mean age 54.3, male 46%, hypertension 36.3%, diabetes 19.9%, COPD 26.5%, CHD 5.4%, obesity 45.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
RECOVERY - Colchicine trial;[104] Horby et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 5610 assigned to colchicine 500 mg twice a day for 10 days and 5730 assigned to SOC	Mean age 63.4 ± 13.8, male 69.5%, diabetes 25.5%, COPD 21.5%, asthma %, CHD 21%, CKD 3%	Corticosteroids 94%	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COL-COVID trial;[105] Figal et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 52 assigned to colchicine 1.5 gr once followed by 1 gr a day for 7 days and 51 assigned to SOC	Mean age 51 ± 12, male 52.4%, hypertension 27.2%, diabetes 14.6%, COPD 1%, CHD 2.9%, CKD 6.8%, cerebrovascular disease 1.9%, immunosuppresive therapy %, cancer %, obesity 21.4%	Corticosteroids 74.8%, remdesivir 32%, lopinavir-ritonavir 1%, tocilizumab 9.7%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PRINCIPLE - Colchicine trial;[106] Dorward et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 156 assigned to colchicine 500µg a day for 14 days and 133 assigned to SOC	Mean age 61, male 50%, hypertension 19.5%, diabetes 10.9%, COPD or asthma 32.2%, CHD 8%, cerebrovascular disease, or other	NR	Low for mortality and mechanical ventilation; high for symptom resolution, hospitalization, and adverse events	

		neurological diseases 5.2%,		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COLCOVID trial;[107] Diaz et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 640 assigned to Colchicine 1.5 mg once followed by 1 mg a day for 14 days and 639 assigned to SOC	Mean age 62 ± 14, male 64.9%, hypertension 47.7%, diabetes 22.7%, COPD 9.6%, CHD 7.1%, CKD 2.3%, cerebrovascular disease 2%, cancer 2.3%	Corticosteroids 91.5%, hydroxychloroquine 0.3%, lopinavir-ritonavir 0.2%, convalescent plasma 7.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Alsultan et al;[108] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to Colchicine 1.5 mg once followed by 1 mg a day for 5 days and 21 assigned to SOC	age 60 to 80 65.3, male 38.8%, diabetes 53.1%, CKD 8.2%, cerebrovascular disease 4.1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Pourdowlat et al;[109] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 89 assigned to Colchicine 0.5 mg for 3 days and then continued 1 mg/day for 12 days and 63 assigned to SOC	Mean age 55, male 56.4%, hypertension 12.7%, diabetes 14.5%, COPD %, asthma 3.6%, CHD 5.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Colchicine + rosuvastatin

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

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

RCT					
Gaitan-Duarte et al;[110] preprint; 2021	Patients with moderate to severe COVID-19 infection. 153 assigned to colchicine + rosuvastatin 1 mg + 40 mg a day for 14 days and 161 assigned to SOC	Mean age 55.4 ± 12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%	Corticosteroids 98%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Convalescent plasma

Convalescent plasma does not reduce mortality nor mechanical ventilation requirements nor improves time to symptom resolution. Convalescent plasma may not reduce hospitalizations and may not increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Li et al;[111] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 52 assigned to	Median age 70 ± 8, male 58.3%, hypertension 54.3%, diabetes 10.6%, coronary heart disease	Corticosteroids 39.2%, antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution,	**Mortality:** RR 0.99 (95%CI 0.94 to 1.05); RD 0% (95%CI -0.2% to 0.8%); High

	convalescent plasma 4 to 13 mL/kg of recipient body weight and 51 assigned to standard of care	25%, chronic kidney disease 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%		infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 1.05 (95% CI 0.96 to 1.14); RD 0.8% (95%CI -0.7% to 2.4%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 0.99 (95% CI 0.95 to 1.03); RD -0.6% (95%CI -3% to 1.8%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.03 (95% CI 0.85 to 1.26); RD 0.3% (95%CI -1.5% to 2.6%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.78 (95% CI 0.57 to 1.06); RD -1.1% (95%CI -2.1% to 0.6%); Low certainty ⊕⊕◯◯
CONCOVID trial; Gharbharan et al;[112] preprint; 2020	Patients with moderate to critical COVID-19 infection. 43 assigned to convalescent plasma 300 ml once or twice and 43 assigned to standard of care	Median age 62 ± 18, male 72%, hypertension 26%, diabetes 24.4%, chronic lung disease 26.7%, coronary heart disease 23.2%, chronic kidney disease 8.1%, immunosuppression 12.8%, cancer 9.3%	NR	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Avendaño-Solá et al;[113] preprint; 2020	Patients with severe COVID-19. 38 assigned to convalescent plasma 250-300 ml once and 43 assigned to standard of care	Mean age 60.8 ± 15.5, male 54.3%, hypertension 39.5%, diabetes 20.9%, chronic lung disease 12.3%, asthma NR%, coronary heart disease 18.5%, chronic kidney disease 4.9%	Corticosteroids 56.8%, remdesivir 4.94%, hydroxychloroquine 86.4%, lopinavir-ritonavir 41.9%, tocilizumab 28.4%, azithromycin 61.7%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLACID trial;[114] Agarwal et al; preprint; 2020	Patients with severe COVID-19. 235 assigned to convalescent plasma 200 ml twice in 24 h and 229 assigned to standard of care	Median age 52 ± 18, male 76.3%, hypertension 37.3%, diabetes 43.1%, chronic lung disease 3.2%, coronary heart disease 6.9%, chronic kidney disease 3.7%, cerebrovascular disease 0.9%, cancer 0.2%, obesity 7.1%	Corticosteroids 64.4%, remdesivir 4.3%, hydroxychloroquine 67.7%, lopinavir-ritonavir 14.2%, tocilizumab 9%, azithromycin 63.8%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse	

				events outcomes results.	
PLASM-AR trial;[115] Simonovich et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 228 assigned to convalescent plasma and 105 assigned to standard of care	Mean age 62 ± 20, male 67.6%, hypertension 47.7%, diabetes 18.3%, COPD 7.5%, asthma 4.2%, coronary heart disease 3.3%, chronic kidney disease 4.2%	Corticosteroids 93.3%, hydroxychloroquine 0.3%, lopinavir-ritonavir 3%, tocilizumab 4.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
ILBS-COVID-02 trial;[116] 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;[117] preprint; 2020	Patients with severe to critical COVID-19. 20 assigned to convalescent plasma 200 ml twice and 20 assigned to standard of care	Mean age 51.6 ± 13.7, male 80%, hypertension 25%, diabetes 30%, COPD 7.5%, asthma %, coronary heart disease 10%, chronic kidney disease 5%	Corticosteroids 12.5%, hydroxychloroquine 92.5%, lopinavir-ritonavir 85%, tocilizumab 30%, azithromycin 87.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Fundacion INFANT-Plasma trial;[118] 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;[119] Ray et al; peer reviewed;	Patients with severe COVID-19. 40	Mean age 61 ± 11.5, male 71.2%,	Steroids 50%, remdesivir 31.2%,	High for mortality and mechanical ventilation;	

2020	assigned to convalescent plasma 200 ml and 40 assigned to standard of care	hypertension 43.7%, diabetes 58.7%, COPD 6.2%, CHD 10%, cerebrovascular disease 2.5%	hydroxychloroquine 37.5%	high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RECOVERY-Plasma trial;[120] Horby et al; Other; 2020	Patients with severe to critical COVID-19 infection. 5795 assigned to CP 275 ml a day for two days and 5763 assigned to SOC	Median age 63.5 ± 14.7, male 64.2%, diabetes 26%, COPD 24%, CHD 22%	Corticosteroids <1%, lopinavir-ritonavir <1%, azithromycin 10%, colchicine 14%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Baklaushev et al;[121] peer reviewed; 2020	Patients with moderate to severe COVID-19. 46 assigned to CP 640 ml divided in two infusions and 20 assigned to SOC	Age 56.3 ± 11, male 60.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
O'Donnell et al;[122] Peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 150 assigned to CP one infusion and 73 assigned to SOC	Median age 61 ± 23, male 65.9%, hypertension 33.6%, diabetes 36.8%, COPD 9%, CHD 37.7%, CKD 9.4%, obesity 48.8%	Corticosteroids 81%, remdesivir 6%, hydroxychloroquine 6%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Sensitivity analysis including loss to follow-up patients significantly modified	

				results. At the time mortality was measured the number of patients on IMV was significantly higher in the intervention arm.	
Beltran Gonzalez et al;[123] preprint; 2021	Patients with severe to critical COVID-19 infection. 130 assigned to CP 200 ml a day for 2 days and 60 assigned to IVIG	Mean age 58 ± 25, male 62.6%, hypertension 35.2%, diabetes 34.7%, COPD 4.7%, CHD 3.1%, CKD 3.1%, cerebrovascular disease 1.05%, cancer 0.53%, obesity 41.5%	Corticosteroids 82.6%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Pouladzadeh et al;[124] peer reviewed; 2021	Patients with severe COVID-19 infection. 30 assigned to CP 500 ml once or twice and 30 assigned to SOC	Mean age 55.3 ± 13.6, male 55%, comorbidities 50%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SBU-COVID19 - Convalescent Plasma trial;[125] Bennett-Guerrero et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 59 assigned to CP 480 ml once and 15 assigned to SOC	Mean age 65.5 ± 16.6, male 59.5%, hypertension 68.9%, diabetes 33.7%, COPD 12.1%, CHD 17.6%, CKD 9.5%, cerebrovascular disease 14.8%, immunosuppressive therapy 8.1%	Corticosteroids 60.8%, remdesivir 24.3%, hydroxychloroquine 31%, tocilizumab 21.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Salman et al;[126] peer reviewed; 2021	Patients with severe COVID-19 infection. 15 assigned to CP 250 ml once and 15	Median age 57 ± 10, male 70%, diabetes 30%, asthma 16.6%, cerebrovascular disease	Corticosteroids 76.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	

	assigned to SOC	43.3%		and adverse events	
CAPSID trial;[127] Koerper et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to CP 850 ml in three infusions and 52 assigned to SOC	Mean age 60 ± 13, male 73.3%, hypertension 56.2%, diabetes 31.4%, COPD 16.2%, CHD 21.9%, cancer 4.7%, obesity 54.2%	Corticosteroids 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP trial;[128] Green et al; 2021	Patients with moderate to critical COVID-19 infection. 1075 assigned to CP 550-700 ml and 904 assigned to SOC	Mean age 62 ± 12.9, male 67.6%, diabetes 30.9%, COPD 23.2%, asthma 19.4%, CHD 8.1%, CKD 10.4%, immunosuppressive therapy 6.4%, cancer 1.4%	Corticosteroids 93.4%, remdesivir 45.1%, tocilizumab 2%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CONCOR-1 trial;[129] Bégin et al; preprint; 2021	Patients with severe COVID-19 infection. 614 assigned to CP 500 ml and 307 assigned to SOC	Mean age 67.5 ± 15.6, male 59.1%, diabetes 35%, COPD 24.1%, CHD 62%	Corticosteroids 80.4%, azithromycin 44.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLACOVID trial;[130] Sekine et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 80 assigned to CP 300 ml twice and 80 assigned to SOC	Median age 60.5 ± 20, male 58.1%, hypertension 61.3%, diabetes 39.4%, COPD 13.8%, CHD 21.9%, obesity 56.9%	Corticosteroids 98.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

				Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVIDIT trial;[131] Kirenga et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 69 assigned to CP 150 -300 ml twice and 67 assigned to SOC	Mean age 50 ± 23.5, male 71.3%, hypertension 36%, diabetes 32%, asthma 3.7%, obesity 33.3%	Corticosteroids 58.8%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
C3PO trial;[132] Korley et al; peer reviewed; 2021	Patients with early mild to moderate COVID-19 infection with risk factors for severe disease. 257 assigned to CP 250 ml and 254 assigned to SOC	Median age 54 ± 21, male 46%, hypertension 42.3%, diabetes 27.8%, COPD 6.1%, CHD 10%, CKD 5.3%, cancer 0.8%, obesity %	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
DAWn-Plasma trial;[133] Devos et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 320 assigned to CP 200 to 250 ml once or twice and 163 assigned to SOC	Mean age 62 ± 14, male 68.7%, hypertension %, diabetes 29.6%, COPD 9.4%, asthma 10.1%, CHD 14.1%, CKD 13.4%,	Corticosteroids 66.4%, remdesivir 14.8%, hydroxychloroquine 1.4%, lopinavir-ritonavir 0.4%, tocilizumab 0.6%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PennCCP2 trial;[134] Bar et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 40 assigned to CP two units and 39 assigned to SOC	Mean age 63 , male 45.6%, hypertension 67.1%, diabetes 40.5%, COPD 29.1%, CHD 29.1%, CKD 32.9%, immunosuppression	Corticosteroids 83.5%, remdesivir 81%, hydroxychloroquine 2.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

		13.9%, cancer 26.6%, obesity 45.6%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
TSUNAMI trial;[135] Manichetti et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 231 assigned to CP 200ml a day for 1 to 3 days and 239 assigned to SOC	Median age 64 ± 20, male 64.3%, hypertension 37.8%, diabetes 19.2%, COPD 5.7%, CKD 4.7%, cancer 3.6%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COnV-ert & CoV-Early trial;[136] Millat-Martinez et al; other; 2021	Patients with mild to moderate COVID-19 infection. 390 assigned to CP 200 to 300 ml once and 392 assigned to SOC	Median age 58 ± 11, male 66.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
CSSC-004 trial;[137] Sullivan et al; preprint; 2021	Patients with mild COVID-19 infection. 592 assigned to CP 250 ml and 589 assigned to SOC	Median age 44, male 43%, hypertension 23.3%, diabetes 8.4%, asthma 11.2%, CHD 2%, CKD 0.9%, cerebrovascular disease 0.2%, cancer 0.5%, obesity 17.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
COP20 trial;[138] Holm et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 17 assigned to CP 200 to 250 ml on three consecutive days and 14 assigned to SOC	Mean age 73.2 ± , male 61.3%, hypertension 41.9%	Corticosteroids 71%, remdesivir 10%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

CONTAIN COVID-19 trial;[139] Ortigoza et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 463 assigned to CP 250 ml once and 463 assigned to SOC	Median age 63, male 59.1%, hypertension 60.7%, diabetes 35.3%, COPD %, asthma 11.7%, CHD 42.9%, CKD 10.5%, cancer 11.3%,	Corticosteroids 76.6%, remdesivir 57.1%, hydroxychloroquine 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
IMPACT trial;[140] Baldeón et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 63 assigned to CP 5 ml/kg and 95 assigned to SOC	Mean age 55.5, male 67.7%, hypertension 22.2%, diabetes 19.6%, obesity 24.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
De Santis et al;[141] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 36 assigned to CP 600 ml a day for 3 days and 71 assigned to SOC	Mean age 59.8, male 62.6%, hypertension 56%, diabetes 38.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Balcells et al;[142] peer reviewed; 2020	Patients with moderate to severe COVID-19. 28 assigned to convalescent plasma at enrolment, 200 mg twice and 30 assigned to convalescent plasma when clinical deterioration was observed (43.3% received CP in this arm)	Mean age 65.8 ± 65, male 50%, hypertension 67.2%, diabetes 36.2%, chronic lung disease %, asthma 5.1%, coronary heart disease %, chronic kidney disease 8.6%, cerebrovascular disease 5.1%, immunosuppression 12%, cancer 7%, obesity 12%	Corticosteroids 51.7%, hydroxychloroquine 12%, lopinavir-ritonavir 1.7%, tocilizumab 3.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Non-RCT					
Joyner et al;[143] 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%

Crizanlizumab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CRITICAL trial;[144] Leucker et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to crizanlizumab 5 mg/kg once and 20 assigned to SOC	Mean age 56.6, male 54.5%, hypertension 70.4%, diabetes 43.1%, COPD 9.1%, asthma 6.8%, CHD 11.3%, CKD 11.3%, cerebrovascular disease 2.2%,	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
Dapagliflozin **Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DARE-19 trial;[145] Kosiborod et al; peer reviewed; 2021	Patients with moderate COVID-19 infection and cardiometabolic risk factors. 625 assigned to dapagliflozin 10 mg for 30 days and 625 assigned to SOC	Mean age 61.4 ± 13.5, male 57.4%, hypertension 84.8%, diabetes 50.9%, COPD 4.6%, CHD 7.2%, CKD 6.6%, obesity 48.1%	Corticosteroids 28.4%, remdesivir 18%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.76 (95%CI 0.51 to 1.12); RD -3.8% (95%CI -7.8% to 1.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.02 (95%CI 0.98 to 1.06); RD 1.2% (95%CI -1.2% to

					3.6%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Darunavir-cobicistat **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DC-COVID-19 trial;[146] Chen et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 15 assigned to darunavir-cobicistat 800 mg/150 mg once a day for 5 days and 15 assigned to standard of care	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, coronary heart disease 26.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information **Hospitalization:** No information
Dimethyl sulfoxide (DSMO) (nasal spray) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hosseinzadeh et al;[147] preprint; 2021	Patients exposed to COVID-19 infection. 116 assigned to DSMO three applications a day for one month and 116 assigned to SOC	Mean age 37.2 ± 8.7	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** No information
Doxycycline **Doxycycline does not improve time to symptom resolution. Further research is needed.**					
Study; publication status	**Patients and interventions**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care**

	analyzed				and GRADE certainty of the evidence
RCT					
DOXYCOV trial;[148] Sobngwi et al; preprint; 2021	Patients with mild COVID-19 infection. 92 assigned to doxycycline 200 mg a day for 7 days and 95 assigned to SOC	Mean age 39 ± 13, male 52.4%, hypertension 1.1%, asthma 1.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1 (95%CI 0.97 to 1.03); RD 0% (95%CI -1.8% to 1.8%); High certainty ⨁⨁⨁⨁ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** RR 1.13 (95%CI 0.73 to 1.74); RD 0.6% (95%CI -1.3% to 3.6%); Low certainty ⨁⨁◯◯
PRINCIPLE trial;[149] Butler et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 780 assigned to doxycycline 200 mg once followed by 100 mg a day for 7 days and 948 assigned to SOC	Mean age 61.1 ± 7.9, male 44.1%, hypertension 41.5%, diabetes 18%, COPD 37.3%, CHD 14.2%, cerebrovascular disease 6.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
DOXPREVENT.ICU trial;[150] Dhar et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 192 assigned to doxycycline 200 mg a day and 195 assigned to SOC	Mean age 58.6, male 63.8%, hypertension 53.2%, diabetes 35.7%, COPD 9%, asthma 7.5%, CHD 13.4%, cancer 1.3%,	Corticosteroids 81.4%, tocilizumab 1.3%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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;[151] 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 ⊕◯◯◯
EAT-DUTA AndroCoV trial;[152] Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 43 assigned to dutasteride 0.5 mg a day for 30 days and 44 assigned to SOC	Mean age 41.9 ± 12.4, male 100%, hypertension 21.8%, diabetes 9.2%, COPD 0%, asthma 1.1%, CHD 1.1%, cancer 0%, obesity 10.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Significant lost to follow-up.	

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;[153] Delgado-Enciso et al; preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to electrolyzed saline nebulizations 4 times a day for 10 days and 39 assigned to standard of	Mean age 47 ± 14.6, male 53.5%, hypertension 18.9%, diabetes 11.9%	Corticosteroids 3.65%, 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 information

	care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⨁◯◯◯
ICU-VR trial; Gutiérrez-García et al;[154] peer reviewed; 2021	Patients exposed COVID-19 infection. 79 assigned to electrolyzed saline nasal sprays and gargles three times a day and 84 assigned to SOC	Mean age 42 ± , male 26.4%, hypertension 6.7%, diabetes 4.9%, obesity 13.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Emtricitabine/tenofovir

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Gaitan-Duarte et al;[155] preprint; 2021	Patients with moderate to severe COVID-19 infection. 160 assigned to emtricitabine/ tenofovir 200/300 mg once a day for 10 days and 161 assigned to SOC	Mean age 55.4 ± 12.8, male 68%, hypertension 28%, diabetes 12%, COPD 4%	Corticosteroids 98%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No

					information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Endothelial dysfunction protocol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
MEDIC-LAUMC trial;[156] Matli et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 17 assigned to Nicorandil 20 mg a day, L-arginine 3 gr a day, Folate 5mg a day, Nebivolol 2.5 to 5mg a day, and atorvastatin 40 mg a day for 14 days, and 20 assigned to SOC	Mean age 56.6, male 81.8%, hypertension 27%, diabetes 21.6%, asthma 10.8%, CHD 5.4%, CKD 2.7%, cancer 2.7%,	Corticosteroids 91.9%, remdesivir 59.5%, tocilizumab 8.1%	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:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Enisamium Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Holubovska et al;[157] Preprint; 2020	Patients with moderate to severe COVID-19. assigned to enisamium 500 mg 4 times a day for 7 days or SOC. Number of patients in each arm not reported.	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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

COVIDENZA trial;[158] Welen et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 30 assigned to enzalutamide 160 mg a day for 5 days and 12 assigned to SOC	Median age 64.9, hypertension 45.2%, diabetes 19%, asthma 14.3%, CHD 9.5%, cancer 11.9%,	Corticosteroids 85.7%, remdesivir 28.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**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

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;[159] preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to famotidine 160 mg for up to 14 days and 10 assigned to SOC	Mean age 47.5 ± 13, male 60%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Favipiravir Favipiravir may increase mortality and mechanical ventilation requirements and it probably does not improve time to symptom resolution. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al; preprint;[160] 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days	Mean age not reported male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.18 (95%CI 0.83 to 1.69); RD 2.9% (95%CI -2.7% to 11%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 1.27 (95%CI 0.91 to 1.76); RD 4.7% (95%CI -1.6% to 13.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.94 to 1.1); RD 1.2% (95%CI -3.6% to 6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.80 (95%CI 0.46 to 1.41); RD -2% (95%CI -5.5% to 4.2%); Very low
Ivashchenko et al[161] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 20 assigned to favipiravir 1600 mg once followed by 600 mg twice a day for 12 days, 20 assigned to favipiravir and 20 assigned to standard of care	Mean age not reported	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Lou et al;[65] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%,	Antivirals 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of	

				allocation is probably inappropriate.	certainty ⊕◯◯◯ **Hospitalization:** RR 0.89 (95%CI 0.16 to 5.05); RD -0.5% (95%CI -4% to 19.4%); Very low certainty ⊕◯◯◯
Doi et al;[162] peer-reviewed; 2020	Patients with mild COVID-19. 44 assigned to favipiravir (early) 1800 mg on day 1 followed by 800 mg twice daily for 10 days and 45 assigned to favipiravir (late) 1800 mg on day 6 followed by 800 mg twice daily for 10 days	Median age 50 ± 26.5, male 61.4%, comorbidities 39%	Corticosteroids 2.3%, ATB 12.5%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Dabbous et al;[153] preprint; 2020	Patients with mild to moderate COVID-19. 50 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 10 days and 50 assigned to hydroxychloroquine + oseltamivir 800 mg once followed by 400 mg a day for 10 days + 75 mg a day for 10 days	Mean age 36.3 ± 12, male 50%, any comorbidities 15%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Zhao et al;[164] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to TCZ 400 mg once or twice and 5 assigned to favipiravir + TCZ	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khamis et al;[165] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 44 assigned to favipiravir	Mean age 55 ± 14, male 58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart	Corticosteroids 67%, tocilizumab 35%, convalescent plasma 58%	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	+ inhaled interferon beta-1B 1600 mg once followed by 600 mg twice a day for 10 days + 8 million UI for 5 days and 45 assigned to standard of care	disease 15%, chronic kidney disease 20%		infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Ruzhentsova et al;[166] preprint; 2020	Patients with mild to moderate COVID-19. 112 assigned to favipiravir 1800 mg once followed by 800 mg twice a day for 10 days and 56 assigned to standard of care	Mean age 42 ± 10.5, male 47%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Promomed; NCT04542694; Other; 2020	Patients with moderate COVID-19. 100 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 14 days and 100 assigned to standard of care	Mean age 49.68 ± 13.09, male 48.5%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Udwadia et al;[167] 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;[168] peer-reviewed; 2020	Patients with moderate to severe	Mean age 49.7 ± 13, male 50%, hypertension	NR	High for mortality and mechanical ventilation;	

	COVID-19. 100 assigned to favipiravir 3200 mf once followed by 1200 mg a day for 14 days and 100 assigned to SOC	28.5%, diabetes 9%, COPD 5%, asthma %, CHD 6%,		high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Solaymani-Dodaran et al;[169] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 190 assigned to favipiravir 1800 mg a day for 7 days and 183 assigned to lopinavir-ritonavir	Mean age 57.6 ± 17.3, male 55%, hypertension 34.9%, diabetes 25.7%, COPD 3.5%, asthma 3.8%, CHD 10.7%, CKD 1.6%	Corticosteroids 27.6%, remdesivir 1.1%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Zhao et al;[170] peer reviewed; 2021	Patients with COVID-19 infection who were discharged from hospital. 36 assigned to Favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 19 assigned to SOC	Mean age 55.7 ± 13.6, male 45.5%, hypertension 30.9%, diabetes 14.5%, CHD 7.3%, cancer 7.3%	Corticosteroids 3.6%, remdesivir 0%, hydroxychloroquine 5.5%, lopinavir-ritonavir 16.4%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
FACCT trial;[171] Bosaeed et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 125 assigned to favipiravir + HCQ 3600 mg + 800 mg once followed by 2400 mg + 400 mg a day for 5 days and 129 assigned to SOC	Mean age 52 ± 13, male 59%, hypertension 40.9%, diabetes 42.1%, asthma 11.8%, CKD 2.4%	Corticosteroids 88.6%, tocilizumab 9%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Shinkai et al;[172] peer reviewed; 2021	Patients with moderate COVID-19 infection. 107 assigned to favipiravir 3200 mg once followed by	Mean age 46.2, any comorbidities 75.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	1600 mg a day for 14 days and 49 assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
FIGHT-COVID-19 trial;[173] Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800mg a day or Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day or favipiravil 6000mg followed by 2400mg + Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day for 7 to 14 days.	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
CVD-04-CD-001 trial;[174] Shenoy et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 175 assigned to favipiravir 3600mg on day 1 followed by 1600mg a day for 10 days and 178 assigned to SOC	Mean age 51.9 ± 12.5, male 67.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Holubar et al;[175] preprint; 2021	Patients with mild to moderate COVID-19 infection. 59 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 10 days and 57 assigned to SOC	Mean age 43 ± 12, male 51.9%, hypertension 8.6%, diabetes 8.6%, COPD 4.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Malaysian Favipiravir Study trial;[176] Chuah et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 250 assigned to favipiravir 3601 mg once followed by 1600 mg a day for 5 days and 250 assigned to SOC	Mean age 62.5 ± 8, male 48.4%, hypertension 80.2%, diabetes 49.8%, COPD 1.4%, asthma 7.4%, CHD 15%, CKD 1.4%, immunocompromised therapy 0.4%, cancer 1.4%, obesity 20.6%	Corticosteroids 24.6%, tocilizumab 2%, vaccinated 0.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
FAVI-COV-US201 trial;[177] Finberg et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 25 assigned to favipiravir 3600mg once folowed by 2000mg a day for 14 days and 25 assigned to SOC	Mean age 57.2 ± 13.14, 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.	
Avi-Mild trial;[178] Bosaeed et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 112 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 5 to 7 days and 119 assigned to SOC	Median age 37, male 67%, hypertension 6%, diabetes 10.8%, COPD %, asthma 3.4%, CHD 0.4%, obesity 16.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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

	COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to HCQ	NR%, diabetes 27.8%, chronic lung disease 1.9%		ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Finasteride **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zarehoseinzade et al;[180] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to finasteride 5 mg a day for 7 days and 40 assigned to SOC	Mean age 72 ± 14, male 100%, hypertension 66.3%, diabetes 25%, COPD 12.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

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

Fluvoxamine

Fluvoxamine probably reduces hospitalizations and may not increase severe adverse events. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Lenze et al;[181] 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**
TOGHETER-Fluvoxamine trial;[182] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 741 assigned to Fluvoxamine 100mg a day for 10 days and 756 assigned	Median age 50 ± 18, male 42.5%, hypertension 13.2%, diabetes 16.5%, COPD 0.6%, asthma 1.9%, CHD 1.1%, CKD 0.3%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes:	

	to SOC	obesity 0.2%			**studies):** No information **Adverse events:** RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.77 (95%CI 0.58 to 1.02); RD -1.1% (95%CI -2% to 0.1%); Moderate certainty ⊕⊕⊕◯

Fostamatinib

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Strich et al;[183] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to fostamatinib 300 mg a day for 14 days and 29 assigned to SOC	Mean age 55.6 ± 13.7, male 79.7%, hypertension 54.2%, diabetes 37.3%, asthma 11.9%, CHD 13.6%, obesity 57.6%	Corticosteroids 100%, remdesivir 100%, convalescent plasma 42.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis**

					studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
GB0139 (inhaled) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DEFINE trial;[184] Gaughan et al; preprint; 2021	Patients with severe COVID-19 infection. 20 assigned to GB0139 (inhaled) and 21 assigned to SOC	Mean age 65, male 56%, hypertension 39%, diabetes 17%, asthma 14.6%, CHD 24.4%, CKD 7.3%, cancer 9.7%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

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;[185] peer reviewed; 2020	Patients with severe to critical COVID-19. 38 assigned to helium 50% to 79% mixed with oxygen and 32 assigned to SOC	Mean age 53.5 ± 16, male 51.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Hesperidin

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

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

HESPERIDIN trial;[186] Dupuis et al; preprint; 2021	Patients with mild COVID-19 infection. 104 assigned to hesperidin 1000 mg once a day and 107 assigned to SOC	Mean age 41 ± 12.1, male 44.9%, hypertension 10.6%, diabetes 3.2%, COPD 0.9%, asthma 13.5%, CHD 0%, cerebrovascular disease 0%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.87 (95%CI 0.57 to 1.34); RD -7.9% (95%CI -26.1% to 20.6%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

Hemadsorption

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CYTOCOV-19 trial;[187] Jarczak et al; preprint; 2021	Patients with critical COVID-19 infection. 12 assigned to hemadsorption and 12	Mean age 64.5 , male 75%, hypertension 66.6%, diabetes 33.3%, CHD 4%, CKD 25%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical**

	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

Hydroxychloroquine and chloroquine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CloroCOVID19 trial;[188] Borba et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 41 assigned to chloroquine 600 mg twice a day for 10 days and 40 assigned to chloroquine 450 mg twice on day 1 followed by 450 mg once a day for 5 days	Mean age 51.1 ± 13.9, male 75.3%, hypertension 45.5%, diabetes 25.5%, chronic lung disease NR%, asthma 7.4%, coronary heart disease 17.9%, chronic kidney disease 7.4%, alcohol use disorder 27.5%, HIV 1.8%, tuberculosis 3.6%,	Azithromycin 100%, oseltamivir 89.7%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.93 to 1.24); RD 1.2% (95%CI -1.2% to 4.2%); Moderate certainty
Huang et al;[189] peer-	Patients with	Mean age 44 ± 21, male	NR	High for mortality and	

reviewed; 2020	moderate to severe COVID-19 infection. 10 assigned to chloroquine 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	59.1%		invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% to 6.1%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.87 (95%CI 0.65 to 1.15); RD -2.2% (95%CI -6.1% to 2.7%); Low certainty ⊕⊕◯◯ **Severe Adverse events:** RR 0.94 (95%CI 0.66 to 1.34); RD -0.6% (95%CI -3.5% to 3.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
RECOVERY - Hydroxychloroquine trial;[190] 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;[191] 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;[192] Boulware et al; peer-reviewed; 2020	Patients exposed to COVID-19. 414 assigned to hydroxychloroquine	Median age 40 ± 6.5, male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	7.6%, comorbidities 27.4%		infection, and adverse events Notes: Significant loss of information that might have affected the study's results.	
Cavalcanti et al trial;[193] Cavalcanti et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 159 assigned to hydroxychloroquine 400 mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to standard of care	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%, diabetes 19.1%, chronic lung disease 1.8%, asthma 16%, coronary heart disease 0.8%, chronic kidney disease 1.8%, cancer 2.9%, obesity 15.5%	Corticosteroids 1.5%, ACE inhibitors 1.2%, ARBs 17.4%, NSAID 4.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Kamran SM et al trial;[194] Kamran et al; preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to hydroxychloroquine 400 mg twice a day once then 200 mg twice a day for 4 days and 151 assigned to standard of care	Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%	NR	High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PET trial;[195] 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;[196] Mitja et al; preprint; 2020	Patients with mild COVID-19 infection. 136 assigned to hydroxychloroquine	Mean age 41.6 ± 12.6, male 49%, comorbidities 53.2%	NR	High for symptom resolution, infection, and adverse events	

	800 mg once followed by 400 mg a day for 6 days and 157 assigned to standard of care			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tang et al; peer-reviewed;[197] 2020	Patients with mild to moderate COVID-19 infection. 75 assigned to hydroxychloroquine 1200 mg daily for three days followed by 800 mg daily to complete 7 days and 75 assigned to standard of care	Mean age 46.1 ± 14.7, male 54.7%, hypertension 6%, diabetes 14%, other comorbidities 31%	Corticosteroids 7%, lopinavir-ritonavir 17%, umifenovir 47%, oseltamivir 11%, entecavir 1%, ATB 39%, ribavirin 47%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcome results.	
Chen et al;[198] preprint; 2020	Patients with moderate COVID-19 infection. 31 assigned to hydroxychloroquine 200 mg twice a day for 5 days and 31 assigned to standard of care	Mean age 44 ± 15.3, male 46.8%,	ATB 100%, IVIG 100%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Chen et al;[199] preprint; 2020	Patients with moderate COVID-19 infection. 18 assigned to hydroxychloroquine 200 mg twice a day for 10 days, 18 assigned to chloroquine and 12 assigned to standard of care	Mean age 47.4 ± 14.46, male 45.8%, hypertension 16.7%, diabetes 18.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Chen et al;[200] preprint; 2020	Patients with mild to severe COVID-19	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and invasive mechanical	

	infection. 21 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg twice a day for 6 days and 12 assigned to standard of care			ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HC-nCoV trial;[201] Jun et al; peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 15 assigned to hydroxychloroquine 400 mg once a day for 5 days and 15 assigned to standard of care	Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%, chronic lung disease 3.3%	Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Abd-Elsalam et al;[202] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg tablets twice daily for 15 days and 97 assigned to standard of care	Mean age 40.7 ± 19.3, male 58.8%, chronic kidney disease 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PREP trial;[203] 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;[204] Ulrich et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 67 assigned to hydroxychloroquine 800 mg on day 1 followed by 200 mg twice a day for 2 to 5 days and 61 assigned to standard of care	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart disease 26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%	Corticosteroids 10.2%, remdesivir 0.8%, lopinavir-ritonavir 0.8%, azithromycin 23.4%, convalescent plasma 13.3%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
PrEP_COVID trial;[205] Grau-Pujol et al; preprint; 2020	Patients exposed to COVID-19. 142 assigned to hydroxychloroquine 400 mg daily for four days followed by 400 mg weekly for 6 months and 127 assigned to standard of care	Median age 39 ± 20, male 26.8%, hypertension 1.8%, diabetes 0.4%, chronic lung disease 2.6%	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
PATCH trial;[206] 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;[207] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 947 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 10 days and 906 assigned to standard of care	Age < 70 years 61%, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%, chronic kidney disease %	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Davoodi et al;[179] peer-reviewed; 2020	Patients with moderate to severe	Mean age 57.7 ± 8.4, male 59%, hypertension	NR	High for mortality and invasive mechanical	

	COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	NR%, diabetes 27.8%, chronic lung disease 1.9%		ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVID-19 PEP (University of Washington) trial; Barnabas et al;[208] Abstract; 2020	Patients exposed to COVID-19. 381 assigned to hydroxychloroquine 400 mg for three days followed by 200 mg for 11 days and 400 assigned to standard of care	Median age 39 ± 24, male 40%	NR	Low for symptom resolution, infection, and adverse events	
PETAL trial;[209] Self et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 242 assigned to hydroxychloroquine 800 mg on day 1 followed for 200 mg twice a day for 5 days and 237 assigned to standard of care	Median age 58.5 ± 24.5, male 56%, hypertension 52.8%, diabetes 34.6%, COPD 8.1%, asthma %, coronary heart disease %, chronic kidney disease 8.8%,	Corticosteroids 18.4%, remdesivir 21.7%, azithromycin 19%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
HAHPS trial;[210] Brown et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19. 42 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 5 days and 43 assigned to azithromycin	Median age 55 ± 23, male 61%, diabetes 26%, coronary heart disease 11%, chronic kidney disease 9%, cerebrovascular disease 8%, cancer 2%	Corticosteroids 15%, remdesivir 11%, lopinavir-ritonavir 1%, tocilizumab 24%, convalescent plasma 24%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Co-interventions were not balanced between study arms	
HYCOVID trial;[211] Dubee et al; peer reviewed; 2020	Patients with mild to moderate COVID-19. 124 assigned to	Median age 77 ± 28, male 48.4%, hypertension 53.4%,	Corticosteroids 9.6%, lopinavir-ritonavir 1.2%, azithromycin	Low for mortality and mechanical ventilation; low for symptom	

	hydroxychloroquine 800 mg once followed by 400 mg a day for 8 days and 123 assigned to standard of care	diabetes 17.3%, COPD 11.2%, cerebrovascular disease 17.3%, obesity 27.7%	8.4%	resolution, infection, and adverse events	
Q-PROTECT trial;[212] 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;[213] peer reviewed; 2020	Patients with mild to moderate COVID-19. 44 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 10 days and 48 assigned to CQ	Mean age 35.5 ± 16.8, male 48.9%, comorbidities 18.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
HYDRA trial;[214] Hernandez-Cardenas et al; Preprint; 2020	Patients with severe to critical COVID-19. 106 assigned to HCQ 400 mg a day for 10 days and 108 assigned to SOC	Mean age 49.6 ± 12, male 75%, hypertension 16%, diabetes 47%, CHD 11%, CKD 0%, obesity 66%	Corticosteroids 52.4%, lopinavir-ritonavir 30.4%, tocilizumab 2.5%, azithromycin 24.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COVID-19 Early Treatment trial;[215] Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to HCQ 800 mg once followed by 400 mg a day for 10 days, 65 assigned to HCQ + AZT 500 mg once followed by 250 mg a day for 5 days and 65 assigned to SOC	Median age 37 ±, male 43.3%, hypertension 20.9%, diabetes 11.6%, COPD 9.3%, asthma 1.6%, immunosuppressive therapy 0.8%, obesity 76%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Purwati et al;[216] peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to HCQ 200 mg a day and 119 to SOC	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Beltran et al;[217] Preprint; 2020	Patients with moderate to severe COVID-19. 33 assigned to HCQ 800 mg once followed by 400 mg a day for 5 days and 37 assigned to SOC	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
PATCH 1 trial;[218] Amaravadi et al; Preprint; 2020	Patients with mild COVID-19 infection. 17 assigned to HCQ 400 mg a day and 17 assigned to SOC	Median age 53 ± 37, male 26%, hypertension 18%, diabetes 9%, , asthma 12%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Bermejo Galan et al;[219] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to ivermectin 42 mg and 115 assigned to HCQ or CQ	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer 3%, obesity 37.5%	Corticosteroids 98%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Seet et al;[220] peer reviewed; 2021	Patients exposed to COVID-19 infection. 432 assigned to HCQ 400 mg once followed	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection,	

	by 200 mg a day for 42 days and 619 assigned to SOC (vitamin C)			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOGETHER trial;[221] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to HCQ 800 mg once followed by 400 mg a day for 9 days and 227 assigned to SOC	Mean age 53, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CLOROTRIAL trial;[222] Réa-Neto et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to HCQ 800 mg once followed by 400 mg a day for 5 days and 52 assigned to SOC	Median age 53 ±, male 66.7%, hypertension 38.1%, diabetes 25.7%, COPD 8.6%, immunosuppressive therapy 5.7%	Corticosteroids 72.4%, azithromycin 89.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
CHEER trial;[223] Syed et al; peer reviewed; 2021	Health care workers exposed to COVID-19 infection. 154 assigned to HCQ 200-400 mg once a week to three weeks and 46 assigned to SOC	Mean age 30.6 ± 8, male 54.5%, hypertension 4.5%, diabetes 3.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
ProPAC-COVID trial;[224] Sivapalan et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 61 assigned to HCQ + AZT 400 mg plus 500 to 250 mg a day and 56 assigned to SOC	Median age 65 ± 25, male 56%, hypertension 38%, diabetes 24%, COPD 9%, asthma 22%, CHD 7%, CKD 7%	Corticosteroids 32%, remdesivir 25%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

HONEST trial;[225] Byakika-Kibwika et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 55 assigned to HCQ 800 mg once followed by 400 mg a day for 5 days and 50 assigned to SOC	Median age 32 ± 27, male 72%, hypertension 2.8%, diabetes 2.8%, COPD %, CHD 0.9%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ALBERTA HOPE-Covid19 trial;[226] Schwartz et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 111 assigned to HCQ 800 mg once followed by 400 mg for 5 days and 37 assigned to SOC	Mean age 46.8 ± 11.2, male 55.4%, hypertension 27.8%, diabetes 19.6%, asthma 13.5%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
HERO-HCQ trial ;[227] Naggie et al ; preprint ; 2021	Patients with exposed to COVID-19 infection. 683 assigned to HCQ 1200 mg once followed by 400 mg daily for 29 days and 676 assigned to SOC	Mean age 43.6 ± , male 44.7%, hypertension 14.6%, diabetes 4%, COPD 0.2%, asthma 9.9%, CHD 0.8%, obesity 33.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Rodrigues et al;[228] peer reviewed; 2021	Patients with mild COVID-19 infection. 42 assigned to HCQ + azithromycin 400/500 mg a day for 7 days and 42 assigned to SOC	Mean age 36.5 ± 9.6, male 40.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Babalola et al;[229] preprint; 2021	Patients with mild to severe COVID-19 infection. 31 assigned to HCQ + AZT 200/500 mg a day for 3 days and 30 assigned to SOC	Mean age 40.4 ± 1.9, male 63%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of	

				allocation probably inappropriate.	
FIGHT-COVID-19 trial;[173] Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800mg a day or Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day or favipiravil 6000mg followed by 2400mg + Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day for 7 to 14 days.	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
SEV-COVID trial;[230] Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 37 assigned to Hydroxychloroquine 400 mg twice on first day followed by 400 mg per oral daily for 10 days + Ribavirin (1.2 g orally as a loading dose followed by 600mg orally every 12 hours) for 10 days and 40 assigned to SOC	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ahmad et al;[231] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to HCQ 800 once followed by 400 mg a day for 5 days or	Mean age 37.6, male 95.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	chloroquine 500 mg a day for 7 days and 50 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
WHIP COVID-19 trial;[232] McKinnon et al; peer reviewed; 2021	Patients with exposed COVID-19 infection. 398 assigned to HCQ 400 mg a week or 400 mg once followed by 200 mg a day and 200 assigned to SOC	Mean age 44.9 ± 11.9, male 42%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
PHYDRA trial;[233] Rojas-Serrano et al; peer reviewed; 2021	Patients with exposed COVID-19 infection. 62 assigned to HCQ 200 mg a day for 60 days and 65 assigned to SOC	Mean age 31.1, male 42.5%, obesity 18.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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;[234] preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric oxygen two sessions a day for 4 days and 9 assigned to SOC	Median age 65.4 ± 7.8, male 60%, hypertension 72%, diabetes 60%, COPD %, asthma 8%, CHD 24%, cancer 4%, obesity 8%	Corticosteroids 92%, tocilizumab 24%, convalescent plasma 80%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment are probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic**
Cannellotto et al;[235] peer reviewed; 2021	Patients with severe COVID-19 infection. 20 assigned to Hyperbaric Oxygen 5 sesions (90 minutes	Mean age 55.2 ± 9.2, male 65%, hypertension 32.5%, diabetes 17.5%, COPD 5%, asthma 5%, CHD %, CKD 5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	duration each) and 20 assigned to SOC	cancer 5%, obesity 35%		Notes: Non-blinded study. Concealment of allocation probably inappropriate. The study was stopped early for benefit.	**infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Hyperimmune anti-COVID-19 intravenous immunoglobulin (C-IVIG) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Ali et al;[236] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to C-IVIG 0.15-0.3 g/kg once and 10 assigned to SOC	Mean age 56.5 ± 13.1, male 70%, hypertension 52%, diabetes 36%, COPD 10%, CHD 8%	Corticosteroids 100%, remdesivir 94%, tocilizumab 6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty
Parikh et al;[237] preprint; 2021	Patients with moderate to severe COVID-19 infection. 30 assigned to C-IVIG 30ml twice and 30 assigned to SOC	Mean age 52 ± 10.1, male 73.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

ITAC trial; Polizzotto et al;[238] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 295 assigned to C-IVIG 400 mg/kg and 284 assigned to SOC	Mean age 59 ± 21, male 57%, hypertension 43%, diabetes 28%, COPD 7%, asthma 10%, CHD 5%, CKD 7%, immunosuppression 5%	Corticosteroids 56%; Vaccinated 2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	⊕◯◯◯ **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;[239] 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

Icosapent ethyl

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
VASCEPA COVID-19 CARDIOLINK-9 trial;[240] kosmopoulos et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 46 assigned to icosapent ethyl 8 g a day for three days followed 4 g a day for 11 days and 49 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

IFX-1

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Vlaar et al;[241] peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1	Mean age 60 ± 9, male 73%, hypertension 30%, diabetes 27%, obesity	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** Very low certainty ⊕◯◯◯

	800 mg IV with a maximum of seven doses and 15 assigned to standard of care	20%		symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Imatinib

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COUNTER-COVID trial;[242] Aman et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 197 assigned to imatinib 800 mg once followed by 400 mg a day for 10 days and 188 assigned to SOC	Median age 64 ± 17, male 69%, hypertension 37.6%, diabetes 25%, COPD 18.4%, asthma 18%, CHD 22%, obesity 38%	Corticosteroids 72%, remdesivir 21%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** RR 1.05 (95%CI 0.84 to 1.32); RD 0.5% (95%CI -1.6% to 3.3%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Indomethacin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Ravichandran et al;[243] preprint; 2021	Patients with moderate COVID-19 infection. 102 assigned to indomethacin 75 mg a day and 108 assigned to SOC	Mean age 47 ± 16, male 56.2%, hypertension 19%, diabetes 29%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Infliximab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
CATALYST trial;[244] Fisher et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 29 assigned to infliximab and 34 assigned to SOC	Median age 64.5 ± 20, male 61.8%	Corticosteroids 94.3%, remdesivir 61.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
INM005 (polyclonal fragments of equine antibodies) **INM005 may not improve symptom resolution and may not increase severe adverse events. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Lopardo et al;[245] peer reviewed; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005 4 mg/kg in two doses on days 1 and 3 and 123 assigned to SOC	Mean age 53.8 ± 12.5, male 65.1%, comorbidities 80%	Corticosteroids 57.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 1.06 (95%CI 0.96 to 1.66); RD 3.6% (95%CI -2.4% to 10.3%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information
Interferon alpha-2b and interferon gamma **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE**

					certainty of the evidence
RCT					
ESPERANZA trial;[246] Esquivel-Moynelo et al; preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to interferon alpha-2b plus interferon gamma twice a week for two weeks (standard care) and 33 assigned to interferon alpha-2b three times a week (IM)	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%, coronary heart disease 6.3%, any comorbidities 50.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, antibiotics 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Interferon beta-1a **IFN beta-1a probably does not reduce mortality nor invasive mechanical ventilation requirements. Inhaled interferon beta-1a may improve time to symptom resolution.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					

Davoudi-Monfared et al;[247] preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three times a week and 39 assigned to standard of care	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	Corticosteroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.98 (95%CI 0.74 to 1.29); RD -0.3% (95%CI -4.2% to 4.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.97 (95%CI 0.83 to 1.14); RD -0.5% (95%CI -2.9% to 2.4%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 0.96 (95%CI 0.92 to 0.99); RD -2.6% (95%CI -4.8% to -3.2%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.03 (95%CI 0.85 to 1.24); RD 0.3% (95%CI -1.5% to 2.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
WHO SOLIDARITY;[207] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2050 assigned to interferon beta-1a three doses over six days of 44 µg and 2050 assigned to standard of care	Age < 70 years 61%, male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%,	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVIFERON trial;[248] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6, 20 assigned to interferon beta-1b 0.25 mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Darazam et al;[249] 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	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	Corticosteroids 1.1%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	

	interferon beta-1a 44 micrograms on days 1, 3 and 6	8.3%, cerebrovascular disease 5.4%, cancer 0.6%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ACTT-3 trial;[250] Kalil et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 487 assigned to interferon beta-1a 44 μg a day for up to four days and 482 assigned to SOC	Mean age 58.7 ± 15.9, male 58%, hypertension 58%, diabetes 37%, COPD 11%, asthma 13%, CKD 12%, obesity 58%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
INTEREST trial;[251] Ranieri et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 144 assigned to Interferon beta-1a 10 μg a day for 6 days and 152 assigned to SOC	Mean age 58, male 65.8%,	Corticosteroids 35.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Monk P et al;[252] 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;[253] peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to interferon beta-1b 250 mcg subcutaneously every	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%,	Corticosteroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very

	other day for two consecutive weeks and 33 assigned to standard of care	coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%		events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯
COVIFERON trial;[249] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6, 20 assigned to interferon beta-1b 0.25 mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
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;[254] Peer reviewed; 2021	Patients with moderate COVID-19 infection. 18 assigned to interferon gamma 500000 IU a day for 5 days and 18 assigned to SOC	Mean age 63 ± 12, male 44%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Interferon kappa plus TFF2 **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Fu et al;[255] peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2 mg once a day for six days and 40 assigned to standard of care	Mean age 35.2 ± 11.2, male 63.7%, hypertension 5%, diabetes 3.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Iota-carrageenan Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
IVERCAR-TUC trial;[256] Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin + iota-carrageenan 12 mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC	Median age 38 ± 12.5, male 42.7%, hypertension 9%, diabetes, 7.3%, CKD 2.1%, obesity 11.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯
CARR-COV-02 trial;[257] Figueroa et al; preprint; 2021	Patients exposed to COVID-19 infection. 196 assigned to Iota-carrageenan 1 puff four times a day for 21 days and 198 assigned to SOC	Mean age 38.6 ± 9.6, male 24.8%, hypertension 4.8%, diabetes 0.2%, COPD 3.3%, cancer 0%, obesity 5%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Itolizumab Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ITOLI-C19-02-I-00 trial;[258] Kumar et al; preprint; 2020	Patients with severe COVID-19. 20 assigned to itolizumab 1.6 mg/kg once followed by 0.8 mg/kg weekly and 10 assigned to standard of care	Mean age 49 ± 13, male 86.6%, hypertension 20%,	Nr	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Ivermectin Ivermectin probably does not improve time to symptom resolution and may not have an important effect on hospitalizations. It is uncertain if it affects mortality, 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;[259] Shouman et al; peer-reviewed; 2020	Patients exposed to COVID-19. 203 assigned to ivermectin 15 to 24 mg and 101 assigned to standard of care	Mean age 38.72 ± 15.94, male 51.3%, hypertension 10.2%, diabetes 8.1%, CKD 1%, asthma 2.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.81 (95%CI 0.5 to 1.33); RD -3% (95%CI -8% to 5.2%); Very Low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** RR 0.9 (95%CI 0.57 to 1.42); RD -1.7% (95%CI -7.4% to 7.3%); Very Low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.96 to 1.1); RD 1.8% (95%CI -2.4% to 6.1%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** RR 0.22 (95%CI 0.09 to 0.53); RD -13.6% (95%CI -15.8% to -8.2%); Very low certainty ⨁◯◯◯
Chowdhury et al;[260] preprint; 2020	Patients with mild to moderate COVID-19. 60 assigned to ivermectin plus doxycycline 200 µgm/kg single dose + 100 mg BID for 10days and 56 assigned to hydroxychloroquine plus azithromycin	Mean age 33.9 ± 14.1, male 72.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Podder et al;[261] 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 is probably	

				inappropriate.	**Adverse events:** RR 1.63 (95%CI 0.62 to 4.32); RD 6.4% (95%CI -3.9% to 33.8%); Very low certainty ⨁◯◯◯ **Hospitalization:** RR 0.67 (95%CI 0.39 to 1.14); RD -1.6% (95%CI -2.9% to 0.7%); Low certainty ⨁⨁◯◯
Hashim et al;[262] preprint; 2020	Patients with mild to critical COVID-19. 70 assigned to ivermectin plus doxycycline 200 µgm/kg two or three doses + 100 mg twice a day for 5 to 10 days and 70 assigned to standard of care	Mean age 48.7 ± 8.6, male %	Corticosteroids 100%, azithromycin 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Mahmud et al;[263] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 183 assigned to ivermectin plus doxycycline 12 mg once + 100 mg twice a day for 5 days and 180 assigned to standard of care	Mean age 39.6 ± 13.2, male 58.8%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events. Notes: 8% of patients were lost to follow-up.	
Elgazzar et al (mild);[264] preprint (now retracted); 2020	Patients with mild to moderate COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 55.2 ± 19.8, male 69.5%, hypertension 11.5%, diabetes 14.5%, COPD %, asthma 5.5%, coronary heart disease 4%, chronic kidney disease %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elgazzar et al (severe);[264] preprint (now retracted); 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 is probably inappropriate.	

Elgazzar et al (prophylaxis);[264] preprint (now retracted); 2020	Patients exposed to COVID-19. 100 assigned to ivermectin 400 µgm/kg twice (second dose after one week) and 100 assigned to standard of care	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Krolewiecki et al;[265] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 20 assigned to ivermectin 0.6 mg/kg for 5 days and 12 assigned to standard of care	Mean age 40.2 ± 12, male 55.5%, hypertension 13.3%, diabetes 15.5%, COPD 11.1%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Niaee et al;[266] 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;[267] 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;[268] 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;[269] peer-reviewed; 2020	Patients with mild COVID-19. 25 assigned to ivermectin 36 mg once and 25 assigned to SOC	Mean age 40.6 ± 17, male 62%, hypertension 26%, diabetes 40%, obesity 12%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Babalola et al;[270] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 42 assigned to ivermectin 12 to 24 mg a week for 2 weeks and 20 assigned to lopinavir-ritonavir	Mean age 44.1 ± 14.7, male 69.4%, hypertension 14.5%, diabetes 3.2%,	Corticosteroids 3.2%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Kirti et al;[271] Preprint; 2020	Patients with mild to moderate COVID-19. 55 assigned to ivermectin 24 mg divided in two doses and 57 assigned to SOC	Mean age 52.5 ± 14.7, male 72.3%, hypertension 34.8%, diabetes 35.7%, COPD 0.9%, asthma 0.9%, CHD 8.9%, CKD 2.7%, cerebrovascular disease 0%, cancer 5.4%, obesity %	Corticosteroids 100%, remdesivir 20.5%, hydroxychloroquine 100%, tocilizumab 6.3%, convalescent plasma 13.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
IVERCAR-TUC trial;[256] Chahla et al; Preprint; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin + iota-carrageenan 12 mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC	Median age 38 ± 12.5, male 42.7%, hypertension 9%, diabetes, 7.3%, CKD 2.1%, obesity 11.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	

				inappropriate.	
Mohan et al;[272] preprint; 2020	Patients with mild to moderate COVID-19 infection. 80 assigned to ivermectin 12 to 24 mg once and 45 assigned to SOC	Mean age 35.3 ± 10.4, male 88.8%, hypertension 11.2%, diabetes 8.8%, CHD 0.8%,	Corticosteroids 14.4%, remdesivir 1.6%, hydroxychloroquine 4%, azithromycin 11.2%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Shahbaznejad et al;[273] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 35 assigned to ivermectin 0.2 mg/kg once and 34 assigned to SOC	Mean age 46.4 ± 22.5, male 50.7%	Chloroquine 75.4%, lopinavir-ritonavir 79.7%, azithromycin 57.9%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Spoorthi et al;[274] Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to ivermectin 0.2 mg/kg once or SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. RoB assessment from secondary sources as publication not available.	
Samaha et al;[275] peer-reviewed (now retracted); 2020	Patients with mild (asymptomatic) COVID-19 infection. 50 assigned to ivermectin 9 to 12 mg or 150 µg/kg once and 50 assigned to SOC	Mean age 31.6 ± 7.7, male 50%, hypertension 8%, diabetes 6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Randomization process and concealment of allocation is probably inappropriate.	

Bukhari et al;[276] Preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to ivermectin 12 mg once and 41 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Okumus et al;[277] peer-reviewed; 2021	Patients with severe COVID-19. 30 assigned to ivermectin 0.2 mg/kg for 5 days and 30 assigned to SOC	Mean age 62 ± 12, male 66%, hypertension 21.6%, diabetes 45%, COPD 1.6%, CHD 1.6%, cancer 1.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Beltran et al;[217] Preprint; 2021	Patients with moderate to severe COVID-19. 36 assigned to ivermectin 12-18 mg once and 37 assigned to SOC	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
Lopez-Medina et al;[278] peer-reviewed; 2021	Patients with mild to moderate COVID-19 infection. 200 assigned to ivermectin 300 µg/kg a day for 5 days and 198 assigned to SOC	Median age 37 ± 19, male 42%, hypertension 13.4%, diabetes 5.5%, COPD 3%, CHD 1.7%, cancer %, obesity 18.9%	Corticosteroids 4.5%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Bermejo Galan et al;[219] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to ivermectin 42 mg and 115 assigned to	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer	Corticosteroids 98%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

	HCQ or CQ	3%, obesity 37.5%			
Pott-Junior et al;[279] peer-reviewed; 2021	Patients with moderate to critical COVID-19 infection. 27 assigned to ivermectin 100 to 400 mcg/kg and 4 assigned to SOC	Mean age 49.4 ± 14.6, male 45.2%	Corticosteroids 32.3%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Kishoria et al;[280] peer-reviewed; 2021	Patients with moderate to severe COVID-19 infection. 19 assigned to ivermectin 12 mg and 16 assigned to SOC	Mean age 38, male 66%	Hydroxychloroquine 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Seet et al;[220] peer-reviewed; 2021	Patients exposed to COVID-19 infection. 617 assigned to ivermectin 12 mg once and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Abd-Elsalam et al;[281] peer-reviewed; 2021	Patients with moderate COVID-19 infection. 82 assigned to ivermectin 12 mg a day for 3 days and 82 assigned to SOC	Mean age 40.8 ± 16.5, male 50%, hypertension 19.5%, diabetes 16.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events	

				Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Biber et al;[282] preprint; 2021	Patients with mild recent onset COVID-19 infection. 47 assigned to ivermectin 48 to 55 mg administered for three days and 42 assigned to SOC	Mean age 35 ± 19, male 78.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: 5.2% of patients lost to follow-up.	
Faisal et al;[283] peer-reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to ivermectin 12 mg a day for 5 days and 50 assigned to SOC	Mean age 46 ± 3, male 80%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Vallejos et al;[284] peer reviewed; 2021	Patients with mild COVID-19 infection. 250 assigned to ivermectin 24-36 mg and 251 assigned to SOC	Mean age 42.5 ± 15.5, male 52.7%, hypertension 23.8%, diabetes 9.6%, COPD 2.8%, asthma 7.2%, CHD 1.8%, cancer 1.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COVER trial;[285] Buonfrate et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 61 assigned to ivermectin 600 to 1200 μg/kg once a day for 5 days and 32 assigned to SOC	Median age 47 ± 27, male 58.1%, diabetes 9.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Manomaipiboon et al;[286] preprint; 2021	Patients with mild COVID-19 infection. 36 assigned to ivermectin 12 mg a day for 5 days and 36 assigned to SOC	Mean age 48.6 ± 14.8, male 37.5%, hypertension 40.3%, diabetes 23.6%, CHD 2.8%, CKD 6.9%, cerebrovascular disease 2.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
I-TECH trial;[287] Chee Loon Lim et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 241 assigned to Ivermectin 6 to 12 mg a day for 5 days and 249 assigned to SOC	Mean age 62.5, male 49.5%, hypertension 82%, diabetes 58.2%, COPD 8.4%, CHD 12.6%, CKD 15.7%, cerebrovascular disease 4.2%, immunosuppressive therapy 0.2%, cancer 3.1%, obesity 26%	Corticosteroids 28.9%, tocilizumab 0.9%, Baricitinib 2.4%; Vaccinated 56.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Ivermectin (inhaled)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Aref et al;[288] peer reviewed; 2021	Patients with mild COVID-19 infection. 57 assigned to inhaled (inh) ivermectin and 57 assigned to SOC	Mean age 45 ± 19, male 71.9%, hypertension 17.5%, diabetes 12.3%, COPD 0.9%, cerebrovascular disease 3.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Randomization and concealment of allocation is probably inappropriate.	**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
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;[289] preprint; 2020	Patients with severe COVID-19 infection. 16 assigned to IVIG 0.5 g/kg/day for 3 days and 17 assigned to standard of care	Mean age 54 ± NR, male 60.6%, hypertension 33.3%, diabetes 36.3%, chronic lung disease 12%, coronary heart disease 3%, chronic kidney disease 3%, immunosuppression 3%	Corticosteroids 78.7%, remdesivir 51.5%, convalescent plasma 15.2%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯
Gharebaghi et al;[290] preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to IVIG 5 g a day for 3 days and 29 assigned to standard of care	Mean age 56 ± 16, male 69.5%, hypertension 22%, diabetes 27.1%, chronic lung disease 3.3%,	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	

Tabarsi et al;[291] peer-reviewed; 2020	Patients with severe COVID-19. 52 assigned to IVIG 400 mg/Kg daily for three doses and 32 assigned to standard of care	Mean age 53 ± 13, male 77.4%, hypertension 20.2%, diabetes 21.4%, COPD 1.2%, asthma %, coronary heart disease %, chronic kidney disease 4.7%, cancer 1.2%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Hospitalization:** No information
Raman et al;[292] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to IVIG 0.4 g/kg for 5 days and 50 assigned to SOC	Mean age 48.7 ± 12, male 33%, hypertension 31%, obesity 16%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

KB109 (microbiome modificator)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Haran et al;[293] preprint; 2021	Patients with mild to moderate COVID-19 infection. 169 assigned to KB109 9-36 g twice a day for 14 days and 172 assigned to SOC	Median age 36 ± 56, male 40.8%, hypertension 18%, diabetes 2.5%, COPD 8.8%, cerebrovascular disease 2.3%, cancer 0.8%, obesity 3.7%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
L-arginine **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Coppola et al;[294] peer reviewed; 2021	Patients with severe COVID-19 infection. 45 assigned to L-arginine 1.66 g twice a day during hospitalization and 45 assigned to SOC	Mean age 61.6, male 81.2%, hypertension 36.7%, diabetes 10%, CHD 14.5%, obesity 10%	Corticosteroids 100%, remdesivir 27.8%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No

					information
Lactococcus lactis (intranasal) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
PROBCO trial;[295] Endam et al; preprint; 2021	Patients with mild recently diagnosed COVID-19 infection. 12 assigned to *Lactococcus lactis* (intranasal) two nasal irrigations a day and 11 assigned to SOC	Mean age 30.4 ± 9.1, male 30%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Lactoferrin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the**

					evidence
RCT					
Algahtani et al;[296] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 36 assigned to lactoferrin 200 to 400 mg a day and 18 assigned to SOC	Mean age 48.6, male 60.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** 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

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;[297] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50 mg every 12 h (three doses) followed by 20	Mean age 52.5 ± 11.5, male 30%, hypertension 60%, chronic lung disease 10%	Umifenovir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information

	mg a day for 10 days and 5 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Wang et al;[298] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day followed by 20 mg a day for 8 days and 24 assigned to standard of care	Median age 55.7 ± 21.5, male 50%, hypertension 27.2%, diabetes 4.5%, chronic lung disease 4.5%, coronary heart disease 2.3%, cancer 2.3%	Corticosteroids 34.1%, hydroxychloroquine 56.8%, lopinavir-ritonavir 11.4%, umifenovir 75%, IVIG 20.4%, ATB 63.6%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

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;[299] Temesgen et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 236 assigned to lenzilumab 1800 mg once and 243 assigned to SOC	Mean age 60.5 ± 13.9, male 64.7%, hypertension 66%, diabetes 53.4%, COPD 7.3%, asthma 10.6%, CHD 13.6%, CKD 14%,	Corticosteroids 93.7%, remdesivir 72.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.72 (95%CI 0.44 to 1.19); RD -4.5% (95%CI -9% to 3%); 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;[300] Preprint; 2020	Patients with mild to moderate COVID-19. 25 assigned to levamisole 150 mg a day for 3 days and 25 assigned to SOC	Mean age 36.6 ± 13.7, male 60%,	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** **Mortality:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No
Asgardoon et al;[301] preprint; 2021	Patients with mild to moderate COVID-19 infection. 185 assigned to levamisole 50 mg a day for 10 days and 180 assigned to SOC	Median age 40 ± 18.75, male 56.1%, hypertension 8.8%, diabetes 9.4%, CHD 1.6%	Hydroxychloroquine 11.2%,	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded	

				study. Concealment of allocation probably inappropriate.	information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Levilimab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
CORONA trial;[302] Lomakin et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 103 assigned to levilimab 364mg once (subcutaneous) and 103 assigned to SOC	Mean age 58.3 ± 11.8, male 52.9%, CHD 15.5%,	Corticosteroids 7.3%, hydroxychloroquine 67.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement: Mortality:** RR 1.48 (95%CI 1.13 to 1.93); RD 29.1% (95%CI -7.9% to 56.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information **Hospitalization:** No information
Linagliptin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Abuhasira et al;[303] peer reviewed; 2021	Patients with moderate to severe with diabetes COVID-19 infection. 32 assigned to linagliptin 5 mg a day and 32 assigned to SOC	Mean age 66.9 ± 13.9, male 59.4%, diabetes 100%,	Corticosteroids 82.8%, remdesivir 50%, convalescent plasma 10.9%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Covid19DPP4i trial;[304] Guardado-Mendoza et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 34 assigned to linagliptin 5 mg a day and 35 assigned to SOC	Mean age 58.5, male 63.7%, hypertension %, diabetes 66.6%, CHD 5.8%, CKD 14.5%, cerebrovascular disease 2.9%,	Corticosteroids 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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;[56] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Lopinavir-ritonavir

Lopinavir-ritonavir probably does not reduce mortality with moderate certainty. Lopinavir-ritonavir may not be associated with a significant increase in severe adverse events. However, the certainty is low because of risk of bias and imprecision.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
LOTUS China trial;[305] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%,	Corticosteroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for	**Mortality:** RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -

	to lopinavir-ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	cancer 3%		symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	1.3% to 1.8%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Severe Adverse events:** RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -6.5% to -0.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
ELACOI trial;[306] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, intravenous immunoglobulin 6.3%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY - Lopinavir-ritonavir trial;[307] 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;[189] 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of	

				allocation is probably inappropriate.	
Zheng et al; preprint;[308] 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-ritonavir 40 mg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Chen et al; preprint;[309] 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 g IV loading dose followed by orally 400-600 mg every 8 hours for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
WHO SOLIDARITY - trial;[207] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 1399 assigned to lopinavir-ritonavir 200/50 mg twice a day for 14 days and 1372 assigned to standard of care	Age 61% < 70 years, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Sali et al;[310] Peer reviewed; 2020	Patients with moderate to severe	Mean age 56.5 ± 14, male 53.7%, diabetes	NR	High for mortality and mechanical ventilation;	

	COVID-19. 22 assigned to sofosbuvir 400 mg a day and 32 assigned to lopinavir-ritonavir 400/100 mg every 12 hours	33%,		High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Purwati et al;[311] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to HCQ 200 mg a day and 119 to SOC	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Kasgari et al;[312] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Yadollahzadeh et al;[313] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/ daclatasvir 400/60 mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100 mg twice a day for 7 days	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%, immunosuppression 3.6%, cancer 10.7%	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
TOGETHER trial;[221] Reis et al;	Patients with mild to moderate COVID-19	Mean age 53 ± 76, male 45%, hypertension	NR	Low for mortality and mechanical ventilation;	

peer reviewed; 2021	infection. 244 assigned to lopinavir-ritonavir 1600 mg/400 mg once followed by 800 mg/200 mg a day for 9 days and 227 assigned to SOC	49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%		low for symptom resolution, infection, and adverse events	
COPEP trial;[314] Labhardt et al; preprint; 2021	Patients exposed to COVID-19 infection. 209 assigned to lopinavir-ritonavir 400/10 mg a day for 5 days and 109 assigned to SOC	Median age 39 ± 22, male 50.6%, hypertension 8.2%, diabetes 3.1%, COPD 7.8%, CHD 2.5%, cancer 0.6%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Ghanei et al;[63] peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to Lopinavir-Ritonavir 200/50mg twice a day for 7 days and 110 assigned to azithromycin 500mg once followed by 250mg a day for 5 days	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
FIGHT-COVID-19 trial;[173] Atipornwanich et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 320 assigned to favipiravir 6000 mg once followed by 2400 mg a day + lopinavir ritonavir 800/200 mg or lopinavir ritonavir 800/200 mg a day or HCQ 800mg a day or Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day or favipiravil 6000mg	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	followed by 2400mg + Darunavir ritonavir 1200/200 mg a day + HCQ 400mg a day for 7 to 14 days.				
SEV-COVID trial;[230] Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 24 assigned to Lopinavir ritonavir + ribavirin Lopinavir (200 mg) + Ritonavir (50 mg) two tablets twice daily + Ribavirin (1.2 g orally as a loading dose followed by 600 mg orally every 12 hours) for 10 days and 24 assigned to SOC	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %, CHD 11.9%, cancer 1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Low-dose radiation therapy

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COVID-RT-01 trial;[315] Papachristofilou et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 11 assigned to low-dose radiation therapy 0.5 to 1.0 Gy and 11 assigned to SOC	Mean age 75, male 77.3%, diabetes 54.6%, COPD 22.7%, asthma %, CHD 40.9%, cancer 18.2%,	Corticosteroids 100%, remdesivir 50%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯
WINCOVID trial;[316] Ganesan et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 34 assigned to Low dose radiation therapy 0.5Gy single session and 17 assigned to	Age (>56) 58.8% , male 66.6%, hypertension 35.3%, diabetes 68.6%, asthma 2%,	Corticosteroids 100%, remdesivir 50.9%, tocilizumab 21.6%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Mavrilimumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
MASH-COVID trial;[317] 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;[318] peer reviewed; 2020	Patients with mild to moderate COVID-19. 24 assigned to melatonin 9 mg a day for 14 days and 20 assigned to SOC	Mean age 51.85 ± 14.25, male 59.1%, hypertension 25%, diabetes 22.7%, CHD 6.8%, cancer 6.8%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation is probably inappropriate. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Davoodian et al;[319] preprint; 2021	Patients with severe COVID-19 infection. 41 assigned to melatonin 6 mg a day for 14 days and 39 assigned to SOC	Median age 56 ± 40, male 56.8%, hypertension 18.5%, diabetes 14.8%, CHD 19.8%, CKD 3.7%	Corticosteroids 12.3%, hydroxychloroquine 69%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Alizadeh et al;[320] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 14 assigned to melatonin 6 mg a day for 14 days and 17 assigned to SOC	Mean age 36 ± 8.2, male 64.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Mousavi et al;[321] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 48 assigned to melatonin 3 mg a day for 10 days and 48 assigned to SOC	Mean age 52.9, male 44.8%, hypertension 30.2%, diabetes 28.1%, COPD 3.1%, asthma 5.2%, CHD 15.6%, CKD 5.2%,	Corticosteroids 82.3%, hydroxychloroquine 97.9%, lopinavir-ritonavir 2.1%, azithromycin 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hasan et al;[322] peer reviewed; 2021	Patients with severe COVID-19 infection. 82 assigned to melatonin 10mg a day for 14 days and 76 assigned to SOC	Mean age 56.3 ± 7.7, male 72.2%, hypertension 53.2%, diabetes 29.7%, asthma 10.1%, cerebrovascular disease 15.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Mefenamic acid

Mesenchymal stem-cell transplantation may reduce mortality.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
MEFECOVID-19 trial;[323] Guzman-Esquivel et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 19 assigned to mefenamic acid 1500 mg a day for 7 days and 17 assigned to SOC	Mean age 39.5 ± 15.4, male 33.3%, diabetes 5.6%, asthma 2.8%, obesity 47.2%	Corticosteroids 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Mesenchymal stem-cell transplantation **Mesenchymal stem-cell transplantation may reduce mortality.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Shu et al;[324] peer-reviewed; 2020	Patients with severe COVID-19 infection. 12 assigned to mesenchymal stem cell 2 × 10^6 cells/kg one infusion and 29 assigned to standard of care	Median age 61 ± 10, male 58.5%, hypertension 22%, diabetes 19.5%	Corticosteroids 100%, antibiotics 87.8%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.57 (95%CI 0.37 to 0.90); RD -6.7% (95%CI -10.1% to -1.6%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information
Shi et al;[325] 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%	Corticosteroids 22%	Low for mortality and mechanical ventilation	
Lanzoni et al;[326]	Patients with severe to	Mean age 58.7 ± 17.5,	Corticosteroids 90.4%,	High for mortality and	

preprint; 2020	critical COVID-19. 12 assigned to mesenchymal stem cell 100±20 ×106 UC-MSC twice and 12 assigned to standard of care	male 54.1%, hypertension 66.7%, diabetes 45.8%, coronary heart disease 12.5%, , cancer 4.2%, obesity 66.6%	remdesivir 66.7%, hydroxychloroquine 12.5%, tocilizumab 20.8%, convalescent plasma 29.1%	mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Adverse events:** No information **Hospitalization:** No information
Dilogo et al;[327] peer reviewed; 2021	Patients with critical COVID-19 infection. 20 assigned to mesenchymal stem cell one 100 ml infusion and 20 assigned to SOC	age >60, 45%, male 75%, hypertension 42.5%, diabetes 50%, CHD 25%, CKD 17.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Zhu et al;[328] peer reviewed; 2021	Patients with Severe COVID-19 infection. 29 assigned to mesenchymal stem cell 1 × 106 cells per kilogram body weight, once and 29 assigned to SOC	Median age 65, male 37.9%, hypertension 25.8%, diabetes 13.8%, COPD 1.7%, CHD 10.3%, cerebrovascular disease 8.6%	Corticosteroids 67.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Metformin

Metformin may not reduce hospitalizations. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
TOGETHER 2 trial;[329] Reis et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 215 assigned to MTF 1500mg a day and 203 assigned to SOC	Median age 52, male 42.8%, hypertension 40%, diabetes 14.6%, COPD 1.2%, asthma 8.1%, CHD 3%, CKD 0.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information

					Symptom resolution or improvement: No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** RR 1.14 (95%CI 0.72 to 1.82); RD 0.7% (95%CI -1.3% to -3.9%); Low certainty ⊕⊕◯◯
Methylene blue **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hamidi-Alamdari et al;[330] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to methylene blue 1 mg/kg every 12 to 8 h for 14 days and 40 assigned to SOC	Mean age 54 ± 13, male 52.5%, hypertension 17.5%, diabetes 10%	Corticosteroids 87.5%, azithromycin 92.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** No information **Hospitalization:** No information
Metisoprinol **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Borges et al;[331] peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to metisoprinol 1500 mg/kg/day for 14 days and 30 assigned to SOC	Mean age 33.2 ± 16, male 53.3%, COPD 10%, CKD 16.6%, cancer 3.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Metoprolol Mesenchymal stem-cell transplantation may reduce mortality.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
MADRID-COVID trial;[332] Clemente-Moragón et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 12 assigned to metoprolol 15 mg a day for 3 days and 8 assigned to SOC	Median age 60 ± 14.2, male 65%, hypertension 30%, diabetes 10%,	Corticosteroids 100%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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

Kazempour et al;[333] peer reviewed; 2021	Patients with moderate COVID-19 infection. 20 assigned to metronidazole 1 gr a day for 7 days and 24 assigned to SOC	Mean age 63 ± 16.3, male 59.1%, hypertension 47.7%, diabetes 18.2%, COPD 6.8%, asthma %, CHD 4.5%,	Hydroxychloroquine 59%, lopinavir-ritonavir 43.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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

Molnupiravir

Molnupiravir probably reduces hospitalizations in patients with recent onset mild to moderate disease, and it may not increase severe adverse events.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Painter et al;[334] Preprint; 2020	Healthy volunteers. 64 assigned to molnupiravir 80 to 1600 mg twice a day for 5.5 days	Mean age 39.6 ± 39, male 82.8%,	NR	Low for adverse events	**Mortality:** RR 0.13 (95%CI 0.02 to 0.77); RD -13.9% (95%CI -15.7% to -3.6%); Very low certainty ⊕◯◯◯ **Invasive mechanical**
AGILE trial;[335] Khoo et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 12 assigned	Median age 56 ± 58, male 27.8%	NR	Low for mortality and mechanical ventilation; High for symptom	

	to molnupiravir 600-1600 mg a day and 6 assigned to SOC			resolution, 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):** No information **Adverse events:** RR 0.49 (95%CI 0.23 to 1.05); RD -5.2% (95%CI -7.8% to 0.5%); Low certainty ⨁⨁◯◯ **Hospitalization:** RR 0.56 (95%CI 0.29 to 1.07); RD -2.1% (95%CI -3.3% to 0.3%); Moderate certainty ⨁⨁⨁◯
Fischer et al;[336] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 140 assigned to molnupiravir 200 to 800 mg twice a day for 5 days and 62 assigned to SOC	Age >65 6%±, male 48.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
MOVe-OUT trial; et al;[337] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 709 assigned to molnupiravir 1600 mg a day for 5 days and 699 assigned to SOC	Median age 43, male 48.7%, diabetes 15.9%, COPD 4%, asthma %, CHD 11.7%, CKD 5.9%, cancer 2%, obesity 73.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
HCR/III/MOLCOV/04/2021-01 trial; Hetero et al; other; 2021	Patients with mild COVID-19 infection. 371 assigned to molnupiravir 1600 mg a day and 370 assigned to SOC	NR	NR	Not assessed	

Montelukast

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Kerget et al;[338] peer reviewed; 2021	Patients with moderate COVID-19	Mean age 54.6 ± 15.3, male 42.2%,	NR	High for mortality and mechanical ventilation;	**Mortality:** Very low certainty ⨁◯◯◯

	infection. 120 assigned to montelukast 10 to 20 mg a day and 60 assigned to SOC	hypertension 30%, diabetes 19%, asthma 1.7%, CHD 1.1%, CKD %,		High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Mouthwash

Mouthwash may improve time to symptom resolution. Uncertainty in potential benefits and harms on other outcomes. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mukhtar et al;[339] preprint ; 2020	Patients with mild to critical COVID-19. 46 assigned to mouthwash with hydrogen peroxide 2% and chlorhexidine gluconate mixed solution three times a day and 46 assigned to standard of care	Mean age 49, male 78.2%, hypertension 37%, diabetes 41.3%, coronary heart disease 6.5%, chronic kidney disease 12%, c obesity 31.5%	Corticosteroids 53.2%, remdesivir 26%, hydroxychloroquine 21.7%, lopinavir-ritonavir 54.3%, azithromycin 57.6%, convalescent plasma 13%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 1.36 (95%CI 1.04 to
GARGLES trial;[340] Mohamed et al;	Patients with COVID-19. 10 assigned to	Median age 28.9, male 80%	NR	High for mortality and mechanical ventilation;	

preprint; 2020	mouthwash with povidone iodine or essential oils 3 times a day and 10 assigned to mouthwash with water or no mouthwash			high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	1.78); RD 21.8% (95%CI 2.4% to 47.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
KILLER trial;[341] Guenezan et al; peer reviewed; 2020	Patients with mild COVID-19. 12 assigned to mouthwash with 25 ml of 1% povidone iodine and 12 assigned to SOC	Mean age 45 ± 23, male 33%, hypertension 12.5%, diabetes 4%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Elzein et al;[342] preprint; 2021	Patients with mild to severe COVID-19 infection. 52 assigned to mouthwash with povidone or chlorhexidine and 9 assigned to SOC	Mean age 45.3 ± 16.7, male 40.9%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Santos et al;[343] 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;[344] Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to mouthwash with ß-	Mean age 43.8 ± 15.5, male 45.7%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection,	

	cyclodextrin-citrox three times a day and 78 assigned to SOC			and adverse events	
Huang et al;[345] peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 66 assigned to mouthwash chlorhexidine 0.12% 15 ml twice a day for 4 days and 55 assigned to SOC	Median age 62 ± 66, male 58%	Corticosteroids 100%, remdesivir 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Eduardo et al;[346] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 34 assigned to mouthwash cetylpyridinium chloride, zinc, chlorhexidine, hydrogen peroxide and 9 assigned to SOC	Mean age 54.7, male 74.4%, hypertension 30.2%, diabetes 23.2%, COPD 11.6%, CHD 18.6%, CKD 11.6%, obesity 13.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Di-Domênico et al;[347] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 63 assigned to mouthwash with hydrogen peroxide 1% three time a day and nasal wash with hydrogen peroxide 0.5% and 43 assigned to SOC	Age >60 17%, male 39.6%, hypertension 22.6%, diabetes 11.3%, COPD 5.7%, CHD 3.8%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant number of patients excluded post-randomization resulting in potential inbalances in baseline risks	
ACPREGCOV trial;[348] Damião Costa et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to Mouthwash 15 mL of 0.12% chlorhexidine gluconate and 50	Mean age 39 ± 12, male 50%, hypertension 17%, diabetes 4%, obesity 25%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	assigned to SOC				
BUCOSARS trial;[349] Ferrer et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 54 assigned to mouthwash with povidone-iodine, hydrogen peroxide, cetylpyridinium chloride or chlorhexidine and 13 assigned to SOC	Mean age 54 - 55 ± , male 67%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Poleti ML et al trial;[350] Poleti et al; ; 2021	Patients with mild COVID-19 infection. 59 assigned to mouthwash with antimicrobial phthalocyanine derivative and 75 assigned to SOC	Mean age 34 ± 21, male 38%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow-up.	

Mupadolimab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Miller et al;[351] preprint; 2021	Patients with moderate to severe COVID-19 infection. 29 assigned to mupadolimab 1-2 mg/kg and 11 assigned to SOC	Median age 55, male 57.5%, any comorbidities 45%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯
Mycobacterium w **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ARMY-1 trial;[352] Sehgal et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to Mycobacterium w 0.3 ml SC once a day for 3 days and 20 assigned to SOC	Mean age 56 ± 15, male 69%, hypertension 31%, diabetes 33.3%, COPD 4.8%, asthma 4.8%	Corticosteroids 100%, hydroxychloroquine 26.2%, tocilizumab 12%, convalescent plasma 7%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

N-acetylcysteine Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
de Alencar et al;[353] peer-reviewed; 2020	Patients with severe COVID-19. 68 assigned to NAC 21 g once and 67 assigned to standard of care	Mean age 58.5 ± 22.5, male 59.2%, hypertension 46.6%, diabetes 37.7%, cancer 12.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Gaynitdinova et al;[354] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 24 assigned to NAC 1200-1500 mg once and 22 assigned to SOC	Mean age 57.9 ± 12.7	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Taher et al;[355] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 47 assigned to NAC 40 mg/kg a day for 3 days and 45 assigned to SOC	Mean age 57.6 ± 18.7, male 58.7%, diabetes 23.9%, COPD 15.2%, asthma %, CHD 28.2%,	Corticosteroids 69.6%, hydroxychloroquine 90.2%, azithromycin 51.1%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	

Nafamostat Mesylate Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE**

					certainty of the evidence
RCT					
DEFINE trial;[356] Quinn et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 21 assigned to nafamostat 0.2 mg/kr/hr for 7 days and 21 assigned to SOC	Mean age 63.6, male 59.5%, hypertension 38.1%, diabetes 21.4%, COPD %, asthma 9.5%, CHD 14.3%, CKD 4.8%, immunosuppression 7.1%, cancer 9.5%, obesity %	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Namilumab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CATALYST trial;[244] Fisher et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 55 assigned to namilumab and 54	Median age 62.8 ± 18, male 68.5%	Corticosteroids 90.7%, remdesivir 53.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No

	assigned to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Nano-curcumin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Hassaniazad et al;[357] peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 20 assigned to nano-curcumin 160mg a day for 14 days and 20 assigned to SOC	Mean age 48.5 ± 10.9, male 55%	Corticosteroids 87.5%, hydroxychloroquine 45%, lopinavir-ritonavir 52.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Nasal hypertonic saline **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Kimura et al;[358] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 14 assigned to nasal hypertonic saline 250 cc twice daily, 14 assigned to nasal hypertonic saline plus surfactant and 17 assigned to standard of care	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%, diabetes 6.6%, chronic lung disease 15.5%, coronary heart disease 4.4%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Yildiz et al;[359] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 50 assigned to nasal hypertonic saline and 50 assigned to SOC	Mean age 38.8 ± , male 58%, hypertension 12%, diabetes 6%, COPD/asthma 4%, CHD 15%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
George et al;[360]	Patients with mild	Age range 22-45		Low for mortality and	

preprint; 2021	COVID-19 infection. 20 assigned to nasal hypertonic saline (Caclium rich hypertonic salts) and 20 assigned to SOC			mechanical ventilation; low for symptom resolution, infection and adverse events	
Baxter et al;[361] preprint; 2021	Patients with mild to moderate COVID-19 infection. 37 assigned to nasal saline 240 ml + povidone-iodine twice a day for 14 days and 42 assigned to nasal saline 240 ml +2.5 mL sodium bicarbonate twice a day for 14 days	Mean age 64 ± 7.9, male 54.4%, hypertension 43.4%, diabetes 11.3%, COPD %, asthma 5.7%, immunocompromised 3.8%, obesity 45%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Neem (*Azadirachta indica* A. Juss)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Nesari et al;[362] other; 2021	Patients exposed to COVID-19 infection. 70 assigned to neem 50 mg for 28 days and 84 assigned to SOC	Mean age 37, male %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate. Significant loss to follow-up.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low

					certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** No information
Niclosamaide **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Abdulamir et al;[363] preprint; 2021	Patients with mild to critical COVID-19 infection. 75 assigned to niclosamaide 4 g once followed by 3 g a day for 7 days and 75 assigned to SOC	Mean age 49.3 ± 16, male 53.3%, hypertension 12.7%, diabetes 8%, asthma 0.7%, cancer 0.7%, obesity 0.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Cairns et al;[364] peer reviewed; 2021	Patients with mild COVID-19 infection. 33 assigned to niclosamide 2 gr a day for 7 days and 34 assigned to SOC	Mean age 36.4 ± 13, male 61.2%, hypertension 7.5%, asthma 7.5%, CHD 1.5%, obesity 7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Nigella sativa +/- Honey Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
HNS-COVID-PK trial;[365] Ashraf et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 157 assigned to honey + *Nigella sativa* 1 g + 80 mg/kg three times a day for 13 days and 156 assigned to SOC	> 60 age 52 ±, male 56.8%, hypertension 31.6%, diabetes 36.7%	Corticosteroids 26.5%, azithromycin 73.8%, ivermectin 36.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Koshak et al;[366] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 91 assigned to *Nigella sativa* 500 mg twice a day for 10 days and 92 assigned to SOC	Mean age 36 ± 11, male 53%, hypertension 9%, diabetes 8%, asthma 4%, CHD 0.5%, obesity 25%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Nirmatrelvir-ritonavir Nirmatrelvir-ritonavir probably reduces 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					
EPIC-HR trial;[367] Hammond et al; peer reviewed; 2021	Patients with COVID-19 infection. 1039 assigned to Nirmatrelvir/ritonavir 600/200 mg a day for 5 days and 1046 assigned to SOC	Median age 46, male 51.1%, hypertension 32.9%, diabetes 12.1%, obesity 35.6%	NR; vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.49 (95%CI 0.30 to 0.80); RD -5.2% (95%CI -7.1% to -2%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.12 (95%CI 0.06 to 0.25); RD -4.2% (95%CI -4.5% to -3.5%); Moderate certainty ⊕⊕⊕◯

Nitazoxanide

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

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

RCT					
SARITA-2 trial;[368] Rocco et al; preprint; 2020	Patients with mild COVID-19. 194 assigned to nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	Age range 18 - 77, male 47%, comorbidities 13.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Fontanesi et al;[369] preprint ; 2020	Patients with mild to critical COVID-19. 25 assigned to nitazoxanide 1200 mg a day for 7 days and 25 assigned to SOC	Age > 65 46%, male 30%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Silva et al;[370] preprint; 2021	Patients with mild to moderate COVID-19 infection. 23 assigned to nitazoxanide 2-3 g a day for 14 days and 13 assigned to SOC	Male 72.2%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Vanguard trial;[371] Rossignol et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 184 assigned to nitazoxanide 600 mg a day for 5 days and 195 assigned to SOC	Mean age 40.3 ± 15.4, male 43.5%, comorbidities 34%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

NACOVID trial;[372] Fowotade et al; preprint; 2021	Patients with mild to severe COVID-19 infection. 31 assigned to nitazoxanide 2000 mg plus atazanavir/ritonavir 300/100 mg a day and 26 assigned to SOC	Mean age 38 ± 16, male 67%, obesity 19%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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;[373] preprint; 2021	Patients with severe COVID-19 infection. 14 assigned to iNO pulses of 30 min for 3 days and 11 assigned to SOC	Mean age 59.8 ± 10, male 72%, hypertension 44%, diabetes 56%, COPD 12%, CHD 24%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Winchester et al;[374] peer-reviewed; 2021	Patients with mild COVID-19 infection. 40 assigned to nitric oxide nasal spray (NONS) 4 sprays 5 to 6 times a day for 9 days and 40 assigned to SOC	Mean age 44, male 36.7%, hypertension 6.3%, diabetes 6.3%, COPD 1.2%, CHD 0%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

					Hospitalization: No information

Non-steroidal anti-inflammatory drugs (NSAID)

Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However, the certainty of the evidence is very low because of the risk of bias. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mobarak et al;[375] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 39 assigned to naproxen 1000 mg a day and 38 assigned to SOC	Mean age 47 , male 55.8%, hypertension 9%, diabetes 17%, CHD 13%, CKD 5.2%, obesity 1.3%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:	**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
Non-RCT					
Eilidh et al;[376] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection.	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%,	NR	High for mortality Notes: Non-randomized	**Mortality:** OR 0.82 (95%CI 0.66 to 1.02); Very low certainty

	54 received NSAID and 1168 received alternative treatment schemes	coronary heart disease 22.3%, chronic kidney disease 38.7%,		study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function).	⊕◯◯◯
Jeong et al;[377] 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;[378] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 224 received NSAID and 896 received alternative treatment schemes	Median age 54 ± 23, male 41.5%, chronic lung disease 3.9%, asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%	Corticosteroids 7.1%	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and matching were	

				implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, and phase of the outbreak.	
Rinott et al;[379] 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;[380] preprint; 2020	Patients exposed to COVID-19 infection. 535519 received NSAID and 1924095 received alternative treatment schemes	Median age 51 ± 23, male 42.7%, hypertension 19.6%, diabetes 9.6%, chronic lung disease 2.4%, asthma %, coronary heart disease 0.5%, chronic kidney disease 2.8%, cancer 5.2%,	Corticosteroids 2.2%, hydroxychloroquine 0.6%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, vaccination, and deprivation).	
Imam et al;[381] 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;[382] preprint; 2020	Patients with mild to severe COVID-19 infection. 146 received NSAID and 357 received alternative treatment schemes	Median age 41.7 ± 30, male 57.2%, hypertension 20.4%, diabetes 22.5%, chronic lung disease 5.2%, chronic kidney disease 3.2%, cancer 1.4%	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age; sex; comorbidities: hypertension, diabetes mellitus (DM), dyslipidemia, asthma, or chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), renal or liver impairment, and malignancy).	

Novaferon

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zheng et al;[308] preprint; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No

					information **Adverse events:** No information **Hospitalization:** No information
Nutritional support **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Leal et al;[383] preprint; 2021	Patients with severe COVID-19 infection. 40 assigned to nutritional support with spirulin, folic acid, glutamine, vegetable protein, vitamin C, zinc, selenium, vitamin D, resveratrol, Omega-3, L-Arginine, magnesium and probiotics and 40 assigned to SOC	Mean age 52.7 ± 10.8, male 65%, CHD 33.7%, obesity 33.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Omega-3 fatty acids **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Sedighiyan et al;[384] Preprint; 2020	Patients with mild to moderate COVID-19. 15 assigned to omega-3 670 mg three times a day for 2 weeks and 15 assigned to SOC	Mean age 66.7 ± 2.5, male 60%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Doaei et al;[385] peer reviewed; 2021	Patients with critical COVID-19 infection. 28 assigned to omega-3 1000 mg a day and 73 assigned to SOC	Mean age 64 ± 14, male 59.4%	NR	Some concerns for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding is probably inappropriate. Significant loss to follow-up.	
COVID-Omega-F trial;[386] Arnardottir et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to omega-3 10 gr a day for 5 days and 12 assigned to SOC	Mean age 81.1 ± 6.1, male 45%, hypertension 64%, diabetes 41%, COPD 13%, CHD 64%, CKD 23%, cancer 18%,	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Opaganib **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ABC-110 trial;[387] Winthrop et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 22 assigned to Opaganib 1000mg a day for 14 days and 18 assigned to SOC	Median age 58 ± 29.8, male 64.3%	Corticosteroids 92.8%, remdesivir 45.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** 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

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;[388]	Patients with severe to	Mean age 59.6 ± 12,	Corticosteroids 83%,	Low for mortality and	**Mortality:** Very low

Patel et al; preprint; 2021	critical COVID-19 infection. 386 assigned to otilimab 90 mg once and 393 assigned to SOC	male 71.6%, hypertension 49.7%, diabetes 36.7%, CHD 11.9%	remdesivir 34%, tocilizumab 1.2%, convalescent plasma 6%	mechanical ventilation; low for symptom resolution, infection, and adverse events	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;[389] Araimo et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 14 assigned to ozone 250 ml ozonized blood and 14 assigned to standard of care	Mean age 61.7 ± 13.2, male 50%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very

SEOT trial;[390] Shah et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to ozone 150 ml rectal insufflation plus 5 ml with venous blood once a day for 10 days and 30 assigned to SOC	Mean age 43.8 ± 9, male 80%, diabetes 10%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
P2Y12 inhibitors **P2Y12 in combination with full dose anticoagulants may increase mortality and may 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					
ACTIV-4a trial;[391] Berger et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 293 assigned to P2Y12 inhibitors (ticagrelor 120mg a day or prasugrel 5 to 10 mg a day or clopidogrel 75 mg a day) in combination with full dose anticoagulants and 269 assigned to SOC in combination with full dose anticoagulants	Mean age 52.7, male 58.5%, hypertension 48.4%, diabetes 25.8%, COPD 5.4%, asthma 11.2%, CKD 3.9%, cerebrovascular disease 0.7%	Corticosteroids 64.1%, remdesivir 52%, tocilizumab 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 1.5 (95%CI 0.72 to 3.12); RD 2.4% (95%CI -4.5% to 33.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 0.97 (95%CI 0.94 to 1.02); RD -1.8% (95%CI -3.6% to 1.2%); Low certainty ⊕⊕◯◯

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Peg-interferon (IFN) alfa **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
PEGI.20.002 trial;[392] Pandit et al; Peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to pegylated interferon alfa 1 µg/kg once and 19 assigned to SOC	Mean age 49.2 ± 13.5, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Bushan et al;[393] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 119 assigned to Peg Interferon Alfa 1 µg/kg subcutaneous [SC] injection once and 123 assigned to SOC	Mean age 49.9 ± 15.3, male 70.8%	Corticosteroids 59.9%, remdesivir 21.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

					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;[394] Feld et al; preprint; 2020	Patients with mild to severe COVID-19. 30 assigned to peg-IFN lambda 180 μg subcutaneous injection once and 30 assigned to standard of care	Median age 46 ± 22, male 58%, comorbidities 15%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯
COVID-Lambda trial;[395] 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;[396] peer-reviewed; 2020	Patients with severe to critical COVID-19. 26 assigned to pentoxifylline 400 mg three times a day while hospitalized and 12 assigned to standard of care	Mean age 57.5 ± 11.7, male 55.2%, hypertension 39.4%, diabetes 50%, obesity 55.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Azizi et al;[397] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to pentoxifylline 1200mg a day for 10 days and 32 assigned to SOC	Mean age 59, male 35%, hypertension 18%, diabetes 32%, CHD 12.5%, cerebrovascular disease 5.5%	Corticosteroids 55.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	

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

APLICOV-PC trial;[398] Varona et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 45 assigned to Plitidepsin Three doses of 1.5 to 2.5 mg	Mean age 51, male 66.6%, hypertension 20%, diabetes 17.8%, COPD 6.7%, asthma 11.1%, CHD 4.4%, CKD 2.2%, obesity 22.2%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes:	**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

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;[399] Lattaman et al; preprint; 2021	Patients with moderate COVID-19 infection. 20 assigned to PNB001 200 mg a day for 14 days and 20 assigned to SOC	Mean age 52, 65% male	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Polymerized type I collagen (PT1C) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Mendez-Flores et al;[400] preprint; 2021	Patients with mild to moderate COVID-19 infection. 44 assigned to PT1C 25 mg intramuscular for 3 days followed by 12.5 mg for another 4 days and 43 assigned to SOC	Mean age 48.5 ± 14.1, male 41.6%, hypertension 20.2%, diabetes 16.9%, COPD 2.3%, asthma 4.5%, CHD 0%, cancer 0%, obesity 28.1%	Corticosteroids 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯

Povidone iodine spray Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Seet et al;[220] peer reviewed; 2021	Patients exposed to COVID-19 infection. 735 assigned to povidone iodine spray 3 times a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯

Probiotics Probiotics may improve time to symptom resolution. The effect on other outcomes is uncertain. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Wang et al;[401] peer reviewed; 2021	Patients exposed to COVID-19 infection. 98 assigned to probiotics 2 lozenges a day for 30 days and 95 assigned to SOC	Mean age 36 ± 8, male 29%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** RR 1.89 (95%CI 1.4 to 2.56); RD 53.9.8% (95%CI 24.2% to 94.5%); Low certainty ⊕⊕◯◯ **Adverse events:** No information **Hospitalization:** No information
PROCOV-19-2020 trial;[402] Ivashkin et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 99 assigned to probiotics three times a day for 14 days and 101 assigned to SOC	Mean age 64 ± , male 46%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PROTECT-EHC trial;[403] Wischmeyer et al; peer reviewed; 2022	Patients with exposed COVID-19 infection. 91 assigned to probiotics 1 capsule a day for 28 days and 91 assigned to SOC	Age 18-64 62%, male 36.8%, hypertension 12.1%, diabetes 3.8%, COPD 1.1%, cancer 2.7%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
ABB-COVID19 trial;[404] Gutiérrez-Castrellón et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 147 assigned to probiotics 1 capsule a day for 30 days and 146 assigned to SOC	Median age 37 ± , male 46.3%, hypertension 19.6%, diabetes 10.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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

Prolectin-M Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Prolectin-M trial;[406] Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 g a day and 5 assigned to standard of care	Mean age 28.5 ± 3.85, male 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Propolis Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Bee-Covid trial;[407] Duarte Silveira et al; Preprint; 2020	Patients with moderate to critical COVID-19. 82 assigned to propolis 400-800 mg a day for 7 days and 42 assigned to SOC	Mean age 50 ± 12.8, male 69.4%, hypertension 45.2%, diabetes 21%, COPD 7.3%, asthma %, obesity 51.6%	Corticosteroids 80.6%, hydroxychloroquine 3.2%, azithromycin 95.2%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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

COMBAT-COVID trial;[408] Johansson et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 41 assigned to prostacyclin 1 ng/kg/min for 3 days and 39 assigned to SOC	Mean age 67, male 66.2%, hypertension 61.2%, COPD 12.5%, CKD 2.5%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Proxalutamide Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Cadegiani et al;[409] Preprint; 2020	Patients with mild COVID-19. 114 assigned to proxalutamide 200 mg a day for 15 days and 100 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Randomization and concealment methods probably not appropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** RR 0.07 (95%CI 0.01 to 0.52); RD -4.5% (95%CI -4.7% to -2.3%); Very low certainty ⨁◯◯◯
AB-DRUG-SARS-004 trial;[410] Cadegiani et al; peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 171 assigned to proxalutamide 200 mg a day for 15 days and 65 assigned to SOC	Mean age 45.3 ± 13, male 54.2%, hypertension 22.5%, diabetes 8.9%, COPD 0%, asthma 5%, CKD 0.4%, cancer 17%, obesity 15.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
KP-DRUG-SARS-003 trial;[411] Cadegiani et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 423 assigned to proxalutide 300mg a day for 14 days and 355 assigned to SOC	Median age 51 ± , male 59.6%, hypertension 27.6%, diabetes 12.5%, COPD 2.3%, asthma %, CHD %, CKD 0%, cerebrovascular disease %, immunosuppresive therapy %, cancer %, obesity %	Steroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Randomization scheme was modified during the study.	
AB-DRUG-SARS-005 trial;[412] Cadegiani et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 75 assigned to proxalutamide	Mean age 44.2 ± 12.1, male 0%, hypertension 31.1%, diabetes 8.5%, COPD 0.6%, obesity	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection,	

	200 mg a day for 7 days and 102 assigned to SOC	18.1%		and adverse events Notes: Randomization process presented as "Blocked" but described as a cluster randomization.	

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;[413] Fragoso-Saavedra et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 94 assigned to pyridostigmine 60 mg a day for 14 days and 94 assigned to SOC	Median age 52 ± 20, male 59.6%, hypertension 35.1%, diabetes 36.2%, COPD 4.3%, asthma %, CHD 2.1%, obesity 43.1%	Corticosteroids 74.5%, tocilizumab 5.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Quercetin Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Onal et al;[414] peer review; 2020	Patients with moderate to severe COVID-19. 49 assigned to Quercetin 1000 mg and 380 assigned to SOC	Age > 50 65.7%, male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma 13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⨁◯◯◯
Di Pierro et al;[415] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 21 assigned to quercetin 400-600 mg a day for 14days and 21 assigned to SOC	Mean age 49.3 ± 19.5, male 47.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Shohan et al;[416] peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 30 assigned to quercetin 1000 mg a day for 7 days and 30 assigned to SOC	Mean age 51.8, male 56.6%, hypertension 20%, asthma 6.6%, CHD 15%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes:	
Rondanelli et al;[417] peer reviewed; 2021	Patients with exposed COVID-19 infection. 60 assigned to quercetin 500 mg a day and 60 assigned to SOC	Mean age 49.3 ± 12.9, male 52.5%	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.	

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

RD-X19 (light therapy)

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

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

					and GRADE certainty of the evidence
RCT					
EB-P12-01 trial;[419] Stasko et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 20 assigned to RD-X19 light dose of 16 J/cm2 twice a day and 11 assigned to SOC	Median age 40 ± 20.6, male 52%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** 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;[420] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 46 assigned to recombinant super-	Median age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, chronic lung disease 1.1%,	Corticosteroids 9.6%, ATB 22.3%, intravenous immunoglobulin 3.2%, lopinavir-ritonavir	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No

	compound interferon 12 million IU twice daily (nebulization) and 48 assigned to interferon alfa	coronary heart disease 7.4%, cerebrovascular disease 5.3%, liver disease 6.4%	44.7%	events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Regdanvimab (monoclonal antibody)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Eom et al;[421] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 204 assigned to regdanvimab 40-80 mg/kg once and 103 assigned to SOC	Mean age 51 ± 20, male 44.6%, comorbidities 73%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.24 (95%CI 1.05 to 1.46); RD 4.2% (95%CI 9% to 80%);
CT-P59 1.2 trial;[422] Kim et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 15 assigned to regdanvimab 20 to 80mg once and 3 assigned to SOC	Median age 52 ± 8, male 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	

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

REGEN-COV (casirivimab and imdevimab)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Weinreich et al;[423] preprint; 2020	Patients with recent onset mild disease with risk factors for severe COVID-19 infection. 2091 assigned to REGEN-COV (casirivimab and imdevimab) 1.2 to 2.4 g single infusion and 2089 assigned to SOC	Median age 50 ± 21, male 48.7%, obesity 58%, comorbidities 100%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.83 (95%CI 0.64 to 1.07); RD -3.4% (95%CI -5.8% to 1.1%); Low certainty ⊕⊕◯◯ **Mortality (seronegative):** RR 0.79 (95%CI 0.71 to 0.89); RD -3.2% (95%CI -4.6% to -1.8%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.79 (95%CI 0.54 to
RECOVERY - REGEN-COV trial;[424] Horby et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 4839 assigned to REGEN-COV (Regeneron) 8 g	Mean age 61.9 ± 14.4, male 63%, diabetes 26.5%, COPD %, CHD 21%, CKD 5%	Corticosteroids 94%, azithromycin 3%, Baricitinib 9%; Vaccinated 8%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection, and adverse	

	once and 4946 assigned to SOC			events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	1.14); RD -3.6% (95%CI -8% to 2.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation (seronegative):** RR 0.82 (95%CI 0.74 to 0.9); RD -3.1% (95%CI -4.5% to -1.7%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.06 (95%CI 1 to 1.12); RD 3.6% (95%CI 0% to 7.2%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement (seronegative):** RR 1.1 (95%CI 1.06 to 1.14); RD 6% (95%CI 3.6% to 8.5%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.43 (95%CI 0.31 to 0.59); RD -9.9% (95%CI -12% to -7.1%); High certainty ⊕⊕⊕⊕ **Adverse events:** RR 0.54 (95%CI 0.27 to 1.07); RD -4.7%
O'Brien et al;[425] peer reviwed; 2021	Patients with early asymptomatic COVID-19 infection. 100 assigned to REGEN-COV (Regeneron) 1.2 g once and 104 assigned to SOC	Mean age 40.9 ± 18, male 45.4%, diabetes 7.8%, CKD 2.5%, immunosuppressive therapy 1.5%, obesity 13.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
O'Brien et al;[426] peer reviewed; 2021	Patients with exposed to COVID-19 infection. 753 assigned to REGN-CoV2 (Regeneron) 1200mg once and 752 assigned to SOC	Median age 42.9, male 45.9%, diabetes 6.8%, CKD 1.9%, immunosuppressive therapy 1%, obesity 13.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
OPTIMISE-C19 trial;[74] McCreary et al; preprint; 2021	Patients with mild COVID-19 infection disease and risk factors for severity. 922 assigned to REGN-CoV2 (Regeneron) and 1013 assigned to bamlanivimab +/- etesevimab	Mean age 56 ± 16, male 46%, hypertension 53%, diabetes 25%, COPD 19%, asthma %, CHD 18%, CKD 6.5%, immunosuppresive therapy 27%, obesity 48%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Somersan-Karakaya et al;[427] preprint; 2021	Patients with moderate to severe COVID-19 infection. 804 assigned to REGN-COV2 (Regeneron) 2.4 to 8 gr once and 393 assigned to SOC	Median age 62 ± , male 54.1%	Corticosteroids 74.8%, remdesivir 54.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
R10933-10987-	Patients with mild	Mean age 34.6, male	NR	Low for mortality and	

COV-20145 trial;[428] Portal Celhay et al; preprint; 2021	COVID-19 infection. 584 assigned to REGN-COV2 (Regeneron) 300 - 2400 mg once and 77 assigned to SOC	44.3%		mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	(95%CI -7.4% to 0.7%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.30 (95%CI 0.20 to 0.46); RD -3.4% (95%CI -3.8% to -2.6%); Moderate certainty ⊕⊕⊕◯
Isa et al;[429] preprint; 2021	Patients with COVID-19 infection. assigned to REGN-COV2 (Regeneron) and assigned to	Median age 48 ± 22, male 55.1%, hypertension 14.7%, asthma 5.2%, CHD 0.8%, CKD 0.2%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Weinreich et al;[430] preprint; 2021	Patients with mild to moderate COVID-19 infection. 434 assigned to REGN-COV2 (Regeneron) 2400 TO 8000 mg once and 231 assigned to SOC	Median age 42 ± 21, male 47.1%, obesity 37.3%, Risk factor for hospitalization 60.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
OPTIMISE-C19 trial;[431] Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD 16%, CKD 4.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Remdesivir

Remdesivir may not reduce mortality, it may reduce mechanical ventilation requirement and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ACTT-1 trial; Beigel et al;[432] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 541 assigned	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%,	NR	Low for mortality and invasive mechanical ventilation; low for	**Mortality:** RR 0.97 (95%CI 0.86 to 1.10); RD -0.5% (95%CI -

	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	diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,		symptom resolution, infection, and adverse events	2.2% to 1.6%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.79 (95%CI 0.55 to 1.14); RD -3.6% (95%CI -7.8% to 2.4%); Low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** RR 1.1 (95%CI 0.96 to 1.28); RD 6% (95%CI -2.4% to 17%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.77 (95%CI 0.46 to 1.29); RD -2.3% (95%CI -5.5% to 3%); Low certainty ⨁⨁◯◯ **Hospitalization:** RR 0.28 (95%CI 0.11 to 0.75); RD -3.4% (95%CI -4.3% to -1.2%); Low certainty ⨁⨁◯◯
SIMPLE trial; Goldman et al;[433] peer-reviewed; 2020	Patients with severe COVID-19 infection. 200 assigned to remdesivir (5 days) 200 mg once followed 100 mg for 5 days and 197 assigned to remdesivir (10 days)	Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CAP-China remdesivir 2 trial;[434] Wang et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 158 assigned to remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions and 79 assigned to standard of care	Median age 65 ± 7.5, male 60.5%, hypertension 43%, diabetes 23.7%, coronary heart disease 7.2%	Corticosteroids 65.6%, lopinavir-ritonavir 28.4%, IFN 32.2%, ATB 91.1%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
SIMPLE 2 trial; Spinner et al;[435] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 384 assigned to remdesivir 200 mg on day 1 followed by 100 mg a day for 5 to 10 days and 200 assigned to standard of care	Median age 57 ± 9, male 61.3%, hypertension 42%, diabetes 40%, asthma 14%, coronary heart disease 56%	Corticosteroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	Some concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Additional	

				treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY;[207] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2743 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 2708 assigned to standard of care	Age < 70 years 61%, male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Corticosteroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Mahajan et al;[436] peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 34 assigned to remdesivir 200 mg once followed by 100 mg once a day for 5 days and 36 assigned to SOC	Mean age 57.7 ± 13.1, male 65.5%, hypertension 45.7%, diabetes 60%, asthma 1.4%, CHD 12.9%, CKD 4.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Abd-Elsalam et al;[437] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to remdesivir 200mg once followed by 100mg a day for 10 days and 100 assigned to SOC	Mean age 53 ± 15, male 59.5%, hypertension 33%, diabetes 34%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Sarhan et al;[438] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 52 assigned to Remdesivir 200 mg	Mean age 57, male 72%, hypertension 61.7%, diabetes 47.6%, COPD 2.8%, asthma 13.1%,	Hydroxychloroquine 52.3%, tocilizumab 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection,	

	once followed by 100 mg a day for 5 days plus tocilizumab and 56 assigned to HCQ 400mg once followed by 200mg a day for 5 days plus tocilizumab	CHD 21.5%, CKD 4.7%,		and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PINETREE trial;[439] Gottlieb et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 279 assigned to remdesivir 200 mg once followed by 100 mg on days two and three and 283 assigned to SOC	Mean age 50 ± 15, male 53.1%, hypertension 47.7%, diabetes 61.6%, COPD 24%, CKD 3.2%, immunosuppresion 4.1%, cancer 5.3%, obesity 55.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CATCO trial;[440] Ali et al; peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 170 assigned to Remdesivir 200 mg once followed by 100 mg a day for 10 days and 153 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Reseveratrol

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
McCreary et al;[441] preprint; 2021	Patients with mild COVID-19 infection. 50 assigned to resveratrol 4gr a day for 7 days and 50 assigned to SOC	Mean age 56 ± 9, male 43%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty

Reszinate trial;[442] Kaplan et al; preprint; 2021	Patients with mild COVID-19 infection. 14 assigned to resveratrol + Zinc 4000/150 mg once a day for five days and 16 assigned to SOC	Mean age 42.4, male 40%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes:	⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

rhG-CSF (in patients with lymphopenia)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cheng et al;[443] peer-reviewed; 2020	Patients with moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100 assigned to standard of care	Mean age 45 ± 15, male 56%	Lopinavir-ritonavir 15.5%, IFN 9%, umifenovir 18%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

					Symptomatic infection (prophylaxis studies): No information **Severe Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
rhG-CSF (inhaled) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
SARPAC trial;[444] Lambrecht et al; preprint; 2021	Patients with severe COVID-19 infection. 40 assigned to rhG-CSF (inhaled) 125 µg twice daily for 5 days and 41 assigned to SOC	Mean age 60 ± 20, male 61%, hypertension 17.1%, diabetes 17.1%, CHD 2.4%, CKD 2.4%, cancer 4.9%,	Corticosteroids 22%, hydroxychloroquine 63.4%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty

					⊕◯◯◯ **Hospitalization:** No information

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;[309] preprint; 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2 g IV loading dose followed by orally 400-600 mg every 8 h for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to ribavirin plus lopinavir-ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ribavirin plus interferon beta-1b

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

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

					evidence
RCT					
Hung et al;[445] peer-reviewed; 2020	Patients with mild to moderate COVID-19 infection. 86 assigned to ribavirin plus interferon beta-1b 400 mg every 12 hours (ribavirin), and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]) on alternate days, for 14 days and 41 assigned to standard of care	Median age 52 ± 15, male 54%, hypertension 18.3%, diabetes 13.3%, coronary heart disease 7.9% cerebrovascular disease 1.5%, cancer 1.5%	Corticosteroids 6.2%, ATB 53.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ruxolitinib Ruxolitinib may not improve time to symptom resolution. However the certainty of the evidence was low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Cao et al;[446] peer-reviewed; 2020	Patients with severe COVID-19 infection. 22 assigned to ruxolitinib 5 mg twice a day and 21 assigned to standard of care	Mean age 63 ± 10, male 58.5%, hypertension 39%, diabetes 19.5%, coronary heart disease 7.3%,	Corticosteroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯
RUXCOVID trial; NCT04362137 other; 2021	Patients with moderate to severe COVID-19 infection. 287 assigned to Ruxolitinib 10 mg a day for 14 to 28 days and 145 assigned to SOC	Mean age 56.5 ± 13.3, male 54.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Symptom resolution or improvement:** RR 0.99 (95%CI 0.89 to 1.1); RD -0.6% (95%CI -6.6% to 6%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Sarilumab Sarilumab may reduce mortality and mechanical ventilation requirements; however, the certainty of the evidence is low. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
REMAP-CAP - tocilizumab trial;[447] Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8 mg/kg once or twice, 48 assigned to sarilumab 400 mg once and 402 assigned to SOC	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%, cancer %, obesity %	Corticosteroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.99 (95%CI 0.86 to 1.14); RD -0.2% (95%CI -2.2% to 2.2%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.96 (95%CI 0.67 to 1.36); RD -0.7% (95%CI -5.7% to 6.2%); Low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.97 to 1.06); RD 1.2% (95%CI -1.8% to 3.6%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 1.03 (95%CI 0.91 to 1.17); RD 0.3% (95%CI -0.9% to 1.7%);
Lescure et al;[448] peer-reviewed; 2020	Patients with severe to critical COVID-19. 332 assigned to sarilumab 200-400 mg once and 84 assigned to SOC	Mean age 59 ± 18, male 62.7%, hypertension 42.5%, diabetes 26.4%, COPD 4.3%, asthma 4.1%, CHD 5.3%, CKD 4.3%, cancer 10.1%, obesity 20.7%	Corticosteroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Sarilumab-COVID19 Study trial;[449] Sivapalasingam, et al; preprint; 2021 (two studies reported)	Patients with severe to critical COVID-19 infection. 1148 assigned to sarilumab 200-400 mg once and 376 assigned to SOC	Critical patient population: Mean age 61 ± 20, male 68.4%, hypertension 52.1%, diabetes 18.7%, obesity 46.5%	Corticosteroids 34.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
CORIMUNO-SARI trial;[450] Mariette, et al, peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 68 assigned to sarilumab 400mg once and 76 assigned to	Median age 62, male %, hypertension 25.1%, diabetes 30.5%, COPD 6.3%, asthma 8%, CKD 11.8%, cancer 3%,	Steroids 20.1%, remdesivir 0%, hydroxychloroquine 14.6%, azithromycin 39.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	SOC				Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
CORIMUNO-SARI ICU trial;[451] Hermine et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 48 assigned to sarilumab 400mg once and 33 assigned to SOC	Median age 61, male 76.5%, diabetes 31.2%, COPD 3.7%, asthma 4.9%, CKD 13.5%, cancer 1.2%,	Steroids 19.7%, remdesivir 0%, hydroxychloroquine 4.9%, lopinavir-ritonavir 1.2%, azithromycin 2.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SARCOVID trial;[452] other; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to sarilumab 400 mg once and 10 assigned to SOC	Median age 62	Corticosteroids 83.3%, remdesivir 0%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
SARICOR trial;[453] Merchante et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 76 assigned to sarilumab 200-400mg once and 39 assigned to SOC	Median age 59, male 68%, hypertension 41%, diabetes 15%, COPD 13%, CHD 4%, CKD 2%,	Steroids 90%, remdesivir 12%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SARTRE trial;[454] Sancho-Lopez et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 99 assigned to sarilumab 200-400mg once and 102 assigned to SOC	Median age 60, male 70.2%, hypertension 40.8%, diabetes 16.4%, COPD 9.5%, CHD 12.4%, CKD 3%, cancer 3%, obesity 3.5%	Steroids 100%, remdesivir 1%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have	

				introduced bias to symptoms and adverse events outcomes results.	
Secukinumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
BISHOP trial;[455] Gomes Resende et al; preprint; 2021	Patients with severe COVID-19 infection. 25 assigned to secukinumab 300 mg once and 23 assigned to SOC	Mean age 54 ± 21.5, male 52%, hypertension 48%, diabetes 34%, CHD 8%, obesity 48%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Short-wave diathermy **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE**

					certainty of the evidence
RCT					
Tian et al;[456] peer reviewed; 2021	Patients with moderate COVID-19 infection. 27 assigned to short-wave diathermy and 13 assigned to SOC	Median age 65 ± 18, male 62.5%, hypertension 30%, diabetes %, COPD 45%, CHD 30%, CKD 7.5%, cerebrovascular disease 27.5%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Sildenafil **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
UNAB-003 trial;[457] Santamarina et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 20 assigned to	Median age 57, male 82.5%, diabetes 20%, COPD 0%, asthma 5%	Corticosteroids 82.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical**

	sildenafil 75 mg a day for 7 days and 20 assigned to SOC			adverse events Notes: Blinding and concealment of allocation probably inappropriate.	**ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Siltuximab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COV-AID-2 trial;[452] other; 2021	Patients with severe to critical COVID-19 infection. 77 assigned to siltuximab 11 mg/kg once and 72 assigned to SOC	Median age 64	Corticosteroids 59%, remdesivir 3.4%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Severe adverse events:** No information **Hospitalization:** No information
Sitagliptin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Asadipooya et al;[458] preprint; 2021	Patients with moderate to severe COVID-19 infection. 66 assigned to sitagliptin 100 mg a day and 87 assigned to SOC	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD 6.4%, cancer 5.9%, obesity 18.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information

					Hospitalization: No information
Sofosbuvir +/- daclatasvir, ledipasvir, ravidasvir, or velpatasvir **Sofosbuvir alone or in combination with daclatasvir or ledipasvir may not reduce mortality or mechanical ventilation requirements, and probably does not improve time to symptom resolution.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Kasgari et al;[312] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.14 (95%CI 0.83 to 1.56); RD 2.2% (95%CI -2.7% to 9%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 1.02 (95%CI 0.59 to 1.76); RD 0.3% (95%CI -7.1% to 13.1.7%); Low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.95 to 1.08); RD 0.6% (95%CI -3% to 4.8%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** No information
Sadeghi et al;[459] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 14 days and 33 assigned to standard of care	Median age 58 ± 13, male 20.21%, hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%, coronary heart disease 15.1%, cancer 4.5%, obesity 25.7%	Corticosteroids 30.2%, lopinavir-ritonavir 48.4%, antibiotics 89.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation is probably inappropriate.	
Yakoot et al;[460] preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %,	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection,	

	400/60 mg once a day for 10 days and 45 assigned to standard of care	asthma 1%, coronary heart disease 8%		and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Roozbeh et al;[461] Peer reviewed; 2020	Patients with moderate COVID-19. 27 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 7 days and 28 assigned to SOC	Median age 53 ± 16, male 47%, comorbidities 38%	Azithromycin 100%, hydroxychloroquine 100%	High for symptom resolution, infection, and adverse events Notes: Blinding method possibly inappropriate which might have introduced bias to symptoms and adverse events outcomes results.	
Sali et al;[310] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to sofosbuvir 400 mg a day and 32 assigned to lopinavir-ritonavir 400/100 mg every 12 hours	Mean age 56.5 ± 14, male 53.7%, diabetes 33%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
DISCOVER trial;[462] Mobarak et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 541 assigned to sofosbuvir/daclatasvir 400/60mg a day for 10 days and 542 assigned to SOC	Median age 58, male 54%, hypertension 34%, diabetes 26%, COPD 2.1%, asthma 4.8%, CHD 9.1%,	Steroids 69.9%, remdesivir 15.6%, hydroxychloroquine 12.8%, lopinavir-ritonavir 33.1%, azithromycin 22.1%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Alavi-moghaddam et al;[463] Preprint; 2021	Patients with severe to critical COVID-19 infection. 27 assigned to sofosbuvir 400 mg a day and 30 assigned to SOC	Mean age 57.2 ±, male 49.1%, hypertension 21%, diabetes 29.8%, COPD 7%, CHD 19.3%, CKD 1.7%, obesity 1.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded	

				study. Concealment of allocation is probably inappropriate.	
Yadollahzadeh et al;[313] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 10 days and 54 assigned to lopinavir-ritonavir 400/100 mg twice a day for 7 days	Mean age 57.4 ± 15, male 44.6%, hypertension 25%, diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%, immunosuppression 3.6%, cancer 10.7%	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khalili et al;[464] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 42 assigned to sofosbuvir/ledipasvir 400/90 mg a day for 10 days and 40 assigned to SOC	Median age 62.2 ± 23.1, hypertension 45.1%, diabetes 45.1%, COPD 4.9%, CHD 31.7%, cancer 3.6%,	Corticosteroids 8.5%, hydroxychloroquine 10.9%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Elgohary et al;[465] preprint; 2021	Patients with moderate COVID-19 infection. 125 assigned to sofosbuvir/ledipasvir 400/90 mg once a day for 15 days and 125 assigned to SOC	Mean age 43 ±, male 0.4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
SOVECOD trial;[466] Sayad et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to sofosbuvir/velpatasvir 400/100 mg once a day for 10 days and 40	Mean age 54.1 ± 17.8, male 55%, hypertension 30%, diabetes 20%, COPD 10%, CHD 17.5%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	assigned to SOC			study which might have introduced bias to symptoms and adverse events outcomes results.	
El-Bendari et al;[467] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 96 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 14 days and 78 assigned to SOC	Mean age 53 ± 15, male 54.6%, hypertension 21.3%, diabetes 37.3%, asthma 1.7%, CHD 10.9%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abbass et al;[468] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 80 assigned to sofosbuvir/daclatasvir 400/60 a day or sofosbuvir/ravidasvir 400/200mg a day for 10 days and 40 assigned to SOC	Mean age 44.6 ± 4.7, male 53.3%, diabetes 18.3%, asthma 1.6%, CHD 75.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Table 1 shows more severe patients in SOC (68% vs 59%).	

Sotrovimab Sotrovimab probably reduces hospitalizations in patients with mild recent onset COVID-19 with risk factors for severe disease.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COMET-ICE trial;[469] Gupta et al; peer reviewed; 2021	Patients with recent onset mild to moderate COVID-19 infection, with risk factors for severity progression. 291 assigned to sotrovimab 500 mg once and 292 assigned to SOC	Median age 53 ±, male 46%, diabetes 23%, COPD 4%, asthma 16%, CKD 0.7%, obesity 63%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Stopped early for benefit.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.29 (95%CI 0.12 to 0.63); RD -7.1% (95%CI -8.9% to -3.8%); Low certainty ⨁⨁◯◯ **Hospitalization:** RR 0.14 (95%CI 0.04 to 0.48); RD -4.1% (95%CI -4.6% to -2.5%); Moderate certainty ⨁⨁⨁◯
OPTIMISE-C19 trial;[431] Huang et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 2454 assigned to REGN-COV2 (Regeneron) one infusion and 1104 assigned to sotrovimab one infusion	Mean age 54 ± 18, male %, hypertension 30%, diabetes 12%, CHD 16%, CKD 4.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Spironolactone Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Asadipooya et al;[458] preprint; 2021	Patients with moderate to severe COVID-19 infection. 50 assigned to spironolactone 100 mg a day and 87 assigned to SOC	Mean age 57.5 ±, male 51.2%, hypertension 29%, diabetes 27.1%, COPD 8.4%, asthma %, CHD 21.2%, CKD 6.4%, cancer 5.9%, obesity 18.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No information

Statins Statins may reduce mortality. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
RESIST trial;[49] Ghati et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 221 assigned to atorvastatin 40 mg once a day for 10 days and 219 assigned to SOC	Mean age 53.1 ± 9.2, male 73.3%, hypertension 28.6%, diabetes 27.7%, CHD 1.1%, CKD 2.4%	Corticosteroids 27.3%, remdesivir 20.6%, hydroxychloroquine 9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** RR 0.90 (95%CI 0.72 to 1.12); RD -1.6% (95%CI -4.5% to 2.1%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
INSPIRATION/INSPIRATION-S trial;[470] Bikdeli et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 290 assigned to atorvastatin 20 mg a day for 30 days and 297 assigned to SOC	Median age 57 ± , male 56.4%, hypertension 31.5%, diabetes 16.7%, COPD 8%	Corticosteroids 93.4%, remdesivir 66.3%, hydroxychloroquine 7.5%, lopinavir-ritonavir 0.7%, tocilizumab 14.5%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Stem-cell nebulization Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
SENTAD-COVID trial;[471] Carmenate et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 69 assigned to stem-cell nebulization twice, 24 h apart, and 70 assigned to SOC	Mean age 45.1 ± 10.4, male 46.5%, hypertension 26.6%, diabetes 22.3%, COPD %, asthma 10.7%, CHD 9.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Steroids (corticosteroids) Corticosteroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Corticosteroids may not significantly increase the risk of severe adverse events. Higher doses (i.e., dexamethasone 12 mg a day) may not be more effective than standard doses (i.e., dexamethasone 6 mg a day)					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
GLUCOCOVID trial;[472] Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone 40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	Mean age 69.5 ± 11.5, male 61.9%, hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%, cerebrovascular disease 12.7%	Hydroxychloroquine 96.8%, lopinavir-ritonavir 84.1%, azithromycin 92%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.90 (95%CI 0.80 to 1.01); RD -1.6% (95%CI -3.2% to 0.2%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.87 (95%CI 0.73 to 1.04); RD -2.2% (95%CI -4.7% to 0.7%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.19 (95%CI 0.95 to 1.5); RD 11.5% (95%CI -3% to 30%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 0.89
Metcovid trial;[473] Prado Jeronimo et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 194 assigned to methylprednisolone 0.5 mg/kg twice a day for 5 days and 199 assigned to standard of care	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease 0.5%, asthma 2.5%, coronary heart disease 6.9%, alcohol use disorder 27%, liver disease 5.5%	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	
RECOVERY - Dexamethasone trial;[474] Horby et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 2104 assigned to dexamethasone 6 mg once daily for 10 days and 4321 assigned to standard of care	Mean age 66.1 ± 15.7, male 64%, diabetes 24%, chronic lung disease 21%, asthma NR%, coronary heart disease 27%, chronic kidney disease 8%, liver disease 2%, any comorbidities 56%	Corticosteroids NA%, remdesivir 0.08%, hydroxychloroquine 1%, lopinavir-ritonavir 0.5%, tocilizumab 3%, azithromycin 25%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse	

				events outcomes results.	(95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information
DEXA-COVID19 trial;[475] 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;[476] 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;[477] Arabi et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 278 assigned to hydrocortisone 50 mg every 6 hours for 7 days and 99 assigned to standard of care	Mean age 59.9 ± 13, male 71%, diabetes 32%, chronic lung disease 20.3%, coronary heart disease 7.5%, chronic kidney disease 9.2%, immunosuppression 4.9%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVID STEROID trial;[475] 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	NR	NR	Low for mortality and invasive mechanical ventilation Notes: Risk of bias judgment from	

	standard of care			published SR.	
CAPE COVID trial;[478] Dequin et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 76 assigned to hydrocortisone 200 mg a day progressively reduced to 50 mg a day for 7 to 14 days and 73 assigned to standard of care	Median age 64.7 ± 19.3, male 69.8%, hypertension %, diabetes 18.1%, chronic lung disease 7.4%, immunosuppression 6%	Remdesivir 3.4%, hydroxychloroquine 46.9%, lopinavir-ritonavir 14.1%, tocilizumab 2%, azithromycin 34.2%	Low for mortality and invasive mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Corticosteroids-SARI trial;[475] 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;[479] preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to methylprednisolone 1000 mg/day for three days followed by prednisolone 1 mg/kg for 10 days, and 15 assigned to standard of care	Mean age 64 ± 13.5	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Edalatifard et al;[480] peer-reviewed; 2020	Patients with severe COVID-19. 34 assigned to methylprednisolone 250 mg/day for 3 days and 28 assigned to standard of care	Mean age 58.5 ± 16.6, male 62.9%, hypertension 32.3%, diabetes 35.5%, chronic lung disease 9.7%, coronary heart disease 17.7%, chronic kidney disease 11.3%, cancer 4.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Tang et al;[481] 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;[482] Peer-reviewed; 2020	Patients with moderate to severe COVID-19. 25 assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day until day 10 and 25 assigned to SOC	Median age 62 ± 16.5, male 72%, hypertension 50%, diabetes 54%, COPD 20%, CHD 14%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Rashad et al;[483] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 75 assigned to dexamethasone 4 mg/kg a day for 3 days followed by 8 mg 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 is probably inappropriate. Significant loss to follow-up as patients who died in the first 3 days after randomization were excluded.	
Ghanei et al;[63] peer reviewed; 2021	Patients with severe COVID-19 infection. 116 assigned to predninoslone 25mg a day for 5 days and 110 assigned to SOC	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD 1.2%,	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Ranjbar et al;[484] Preprint; 2020	Patients with severe to critical COVID-19 infection. 44 assigned to Methylprednisolone 2 mg/kg daily for 5 days followed by tapering using same scheme at half dose every 5 days, 42 assigned to dexamethasone 6 mg a day for 10 days	Mean age 58.7 ± 17.4, male 56.9%, hypertension 45.3%, diabetes 32.5%, CHD 30.2%, CKD 2.3%,	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Unbalanced prognostic factors (age and gender).	**Mortality:** RR 0.95 (95%CI 0.67 to 1.34); RD -0.8% (95%CI -5.3% to 5.4%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 0.98 (95%CI 0.90 to 1.09); RD -0.2% (95%CI -1% to 0.9%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.85 (95%CI 0.61 to 1.19); RD -1.5% (95%CI -4% to 1.9%); Low certainty ⨁⨁◯◯ **Hospitalization:** No information
COVID STEROID 2 trial;[485] Munch et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 497 assigned to dexamethasone 12 mg a day for 10 days and 485 assigned to dexamethasone 6 mg a day for 10 days	Median age 64.5 ± 18, male 69%, diabetes 30.3%, COPD 12%, CHD 14%	Remdesivir 62.8%, tocilizumab 10.1%, convalescent plasma 2.8%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Maskin et al;[486] preprint; 2021	Patients with critical COVID-19 infection. 49 assigned to dexamethasone 16 mg a day for 5 days followed by 8 mg a day for 5 days and 49 assigned to dexamethasone 6mg a day for 10 days	Mean age 61.8 ± 13.4, male 70%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Toroghi et al;[487] peer reviewed; 2021	Patients with severe COVID-19 infection. 86 assigned to dexamethasone 16 to 24 mg a day and 47 assigned to dexamethasone 8 mg a day for up to 10 days	Mean age 58, male 60.2%, hypertension 36%, diabetes 22.5%, COPD 6%, CHD 17.3%, CKD 1.5%, cerebrovascular disease 6%, cancer 2.3%,	Remdesivir 75.2%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

HIGHLOWDEXA trial;[488] Taboada et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 98 assigned to dexamethasone 20 mg once a day for 5 days dexamethasone and 102 assigned to dexamethasone 6 mg once a day for 10 days	Mean age 64.3 ± 14.3, male 61.8%, hypertension 48%, diabetes 19%, COPD 7%, asthma 5%, CHD 13.5%, CKD 3.5%, obesity 53%	Remdesivir 10%, tocilizumab 12%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Naik et al;[489] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 21 assigned to dexamethasone 20 mg a day for 3 days and 21 assigned to TCZ 6mg/kg once	Median age 50.5, male 57.1%, hypertension 57.1%, diabetes 35.7%, COPD 4.8%, asthma 2.4%, CHD %, CKD 0%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Steroids (inhaled corticosteroids)

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

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

STOIC trial;[490] Ramakrishnan et al; peer reviewed ; 2020	Patients with mild to moderate COVID-19. 71 assigned to inhlaed budesonide 800 µg twice a day and 69 assigned to SOC	Mean age 45 ± 56, male 42.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.15 (95%CI 1.08 to 1.24); RD 9.7% (95%CI 4.8% to 14.5%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Hospitalization:** RR 0.85 (95%CI 0.58 to 1.26); RD -0.7% (95%CI -2% to 1.2%); Low certainty ⊕◯◯◯ **Adverse events:** No information
PRINCIPLE trial;[491] Yu et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 787 assigned to inhaled budesonide 800µg twice daily for 14 days and 1069 assigned to SOC	Mean age 64.2 ± 7.6, male 48%, hypertension 44.3%, diabetes 21.4%, COPD 12.6%, CHD 15.8%, cerebrovascular disease 5.6%	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study. Significant loss to follow-up.	
Song et al;[492] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 35 assigned to inhaled ciclesonide 320 µg twice per day for 14 days and 26 assigned to SOC	Median age 53 ± 26, male 47%, hypertension 27.8%, diabetes 14.7%, cerebrovascular disease 3.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ALV-020-001 trial;[493] Clemency et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 197 assigned to inhaled ciclesonide 640 µg a day for 30 days and 203 assigned to SOC	Mean age 43.3 ± 16.9, male 44.8%, hypertension 22.3%, diabetes 7.5%, asthma 6.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

CONTAIN trial;[494] Ezer et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 105 assigned to inhaled ciclesonide 1200 µg + 200 µg intranasal a day and 98 assigned to SOC	Median age 35 ± 19, male 46.3%, hypertension 5.9%, diabetes 2.5%, asthma 5%, CHD 0.5%, cancer 1%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Alsultan et al;[108] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to Inhaled steroids Budesonide 200 mcg twice a day for 5 days and 21 assigned to SOC	age 60 to 80 65.3, male 38.8%, diabetes 53.1%, CKD 8.2%, cerebrovascular disease 4.1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Steroids (nasal corticosteroids)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Yildiz et al;[359] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 50 assigned to nasal steroids and 50 assigned to SOC	Mean age 37.8 ± , male 56%, hypertension 10%, diabetes 7%, COPD/asthma 8%, asthma %, CHD 14%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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
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;[495] Gonzalez Ochoa et al; preprint; 2020	Patients with mild (early within 3 days of onset) COVID-19. 124 assigned to sulodexide 500 RLU twice a day for 3 weeks and 119 assigned to standard of care	Median age 52 ± 10.6, male 47.4%, hypertension 34.2%, diabetes 22.2%, COPD 23%, coronary heart disease 21%,	Corticosteroids 62.5%, hydroxychloroquine 33.7%, ivermectin 43%	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events Notes: Significant loss to follow-up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty

					⊕◯◯◯

TD-0903 (inhaled JAK-inhibitor)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Singh et al;[496] Preprint; 2021	Patients with severe to critical COVID-19 infection. 19 assigned to TD-0903 1-10 mg once a day for 7 days and 6 assigned to SOC	Mean age 57.1 ± 12.3, male 68%, hypertension 68%, diabetes 40%	Corticosteroids 92%, remdesivir 12%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Tenofovir + emtricitabine

Uncertainty in potential benefits and harms. Further research is needed

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

RCT					
AR0-CORONA trial;[497] Parientti et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 30 assigned to tenofovir + emtricitabine 245/200 mg twice a day on day one followed by 245/200 mg a day for 7 days and 30 assigned to SOC	Mean age 42 ± 15, male 43%, hypertension 5%, diabetes 3.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯
ARTAN-C19 trial;[498] Lima et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 81 assigned to tenofovir +/- emtricitabine 300/200mg once a day and 41 assigned to SOC	Mean age 38 ± 14.9, male 35%, hypertension 17%, diabetes 10%, asthma 6%, CHD 3%, cancer 1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	

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;[499] preprint; 2021	Patients with severe COVID-19 infection. 28 assigned to thalidomide 100 mg a day for 14 days and 23 assigned to SOC	Mean age 62 ± 10, male 54.9%, hypertension 33.3%, diabetes 37.2%, COPD 5.9%, CHD 9.8%	Corticosteroids 100%, hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯

				allocation is probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Haghighi et al;[500] preprint; 2021	Patients with moderate to severe COVID-19 infection. 25 assigned to Thalidomide 100 mg a day for 14 days and 25 assigned to SOC	Median age 51 ± 18, male 68%, hypertension 24%, diabetes 16%, CHD 8%, cancer 14%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Tissue plasminogen activator (tPA)

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
STARS trial;[501] Barret et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 25 assigned to tPa 50mg bolus with or without drip and heparin and 25 assigned to SOC	Mean age 61, male 74%, hypertension 36%, diabetes 34%, COPD 62%, asthma %, CHD 66%, immunosuppressive therapy 66%	Corticosteroids 52%, remdesivir 40%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Tocilizumab **Tocilizumab reduces mortality and mechanical ventilation requirements without increasing severe adverse events.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COVACTA trial; Rosas et al;[502] peer-reviewed; 2020	Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned to standard of care	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, coronary heart disease 28%, obesity 20.5%	Corticosteroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** RR 0.85 (95%CI 0.79 to 93); RD -2.4% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 0.83 (95%CI 0.78 to 0.90); RD -2.9% (95%CI -3.8% to -1.7%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.07 (95%CI 1.01 to 1.13); RD 4.6% (95%CI 0.6% to 7.9%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No
Wang et al;[503] preprint; 2020	Patients with moderate to severe COVID-19. 34 assigned to tocilizumab 400 mg once or twice and 31 assigned to standard of care	Median age 63 ± 16, male 50.8%, hypertension 30.8%, diabetes 15.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Zhao et al;[170] 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	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	

	7 days, 7 assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir plus tocilizumab			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	information **Adverse events:** RR 0.95 (95%CI 0.86 to 1.04); RD -0.5% (95%CI -1.4% to 0.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
RCT-TCZ-COVID-19 trial;[504] 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;[505] Stone et al; peer-reviewed; 2020	Patients with severe COVID-19. 161 assigned to tocilizumab 8 mg/kg once and 81 assigned to standard of care	Median age 59.8 ± 15.1, male 58%, hypertension 49%, diabetes 31%, COPD 9%, asthma 9%, coronary heart disease 10%, chronic kidney disease 17%, cancer 12%,	Corticosteroids 9.5%, remdesivir 33.9%, hydroxychloroquine 3.7%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CORIMUNO-TOCI 1 trial;[506] Hermine et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 63 assigned to tocilizumab 8 mg/kg once followed by an optional 400 mg dose on day 3 and 67 assigned to standard of care	Median age 63.6 ± 16.2, male 67.7%, diabetes 33.6%, COPD 4.7%, asthma 6.3%, coronary heart disease 31.2%, chronic kidney disease 14%, cancer 7%,	Corticosteroids 43%, remdesivir 0.7%, hydroxychloroquine 6.2%, Lopinavir-ritonavir 3%, azithromycin 15.4%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
EMPACTA trial;[507] 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	Corticosteroids 59.4%, remdesivir 54.6%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

		disease 3.4%, obesity 24.4%			
REMAP-CAP - tocilizumab trial;[447] Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8 mg/kg once or twice, 48 assigned to sarilumab 400 mg once and 402 assigned to SOC	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%, cancer %, obesity %	Corticosteroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Veiga et al;[508] peer reviewed; 2020	Patients with severe to critical COVID-19. 65 assigned to TCZ 8 mg/kg once and 64 assigned to SOC	Mean age 57.4 ± 14.6, male 68%, hypertension 49.6%, diabetes 32.6%, COPD 3%, CHD 5.5%, cancer 7%,	Corticosteroids 71.3%	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY-TCZ trial;[509] Horby et al; peer reviewed; 2020	Patients with severe to critical COVID-19. 2022 assigned to TCZ 400-800 mg once or twice and 2094 assigned to SOC	Mean age 63.6 ± 13.6, male 67.3%, diabetes 28.5%, COPD 23%, asthma %, CHD 23%, CKD 5.5%	Corticosteroids 82%, hydroxychloroquine 2%, lopinavir-ritonavir 3%, tocilizumab %, azithromycin 9%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PreToVid trial;[510] Rutgers et al; preprint; 2021	Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice	Median age 66.5 ± 16.5, male 67%, comorbidities 74.3%	Corticosteroids 88.4%, remdesivir 18.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection,	

	and 180 assigned to SOC			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Talaschian et al;[511] preprint; 2021	Patients with severe COVID-19 infection. 17 assigned to TCZ 8 mg/kg once or twice and 19 assigned to SOC	Mean age 61.7 ± 14.2, male 52.7%, hypertension 50%, diabetes 36.1%, COPD 8.3%, asthma %, CHD 44.4%, CKD 2.8%, cancer 0%	Corticosteroids 33.3%, hydroxychloroquine 63.9%, lopinavir-ritonavir 8.3%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Hamed et al;[512] peer reviewed; 2021	Patients with severe COVID-19 infection. 23 assigned to TCZ 400 mg once and 26 assigned to SOC	Mean age 48 ±, male 85.5%, hypertension 36.8%	Corticosteroids 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
ARCHITECTS trial;[452] other; 2021	Patients with severe to critical COVID-19 infection. 10 assigned to TCZ 8 mg/kg once or twice and 11 assigned to SOC	Median age 61 ±	Corticosteroids 95.2%, remdesivir 90.4%, convalescent plasma 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
CORIMUNO-TOCI ICU trial;[451] Hermine et al; Peer reviewed; 2021	Patients with critcal COVID-19 infection. 49 assigned to TCZ 8mg/kg once or twice and 43 assigned to SOC	Mean age 64.2 ± , male 71.7%, diabetes 35.5%, COPD 7.8%, asthma 5.5%, CHD %, CKD 6.6%, cancer 2.2%,	Steroids 33.6%, remdesivir 0%, hydroxychloroquine 0%, lopinavir-ritonavir 4.3%, azithromycin 4.3%, convalescent	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

			plasma 0%	Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COV-AID trial; et al;[452] other; 2021	Patients with severe to critical COVID-19 infection. 81 assigned to TCZ 8 mg/kg once and 72 assigned to SOC	Median age 63	Corticosteroids 52.6%, remdesivir 5.8%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVIDOSE-2 trial; et al;[452] other; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to TCZ 40-120 mg once and 8 assigned to SOC	Median age 65	Corticosteroids 30%, remdesivir 75%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVIDSTORM trial;[452] other; 2021	Patients with severe to critical COVID-19 infection. 26 assigned to TCZ 8 mg/kg once and 13 assigned to SOC	Median age 66	Corticosteroids 77%, remdesivir 0%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVITOZ-01 trial; et al;[452] other; 2021	Patients with moderate to severe COVID-19 infection. 17 assigned to TCZ 8 mg/kg once or twice and 9 assigned to SOC	Median age 57	Corticosteroids 100%, remdesivir 52.9%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	

HMO-0224-20 trial;[452] other; 2021	Patients with severe to critical COVID-19 infection. 37 assigned to TCZ 8 mg/kg once and 17 assigned to SOC	Median age 63	Corticosteroids 85.2%, remdesivir 22.2%, convalescent plasma 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
REMDACTA trial; et al;[413] Rosas et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 430 assigned to TCZ 8 mg/kg once or twice and 210 assigned to SOC	Median age 6, male 63.2%, hypertension 61.7%, diabetes 39.5%, CHD 23.4%	Corticosteroids 88.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ImmCoVA trial;[452] other; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to TCZ 8 mg/kg once and 27 assigned to SOC	Median age 24	Corticosteroids 96%, remdesivir 14.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
TOCOVID trial;[452] other; 2021	Patients with moderate to severe COVID-19 infection. 136 assigned to TCZ 400 to 600 mg once and 134 assigned to SOC	Median age 53	Corticosteroids 35%, remdesivir 0.5%, convalescent plasma 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes: Risk of bias assessment extracted from a systematic review.	
COVINTOC trial; et al;[514] Soin et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection.	Median age 55 , male 85.5%, hypertension 39.4%, diabetes 41.1%,	Corticosteroids 91%, remdesivir 41.6%, convalescent plasma	Low for mortality and mechanical ventilation; high for symptom	

	91 assigned to TCZ 6 mg/kg once or twice and 88 assigned to SOC	COPD 2.2%, CHD 15%, CKD 4.4%	0%	resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOCIDEX trial;[515] Hermine et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 224 assigned to TCZ 400 mg once and 226 assigned to SOC	Median age 63 ± 21, male 68%, hypertension 37.1%, diabetes 23.8%, COPD %, asthma 8.4%, CHD 13.5%, CKD 7.2%	Corticosteroids 100%, convalescent plasma 1.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
MARIPOSA trial;[516] Kumar et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 49 assigned to TCZ 4 mg/kg and 48 assigned to TCZ 8 mg/kg	Mean age 56.8 ± 14.3, male 58.7%	Corticosteroids 22.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**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
Tofacitinib **Tofacitinib may increase symptom resolution or improvement and may increase severe adverse events.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
STOP-COVID trial;[517] Guimaraes et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 144 assigned to tofacitinib 10 mg twice a day for 14 days and 145 assigned to SOC	Mean age 56 ± 14, male 65.1%, hypertension 50.2%, diabetes 23.5%	Corticosteroids 78.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.1 (95%CI 0.98 to 1.23); RD 6.1% (95%CI 1.2% to 13.9%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⨁⨁◯◯ **Hospitalization:** No
Murugesan et al;[518] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 50 assigned to tofacitinib 20 mg a day for 14 days and 50 assigned to SOC	Mean age 46.5, male 74%, diabetes 36%, COPD 1%, CHD 5%	Corticosteroids 100%, remdesivir 98%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

					information
Triazavirin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Wu et al;[519] peer-reviewed; 2020	Patients with mild to critical COVID-19. 26 assigned to triazavirin 250 mg orally three or four times a day for 7 days and 26 assigned to standard of care	Median age 58 ± 17, male 50%, hypertension 28.8%, diabetes 15.4%, chronic lung disease 5.8%, coronary heart disease 15.4%, cerebrovascular disease 7.7%	Corticosteroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%, umifenovir 61.5%, ribavirin 28.9%,	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Umifenovir Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Chen et al;[160] preprint; 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days	Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
ELACOI trial;[306] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to lopinavir-ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Corticosteroids 12.5%, IVIG 6.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Nojomi et al;[520] 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;[521] peer-reviewed; 2020	Patients with mild COVID-19. 15 assigned to umifenovir 200 mg three times a day for 1 to 5 days and 15 assigned to standard of care	Mean age 35.5 ± 12.1, male 60%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Ghaderkhani S et al (Tehran University of Medical Sciences) trial;[522] Ghaderkhani et al; preprint; 2020	Patients with mild to moderate COVID-19. 28 assigned to umifenovir 200 mg three times a day for 10 days and 25 assigned to standard of care	Mean age 44.2 ± 19, male 39.6%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
UAIIC trial;[523] Darazam et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 51 assigned to umifenovir 600 mg a day for 10 days and 50 assigned to SOC	Mean age 61.2 ± 15.8, male 56.4%, hypertension 46.4%, diabetes 31.6%, COPD 10%, asthma 6.1%, CHD 11.2%, CKD 7.1%, cancer 1%	Corticosteroids 3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Ramachandran et al;[524] preprint; 2021	Patients with mild to moderate COVID-19 infection. 60 assigned to umifenovir 800 mg twice a day for 14 days and 63 assigned to	Mean age 46.7 ± 1.9, male 74.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

	SOC				
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;[525] preprint; 2020	Patients with severe COVID-19 infection. 26 assigned to vitamin C 12 g twice a day for 7 days and 28 assigned to standard of care	Mean age 67.4 ± 12.4, male 66.7%, hypertension 44.4%, diabetes 29.6%, chronic lung disease 5.6%, coronary heart disease 22.2%, chronic kidney disease 1.85%, cancer 5.6%, nervous system disease 20.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⨁◯◯◯
Kumari et al;[526] Peer reviewed; 2020	Patients with severe COVID-19. 75 assigned to Vit C 50 mg/kg a day and 75 assigned to SOC	Mean age 52.5 ± 11.5	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Jamali Moghadam Siahkali et al;[527] Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5 g a day for 5 days and 30 assigned to SOC	Mean age 59.2 ± 17, male 50%, hypertension 41.6%, diabetes 38.3%, COPD 10%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably	

				inappropriate.	
COVIDAtoZ - Vit C trial;[528] Thomas et al; peer reviewed; 2020	Patients with mild COVID-19. 48 assigned to Vit C 8000 mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Corticosteroids 8.4%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
VCACS trial;[529] Tehrani et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 18 assigned to Vit C 8 gr a day for 5 days and 26 assigned to SOC	Mean age 59.5, male 59%, hypertension 40.9%, diabetes 34%, COPD 7%, CHD 22.7%, CKD 9.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Beigmohammadi et al;[530] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin Vitamin D 600000 UI once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000mg a day in addition to others for 7 days. and 30 assigned to SOC	Mean age 52 ± 9, male 51.6%, hypertension 33.3%, diabetes 18.3%, asthma 13.3%, cancer 5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Majidi et al;[531] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 31 assigned to Vit C 500 mg a day and 69 assigned to	Mean age 62.4 ± , male 60%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	SOC			Notes: Concealment of allocation probably inappropriate.	
ALLIANCE trial;[532] Ried et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 162 assigned to Vit C 400 mg/kg a day for 7 days and 75 assigned to SOC	Mean age 62.3 ± 15.7, male 50%, diabetes 35%, COPD 34%, CHD 36%, cancer 4%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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;[533] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to vitamin D 0.532 once followed by 0.266 twice and 26 assigned to standard of care	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, coronary heart disease 3.9%, immunosuppression 9.2%, cancer %, obesity %	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information
SHADE trial;[534] Rastogi et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 16 assigned to vitamin D 60000 IU a day for 7 days and 24 assigned to standard of care	Mean age 48.7 ± 12.4, male 50%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of	

				allocation is probably inappropriate.	**Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information
Murai et al;[535] 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;[536] preprint; 2021	Patients with mild to moderate with low plasmatic vitamin D COVID-19 infection. 44 assigned to Vit D 60000 IU a day for 8 to 10 days and 43 assigned to SOC	Mean age 45.5 ± 13.3, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Sabico et al;[537] peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 36 assigned to Vit D 5000 IU for 14 days and 33 assigned to Vit D 1000 IU for 14 days	Mean age 49.8 ± 14.3, male 49.3%, hypertension 55%, diabetes 51%, COPD %, asthma 4%, CHD 6%, CKD 7%, obesity 33%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Maghbooli et al;[538] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 53 assigned to Vit D3 25 µg a day for 30 days and 53 assigned to SOC	Mean age 49.1 ± 14.1, male 60.4%, hypertension 31.1%, diabetes 23.6%, COPD 10.3%, CHD 12.3%, CKD 2.8%	Corticosteroids 46.2%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	

Beigmohammadi et al;[539] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin Vitamin D 600000 UI once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000mg a day in addition to others for 7 days. and 30 assigned to SOC	Mean age 52 ± 9, male 51.6%, hypertension 33.3%, diabetes 18.3%, asthma 13.3%, cancer 5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
REsCue trial;[540] Bishop et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 65 assigned to Vit D calcifediol 300 mcg a day for three days followed by 60 mcg a day for 27 days and 69 assigned to SOC	Mean age 43, male 41%, hypertension 21.6%, diabetes 6%, asthma 2.2%, CKD 3%, obesity 40%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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;[541] Gaborit et al; preprint; 2021	Patients with severe COVID-19 infection. 12 assigned to XAV-19 0.5 to 2 mg/kg on days 1 and 5 and 5 assigned to SOC	Mean age 71 ± 24, male 64.7%, hypertension 47.1%, diabetes 11.8%, COPD %, asthma 17.6%, CHD 29.4%, CKD 5.9%, cancer 11.8%, obesity 17.6%	Corticosteroids 100%, remdesivir 47.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

					Symptomatic infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
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;[542] 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
Abd-Elsalam et al;[543] peer-reviewed; 2020	Patients with mild to critical COVID-19. 96 assigned to zinc 220 mg twice a day for 15 days and 95 assigned to standard of care	Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Abdelmaksoud et	Patients with mild to	NR	NR	High for mortality and	

al;[544] Peer reviewed; 2020	critical COVID-19. 49 assigned to Zinc 220 mg twice a day and 56 assigned to SOC			mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Hospitalization:** Very low certainty ⨁◯◯◯
COVIDAtoZ -Zinc trial;[528] Thomas et al; ; 2020	Patients with mild COVID-19. 58 assigned to Zinc 50 mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Corticosteroids 8.4%,	Low for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ZINC COVID trial;[545] Patel et al; Peer reviewed; 2020	Patients with severe to critical COVID-19. 15 assigned to Zinc 0.24 mg/kg a day for 7 days and 18 assigned to SOC	Mean age 61.8 ± 16.9, male 63.6%, hypertension 48.4%, diabetes 18.2%, COPD 6%, CHD 21.2%,	Corticosteroids 75.8%, remdesivir 30.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Seet et al;[220] peer reviewed; 2021	Patients exposed to COVID-19 infection. 634 assigned to zinc 80 mg and 500 mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33 , male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Reszinate trial;[442] Kaplan et al; preprint; 2021	Patients with mild COVID-19 infection. 14 assigned to	Mean age 42.4, male 40%	NR	Low for mortality and mechanical ventilation; Low for symptom	

	resveratrol + Zinc 4000/150 mg once a day for five days and 16 assigned to SOC			resolution, infection, and adverse events Notes:	

α-lipoic acid

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zhong et al;[546] preprint; 2020	Patients with critical COVID-19 infection. 8 assigned to α-lipoic acid 1200 mg infusion once daily for 7 days and 9 assigned to standard of care	Median age 63 ± 7, male 76.5%, hypertension 47%, diabetes 23.5%, coronary heart disease 5.9%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Appendix 1. Summary of findings tables

Summary of findings Table 1.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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
Mortality (High vs standard dose) 28 to 90 days	Relative risk: 0.95 (CI 95% 0.67 - 1.34) Based on data from 1166 patients in 3 studies	**160** per 1000	**134** per 1000 Difference: **8 fewer per 1000** (CI 95% 53 fewer - 54 more)	**Low** Due to very serious imprecision.[5]	High dose steroids (i.e dexamethasone 12mg a day) may not decrease mortality in comparison to standard dose steroids (i.e dexamethasone 6mg a day)
	Relative risk: 0.85 (CI 95% 0.61 - 1.19)	**102** per 1000	**87** per 1000	**Low**	High dose steroids (i.e dexamethasone

Severe adverse events (High vs. standard dose) 28 days	Based on data from 982 patients in 1 study	Difference: **15 fewer per 1000** (CI 95% 40 fewer - 19 more)	Due to very serious imprecision[6]	12mg a day) may not increase severe adverse events in comparison to standard dose steroids (i.e dexamethasone 6mg a day)

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

Summary of findings Table 2.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 0.97 (CI 95% 0.86 - 1.1) Based on data from 8031 participants in 8 studies Follow up Median 28 days	**160** per 1000	**155** per 1000 Difference: **5 fewer per 1000** (CI 95% 22 fewer - 16 more)	**Low** Due to serious risk of bias, Due to serious inconsistency[1]	Remdesivir may not decrease mortality
Mechanical ventilation 28 days	Relative risk: 0.79 (CI 95% 0.55 - 1.14) Based on data from 7125 participants in 7 studies Follow up Median 28 days	**173** per 1000	**137** per 1000 Difference: **36 fewer per 1000** (CI 95% 78 fewer - 24 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: 1.1 (CI 95% 0.96 - 1.28) Based on data from 1981 participants in 4 studies Follow up 28 days	**606** per 1000	**667** per 1000 Difference: **61 more per 1000** (CI 95% 24 fewer - 170 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: 0.77 (CI 95% 0.46 - 1.29) Based on data from 2430 participants in 4 studies	**102** per 1000	**79** per 1000 Difference: **23 fewer per 1000** (CI 95% 55 fewer - 30 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Remdesivir may have little or no difference on severe adverse events
Hospitalization (in patients with non-severe disease) 28 days	Relative risk: 0.28 (CI 95% 0.11 - 0.75) Based on data from 562 participants in 1 study Follow up Median 28 days	**48** per 1000	**13** per 1000 Difference: **35 fewer per 1000** (CI 95% 43 fewer - 12 fewer)	**Low** Due to very serious imprecision[5]	Remdesivir may decrease hospitalizations (in patients with non-severe disease)

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; **Inconsistency: serious.** The direction of the effect is not consistent between the included studies;
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;
5. **Imprecision: very serious.**

Summary of findings Table 3.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 15 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 9104 patients in 13 studies Follow up Median 15 days	**160** per 1000	**171** per 1000 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% 0.93 - 1.24) Based on data from 7297 patients in 9 studies Follow up Median 15 days	**173** per 1000	**185** per 1000 Difference: **12 more per 1000** (CI 95% 12 fewer - 42 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: 1.01 (CI 95% 0.93 - 1.1) Based on data from 6601 patients in 10 studies Follow up 28 days	**606** per 1000	**612** per 1000 Difference: **6 more per 1000** (CI 95% 42 fewer - 61 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: 0.88 (CI 95% 0.72 - 1.11) Based on data from 4523 patients in 6 studies	**174** per 1000	**153** per 1000 Difference: **21 fewer per 1000** (CI 95% 49 fewer - 19 more)	**Low** Due to serious imprecision, Due to serious inconsistency[4]	Hcq may reduce covid-19 infections (in exposed individuals)
Hospitalizations (in patients with non-severe disease)	Relative risk: 0.91 (CI 95% 0.56 - 1.47) Based on data from 2789 patients in 7 studies	**48** per 1000	**44** per 1000 Difference: **4 fewer per 1000** (CI 95% 21 fewer - 23 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether hcq increases or decreases hospitalizations
Severe adverse events	Relative risk: 0.94 (CI 95% 0.66 - 1.34) Based on data from 8449 patients in 17 studies	**102** per 1000	**96** per 1000 Difference: **6 fewer per 1000** (CI 95% 35 fewer - 35 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. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies; **Imprecision: serious.** 95%CI includes no infection reduction;
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** 95%CI includes significant benefits and harms;
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;

Summary of findings Table 4.

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

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		SOC	LPV		
Mortality 28 days	Relative risk: 1.01 (CI 95% 0.92 - 1.11) Based on data from 8053 patients in 4 studies Follow-up median 28 days	**160** per 1000	**162** per 1000	**Moderate** Due to serious imprecision[1]	LPV probably has little or no difference on mortality
		Difference: **2 more per 1000** (CI 95% 13 fewer - 18 more)			
Mechanical ventilation 28 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 7622 patients in 4 studies Follow-up median 28 days	**173** per 1000	**185** per 1000	**High**	LPV does not reduce mechanical ventilation
		Difference: **12 more per 1000** (CI 95% 3 fewer - 29 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.03 (CI 95% 0.92 - 1.15) Based on data from 5239 patients in 2 studies Follow-up 28 days	**606** per 1000	**624** per 1000	**Moderate** Due to serious risk of bias[2]	LPV probably has little or no difference on symptom resolution or improvement
		Difference: **18 more per 1000** (CI 95% 48 fewer - 91 more)			
Symptomatic infection (exposed individuals)	Relative risk: 1.4 (CI 95% 0.78 - 2.54) Based on data from 318 patients in 1 study	**174** per 1000	**244** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether LPV increases or decreases symptomatic infection in exposed individuals
		Difference: **70 more per 1000** (CI 95% 38 fewer - 268 more)			
Severe adverse events	Relative risk: 0.6 (CI 95% 0.37 - 0.98) Based on data from 199 patients in 1 study	**102** per 1000	**61** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[4]	LPV may have little or no difference on severe adverse events
		Difference: **41 fewer per 1000** (CI 95% 64 fewer - 2 fewer)			
Hospitalization	Relative risk: 1.24 (CI 95% 0.6 - 2.56)	**48** per 1000	**60** per 1000	**Very low**	We are uncertain whether LPV

	Based on data from 471 patients in 1 study	Difference: **12 more per 1000** (CI 95% 19 fewer - 75 more)	Due to very serious imprecision[5]	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; **Imprecision: Very serious.** 95%CI includes significant benefits and harms;
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients;
5. **Imprecision: Very serious.** 95%CI includes significant benefits and harms.

Summary of findings Table 5.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	CP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (Low RoB studies) 28 days	Relative risk: 0.99 (CI 95% 0.94 - 1.05) Based on data from 19260 patients in 15 studies Follow up Median 28 days	**160** per 1000	**158** per 1000 Difference: **2 fewer per 1000** (CI 95% 10 fewer - 8 more)	**High** [1]	Convalescent plasma has little or no difference on mortality
Mechanical ventilation (Low RoB studies) 28 days	Relative risk: 1.05 (CI 95% 0.96 - 1.14) Based on data from 11110 patients in 9 studies Follow up Median 28 days	**173** per 1000	**182** per 1000 Difference: **9 more per 1000** (CI 95% 7 fewer - 24 more)	**High**	Convalescent plasma has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.95 - 1.02) Based on data from 14261 patients in 11 studies Follow up 28 days	**606** per 1000	**600** per 1000 Difference: **6 fewer per 1000** (CI 95% 30 fewer - 18 more)	**Moderate** Due to serious inconsistency[2]	Cp probably has little or no difference on symptom resolution or improvement
Hospitalizations	Relative risk: 0.78 (CI 95% 0.57 - 1.06) Based on data from 2474 patients in 3 studies	**48** per 1000	**37** per 1000 Difference: **11 fewer per 1000** (CI 95% 21 fewer - 3 more)	**Moderate** Due to serious imprecision[3]	Convalescent plasma probably has little or no difference on hospitalizations
Severe adverse events	Relative risk: 1.03 (CI 95% 0.85 - 1.26) Based on data from 6119 patients in 12 studies	**102** per 1000	**105** per 1000 Difference: **3 more per 1000** (CI 95% 15 fewer - 27 more)	**Low** Due to serious imprecision, Due to serious risk of bias[4]	Convalescent may have little or no difference on 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[5]	We are uncertain whether Ipv increases or decreases severe adverse events

1. **Inconsistency: no serious.** Point estimates vary widely;
2. **Inconsistency: serious.** Point estimates vary widely;
3. **Imprecision: serious.** Wide confidence intervals;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals;
5. **Risk of Bias: very serious.** Although adverse events were rare, we assume that some might have been missed and assumed as related to disease progression. RCT are needed to determine interventions safety.

Summary of findings Table 6.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	TCZ	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 0.85 (CI 95% 0.79 - 0.93) Based on data from 8455 participants in 20 studies Follow up Median 28 days	**160** per 1000	**136** per 1000 Difference: **24 fewer per 1000** (CI 95% 34 fewer - 11 fewer)	**High**	TCZ decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.83 (CI 95% 0.78 - 0.9) Based on data from 7609 participants in 21 studies Follow up Median 28 days	**173** per 1000	**144** per 1000 Difference: **29 fewer per 1000** (CI 95% 38 fewer - 17 fewer)	**High** [1]	TCZ decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.07 (CI 95% 1.01 - 1.2) Based on data from 7077 participants in 11 studies Follow up 28 days	**606** per 1000	**648** per 1000 Difference: **42 more per 1000** (CI 95% 6 more - 121 more)	**Low** Due to serious imprecision, Due to serious risk of bias[2]	TCZ may increase symptom resolution or improvement
Severe adverse events	Relative risk: 0.95 (CI 95% 0.86 - 1.04) Based on data from 5412 participants in 17 studies	**102** per 1000	**97** per 1000 Difference: **5 fewer per 1000** (CI 95% 14 fewer - 4 more)	**Moderate** Due to serious risk of bias[3]	Tcz probably has little or no difference on severe adverse events

1. **Imprecision: no serious.** 95% included significant and trivial reduction mechanical ventilation requirement reduction ;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits ;
3. **Risk of Bias: serious. Imprecision: no serious.** 95%ci included significant severe adverse events increase;

Summary of findings Table 7.

Population: Patients with COVID-19 infection
Intervention & comparator: Anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day); Anticoagulants in full dose (i.e., enoxaparin 1 m/kg twice a day); Anticoagulants in prophylactic dose (i.e., enoxaparin 40 mg a day); No anticoagulants

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	ACO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (full or intermediate dose vs. prophylactic dose in hospitalized patients) (excluding high risk of bias studies)	Relative risk: 0.97 (CI 95% 0.79 - 1.2) Based on data from 5415 patients in 8 studies	**160** per 1000	**155** per 1000 Difference: **5 fewer per 1000** (CI 95% 34 fewer - 32 more)	**Low** Due to very serious imprecision[1]	Anticoagulants in intermediate or full dose may have little or no difference on mortality in comparison with prophylactic dose
Venous thromboembolic events (intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.82 (CI 95% 0.33 - 2.0) Based on data from 921 patients in 3 studies	**70** per 1000	**57** per 1000 Difference: **13 fewer per 1000** (CI 95% 47 fewer - 70 more)	**Low** Due to very serious imprecision[2]	Anticoagulants in intermediate dose may slightly reduce venous thromboembolic events
Venous thromboembolic events (full dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.56 (CI 95% 0.44 - 0.72) Based on data from 4739 patients in 6 studies	**70** per 1000	**39** per 1000 Difference: **31 fewer per 1000** (CI 95% 39 fewer - 20 fewer)	**High**	Anticoagulants in intermediate or full dose probably decreases venous thromboembolic events (full dose)
Major bleeding (full or intermediate dose vs. prophylactic dose in hospitalized patients)	Relative risk: 1.76 (CI 95% 1.19 - 2.62) Based on data from 5780 patients in 8 studies	**19** per 1000	**33** per 1000 Difference: **14 more per 1000** (CI 95% 4 more - 31 more)	**Moderate** Due to serious imprecision[3]	Anticoagulants in intermediate or full dose probably increases major bleeding
Symptom resolution or improvement (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 1.08 (CI 95% 0.92 - 1.27) Based on data from 444 patients in 1 study	**606** per 1000	**654** per 1000 Difference: **48 more per 1000** (CI 95% 48 fewer - 164 more)	**Moderate** Due to serious imprecision[4]	Anticoagulants in prophylactic dose probably do not improve time to symptom resolution
Clinically important bleeding (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 2.5 (CI 95% 0.49 - 12.8) Based on data from 444 patients in 1 study	**9** per 1000	**23** per 1000 Difference: **14 more per 1000** (CI 95% 5 fewer - 106 more)	**Very low** Due to very serious imprecision[5]	It is uncertain if anticoagulants in prophylactic dose increase or decrease clinically important bleeding

Hospitalization (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 0.42 (CI 95% 0.11 - 1.64) Based on data from 444 patients in 1 study	**48** per 1000 **20** per 1000 Difference: **28 fewer per 1000** (CI 95% 43 fewer - 31 more)	**Very low** Due to very serious imprecision[6]	It is uncertain if anticoagulants in prophylactic increase or decrease hospitalization

1. **Imprecision: very serious.** 95%CI includes small benefits and harms;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: serious.** 95%CI includes harms and absence of harms;
4. **Imprecision: serious.** 95%CI includes harms and absence of harms;
5. **Imprecision: very serious.** 95%CI includes harms and absence of harms;
6. **Imprecision: very serious.** 95%CI includes harms and absence of harms;

Summary of findings Table 8.

Population: Patients with COVID-19 infection
Intervention: Non-corticosteroids anti-inflammatory drugs (NSAID)
Comparator: Standard of care

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		SOC	NSAID		
Mortality 28 days	Odds Ratio: 0.83 (CI 95% 0.66 - 1.05) Based on data from 2465490 patients in 6 studies	**160** per 1000	**137** per 1000	**Very low** Due to very serious risk of bias[1]	We are uncertain whether NSAID increases or decreases mortality
		Difference: **23 fewer per 1000** (CI 95% 48 fewer - 7 more)			

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

Summary of findings Table 9.

Population: Patients with COVID-19 infection
Intervention: Interferon beta-1a (IFN-B-1a)
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	IFN	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Relative risk: 1.07 (CI 95% 0.91 - 1.26) Based on data from 5210 patients in 4 studies Follow up Median 28 days	**160** per 1000	**171** per 1000 Difference: **11 more per 1000** (CI 95% 14 fewer - 42 more)	**Moderate** Due to serious imprecision[1]	IFN probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.97 (CI 95% 0.83 - 1.14) Based on data from 4881 patients in 4 studies Follow up 28 days	**173** per 1000	**168** per 1000 Difference: **5 fewer per 1000** (CI 95% 29 fewer - 24 more)	**Moderate** Due to serious imprecision[2]	IFN probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 0.96 (CI 95% 0.92 - 0.99) Based on data from 969 patients in 1 study Follow up 28 days	**606** per 1000	**582** per 1000 Difference: **24 fewer per 1000** (CI 95% 48 fewer - 6 fewer)	**Moderate** Due to serious imprecision[3]	Ifn probably has little or no difference on symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.94 (CI 95% 0.65 - 1.37) Based on data from 877 patients in 1 study Follow up 28 days	**102** per 1000	**96** per 1000 Difference: **6 fewer per 1000** (CI 95% 36 fewer - 38 more)	**Low** Due to very serious imprecision[4]	Ifn may have little or no difference on severe adverse events
Symptom resolution or improvement (inhaled)[5] 30 days	Hazard Ratio: 2.19 (CI 95% 1.03 - 4.69) Based on data from 81 patients in 1 study Follow up 28 days	**606** per 1000	**870** per 1000 Difference: **264 more per 1000** (CI 95% 11 more - 381 more)	**Low** Due to very serious imprecision[6]	IFN (inhaled) may increase symptom resolution or improvement

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

Summary of findings Table 10.

Population: Patients with COVID-19 infection
Intervention: Bamlanivimab +/- etesevimab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Bamlanivimab +/- etesevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.68 (CI 95% 0.17 - 2.8) Based on data from 2315 patients in 3 studies	**160** per 1000	**109** per 1000 Difference: **51 fewer per 1000** (CI 95% 133 fewer - 288 more)	**Very low** Due to serious imprecision, Due to very serious imprecision[1]	We are uncertain whether bamlanivimab increases or decreases mortality
Symptom resolution or improvement[2]	Relative risk: 1.02 (CI 95% 0.99 - 1.06) Based on data from 1750 patients in 3 studies	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 6 fewer - 36 more)	**Moderate** Due to serious imprecision[3]	Bamlanivimab probably has little or no difference on symptom resolution or improvement
Symptomatic infection	Relative risk: 0.56 (CI 95% 0.39 - 0.81) Based on data from 961 patients in 1 studies Follow up 28 days	**174** per 1000	**97** per 1000 Difference: **77 fewer per 1000** (CI 95% 106 fewer - 33 fewer)	**Moderate** Due to serious imprecision[4]	Bamlanivimab probably decreases symptomatic infection
Severe adverse events[5]	Hazard Ratio: 1.12 (CI 95% 0.75 - 1.66) Based on data from 3661 patients in 6 studies	**102** per 1000	**114** per 1000 Difference: **12 more per 1000** (CI 95% 24 fewer - 62 more)	**Low** Due to very serious imprecision[6]	Bamlanivimab may increase severe adverse events
Hospitalization[7]	Hazard Ratio: 0.37 (CI 95% 0.21 - 0.65) Based on data from 1804 patients in 3 studies	**48** per 1000	**18** per 1000 Difference: **30 fewer per 1000** (CI 95% 38 fewer - 17 fewer)	**Moderate** Due to serious imprecision[8]	Bamlanivimab +/- etesevimab probably decreases hospitalization

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. Symptomatic infection in persons at risk or exposed to SARS-COV2
3. **Imprecision: serious.** 95%CI includes benefits and absence of benefits;
4. **Imprecision: serious.** OIS not met;
5. Symptomatic infection in persons at risk or exposed to SARS-COV2
6. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
7. Symptomatic infection in persons at risk or exposed to SARS-COV2
8. **Imprecision: serious.** Low number of patients;

Summary of findings Table 11.

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 language summary**
Mortality 28 days	Relative risk: 1.18 (CI 95% 0.83 - 1.69) Based on data from 1829 participants in 8 studies Follow up Median 28 days	**160** per 1000	**189** per 1000 Difference: **29 more per 1000** (CI 95% 27 fewer - 110 more)	**Low** Due to very serious imprecision[1]	Favipiravir may increase mortality
Mechanical ventilation 28 days	Relative risk: 1.27 (CI 95% 0.91 - 1.76) Based on data from 1632 participants in 6 studies Follow up Median 28 days	**173** per 1000	**220** per 1000 Difference: **47 more per 1000** (CI 95% 16 fewer - 131 more)	**Low** Due to very serious imprecision[2]	Favipiravir may increase mechanical ventilation
Symptom resolution or improvement (Low RoB studies) 28 days	Relative risk: 1.02 (CI 95% 0.94 - 1.1) Based on data from 842 participants in 3 studies Follow up 28 days	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 36 fewer - 61 more)	**Moderate** Due to serious imprecision[3]	Favipiravir probably has little or no difference on symptom resolution or improvement
Hospitalization (in patients with non-severe disease)	Relative risk: 0.89 (CI 95% 0.16 - 5.05) Based on data from 515 participants in 3 studies Follow up 28 days	**48** per 1000	**43** per 1000 Difference: **5 fewer per 1000** (CI 95% 40 fewer - 194 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether favipiravir increases or decreases hospitalization (in patients with non-severe disease)
Severe adverse events 30 days	Relative risk: 0.8 (CI 95% 0.46 - 1.41) Based on data from 1264 participants in 7 studies Follow up 28 days	**606** per 1000	**485** per 1000 Difference: **121 fewer per 1000** (CI 95% 327 fewer - 248 more)	**Very low** Due to very serious imprecision, Due to serious risk of bias[5]	We are uncertain whether favipiravir increases or decreases severe adverse events

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

Summary of findings Table 12.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (Low risk of bias studies)	Relative risk: 0.96 (CI 95% 0.58 - 1.59) Based on data from 1412 participants in 6 studies	**160** per 1000	**154** per 1000 Difference: **6 fewer per 1000** (CI 95% 67 fewer - 94 more)	**Very low** Due to very serious imprecision[1]	Ivermectin may have little or no difference in mortality
Mechanical ventilation	Relative risk: 1.05 (CI 95% 0.64 - 1.72) Based on data from 1046 participants in 6 studies	**173** per 1000	**182** per 1000 Difference: **9 more per 1000** (CI 95% 62 fewer - 125 more)	**Very low** Due to very serious imprecision[2]	Ivermectin may have little or no difference on mechanical ventilation
Symptom resolution or improvement (Low risk of bias studies)	Relative risk: 1.03 (CI 95% 0.96 - 1.1) Based on data from 707 participants in 4 studies	**606** per 1000	**624** per 1000 Difference: **18 more per 1000** (CI 95% 24 fewer - 61 more)	**Moderate** Due to serious imprecision[3]	Ivermectin probably has little or no difference on symptom resolution or improvement
Symptomatic infection[4]	Relative risk: 0.22 (CI 95% 0.09 - 0.53) Based on data from 1974 participants 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[5]	We are uncertain whether ivermectin increases or decreases symptomatic infection
Severe adverse events	Relative risk: 1.29 (CI 95% 0.44 - 3.85) Based on data from 917 participants in 5 studies Follow up 28 days	**102** per 1000	**132** per 1000 Difference: **30 more per 1000** (CI 95% 57 fewer - 291 more)	**Very low** Due to very serious imprecision, Due to very serious risk of bias[6]	We are uncertain whether ivermectin increases or decreases severe adverse events
Hospitalization (in non-severe patients)	Relative risk: 0.67 (CI 95% 0.39 - 1.14) Based on data from 1179 participants in 5 studies Follow up 28 days	**48** per 1000	**32** per 1000 Difference: **16 fewer per 1000** (CI 95% 29 fewer - 7 more)	**Low** Due to very serious imprecision[7]	Ivermectin may have little or no difference on hospitalization (in non-severe patients)

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

5. **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);
6. **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 ;
7. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits ;

Summary of findings Table 13.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.64 (CI 95% 0.51 - 0.8) Based on data from 2659 patients in 3 studies	**160** per 1000	**102** per 1000 Difference: **58 fewer per 1000** (CI 95% 78 fewer - 32 fewer)	**High**	Baricitinib decreases mortality
Invasive mechanical ventilation	Relative risk: 0.66 (CI 95% 0.46 - 0.93) Based on data from 922 patients in 1 studies Follow up 30 days	**173** per 1000	**114** per 1000 Difference: **59 fewer per 1000** (CI 95% 93 fewer - 12 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[1]	Baricitinib may decrease invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.27 (CI 95% 1.13 - 1.42) Based on data from 2659 patients in 3 studies Follow up 30 days	**606** per 1000	**770** per 1000 Difference: **164 more per 1000** (CI 95% 79 more - 255 more)	**High**	Baricitinib improves symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.64 - 0.95) Based on data from 2659 patients in 3 studies Follow up 30 days	**102** per 1000	**80** per 1000 Difference: **22 fewer per 1000** (CI 95% 37 fewer - 5 fewer)	**Moderate** Due to serious risk of bias[2]	Baricitinib probably has little or no difference on severe adverse events

1. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up; **Imprecision: serious.** Low number of patients;
2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up;

Summary of findings Table 14.

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

Outcome Time frame	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (quality of evidence)	**Plain text summary**
		SOC	Azithromycin		
Mortality	Relative risk: 1.01 (CI 95% 0.92 - 1.1) Based on data from 8272 patients in 3 studies	**160** per 1000	**162** per 1000	**Moderate** Due to serious imprecision[1]	Azithromycin probably has little or no difference on mortality
		Difference: **2 more per 1000** (CI 95% 13 fewer - 16 more)			
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.78 - 1.13) Based on data from 8544 patients in 3 studies	**173** per 1000	**163** per 1000	**Moderate** Due to serious imprecision[2]	Azithromycin probably has little or no difference on invasive mechanical ventilation
		Difference: **10 fewer per 1000** (CI 95% 38 fewer - 22 more)			
Symptom resolution or improvement[3]	Relative risk: 1.02 (CI 95% 0.99 - 1.04) Based on data from 9287 patients in 4 studies	**606** per 1000	**618** per 1000	**High**	Azithromycin has little or no difference on symptom resolution or improvement
		Difference: **12 more per 1000** (CI 95% 6 fewer - 24 more)			
Severe adverse events	Relative risk: 1.23 (CI 95% 0.51 - 2.96) Based on data from 439 patients in 1 study Follow-up 28 days	**102** per 1000	**125** per 1000	**Very low** Due to very serious imprecision, Due to very serious risk of bias[4]	We are uncertain whether azithromycin increases or decreases severe adverse events
		Difference: **23 more per 1000** (CI 95% 50 fewer - 200 more)			
Hospitalizations	Relative risk: 0.98 (CI 95% 0.52 - 1.86) Based on data from 493 patients in 2 studies Follow-up 21 days	**48** per 1000	**47** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Azithromycin may have little or no difference on hospitalizations
		Difference: **1 fewer per 1000** (CI 95% 23 fewer - 41 more)			

1. **Imprecision: Serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: Serious.** 95%CI includes significant benefits and harms;
3. Symptomatic infection in persons at risk or exposed to SARS-CoV2;
4. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very serious.** 95%CI includes significant benefits and absence of benefits;

5. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow-up; **Imprecision: Serious.** 95%CI includes significant benefits and absence of benefits.

Summary of findings Table 15.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.99 (CI 95% 0.93 - 1.06) Based on data from 17711 patients in 8 studies	**160** per 1000	**158** per 1000 Difference: **2 fewer per 1000** (CI 95% 11 fewer - 10 more)	**Moderate** Due to serious imprecision[1]	Colchicine probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 0.98 (CI 95% 0.89 - 1.08) Based on data from 16721 patients in 5 studies Follow up 30 days	**173** per 1000	**170** per 1000 Difference: **3 fewer per 1000** (CI 95% 19 fewer - 14 more)	**Moderate** Due to serious imprecision[2]	Colchicine probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement	Relative risk: 1.01 (CI 95% 0.96 - 1.06) Based on data from 11754 patients in 4 studies Follow up 30 days	**173** per 1000	**175** per 1000 Difference: **2 more per 1000** (CI 95% 7 fewer - 10 more)	**High**	Colchicine has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 0.99) Based on data from 4880 patients in 3 studies Follow up 30 days	**102** per 1000	**80** per 1000 Difference: **22 fewer per 1000** (CI 95% 40 fewer - 1 fewer)	**High**	Colchicine has little or no difference on severe adverse events
Pulmonary embolism	Relative risk: 5.55 (CI 95% 1.23 - 25.0) Based on data from 4399 patients in 1 study Follow up 30 days	**0.9** per 1000	**5.0** per 1000 Difference: **4.1 more per 1000** (CI 95% 0.21 more - 21.6 more)	**Low** Due to very serious imprecision[3]	Colchicine may have little or no difference on pulmonary embolism
Hospitalization (in patients with non-severe disease)	Relative risk: 0.81 (CI 95% 0.63 - 1.04) Based on data from 4777 patients in 2 studies Follow up 30 days	**48** per 1000	**39** per 1000 Difference: **9 fewer per 1000** (CI 95% 18 fewer - 2 more)	**Moderate** Due to serious imprecision[4]	Colchicine probably has little or no difference on hospitalization (in patients with non-severe disease)

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

Summary of findings Table 16.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (Low RoB studies)	Relative risk: 1.14 (CI 95% 0.83 - 1.56) Based on data from 1163 patients in 2 studies	**160** per 1000	**182** per 1000 Difference: **22 more per 1000** (CI 95% 27 fewer - 90 more)	**Low** Due to very serious imprecision[1]	Sofosbuvir alone or in combination may have little or no difference on mortality
Invasive mechanical ventilation (Low RoB studies)	Relative risk: 1.02 (CI 95% 0.59 - 1.76) Based on data from 1163 patients in 2 studies Follow up 30 days	**173** per 1000	**176** per 1000 Difference: **3 more per 1000** (CI 95% 71 fewer - 131 more)	**Low** Due to very serious imprecision[2]	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir may have little or no difference on invasive mechanical ventilation
Symptom resolution or improvement (Low RoB studies)	Relative risk: 1.01 (CI 95% 0.95 - 1.08) Based on data from 1163 patients in 2 studies Follow up 7 days	**606** per 1000	**612** per 1000 Difference: **6 more per 1000** (CI 95% 30 fewer - 48 more)	**Moderate** Due to serious imprecision[3]	Sofosbuvir alone or in combination probably has little or no difference on symptom resolution or improvement

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

Summary of findings Table 17.

Patients with COVID-19 infection
Intervention: REGEN-COV (casirivimab and imdevimab)
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	REGEN-COV (casirivimab and imdevimab)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.83 (CI 95% 0.64 - 1.07) Based on data from 16667 patients in 4 studies	**160** per 1000	**133** per 1000 Difference: **27 fewer per 1000** (CI 95% 58 fewer - 11 more)	**Low** Due to serious inconsistency, due to serious imprecision[1]	Regen-cov (casirivimab and imdevimab) may decrease mortality
Mortality (seronegative)	Relative risk: 0.79 (CI 95% 0.71 - 0.89) Based on data from 3673 patients in 2 studies	**160** per 1000	**128** per 1000 Difference: **34 fewer per 1000** (CI 95% 46 fewer - 18 fewer)	**Moderate** Due to serious indirectness[2]	Regen-cov (casirivimab and imdevimab) probably decreases mortality in seronegative patients
Invasive mechanical ventilation	Relative risk: 0.79 (CI 95% 0.54 - 1.14) Based on data from 14575 patients in 3 studies Follow up 30 days	**173** per 1000	**137** per 1000 Difference: **36 fewer per 1000** (CI 95% 80 fewer - 24 more)	**Low** Due to very serious imprecision[3]	Regen-cov (casirivimab and imdevimab) may decrease invasive mechanical ventilation
Invasive mechanical ventilation (seronegative)	Relative risk: 0.82 (CI 95% 0.74 - 0.9) Based on data from 3603 patients in 2 studies	**173** per 1000	**142** per 1000 Difference: **31 fewer per 1000** (CI 95% 45 fewer - 17 fewer)	**Moderate** Due to serious indirectness, due to serious imprecision[4]	Regen-cov (casirivimab and imdevimab) probably decreases invasive mechanical ventilation in seronegative patients
Symptom resolution or improvement	Relative risk: 1.06 (CI 95% 1.0 - 1.12) Based on data from 14746 patients in 3 studies	**606** per 1000	**642** per 1000 Difference: **36 more per 1000** (CI 95% 0 fewer - 73 more)	**Low** Due to serious imprecision, Due to serious inconsistency[5]	Regen-cov (casirivimab and imdevimab) may increase symptom resolution or improvement
Symptom resolution or improvement (seronegative)	Relative risk: 1.1 (CI 95% 1.06 - 1.14) Based on data from 6277 patients in 3 studies Follow up 30 days	**606** per 1000	**679** per 1000 Difference: **61 more per 1000** (CI 95% 36 more - 85 more)	**Moderate** Due to serious indirectness[6]	Regen-cov (casirivimab and imdevimab) probably increases symptom resolution or improvement in seronegative patients
	Relative risk: 0.3 (CI 95% 0.2 - 0.46)	**48** per 1000	**14** per 1000	**Moderate**	Regen-cov (casirivimab and imdevimab)

Hospitalization (in patients with non-severe disease)	Based on data from 5049 patients in 3 studies Follow up 30 days	Difference: **34 fewer per 1000** (CI 95% 38 fewer - 26 fewer)	Due to serious imprecision[7]	probably reduces hospitalization in patients with recent onset non-severe disease
Symptomatic infection (in exposed individuals)	Relative risk: 0.43 (CI 95% 0.31 - 0.59) Based on data from 2678 patients in 3 studies Follow up 30 days	**174** per 1000 / **75** per 1000 Difference: **99 fewer per 1000** (CI 95% 120 fewer - 71 fewer)	**High**	Regen-cov (casirivimab and imdevimab) decreases symptomatic infection in exposed individuals
Severe adverse events	Relative risk: 0.54 (CI 95% 0.27 - 1.07) Based on data from 9697 patients in 6 studies	**102** per 1000 / **55** per 1000 Difference: **47 fewer per 1000** (CI 95% 74 fewer - 7 more)	**Moderate** Due to serious imprecision[8]	Regen-cov (casirivimab and imdevimab) probably has little or no difference on severe adverse events

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

Summary of findings Table 18.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.9 (CI 95% 0.46 - 1.77) Based on data from 1891 patients in 2 studies	**160** per 1000	**144** per 1000 Difference: **16 fewer per 1000** (CI 95% 86 fewer - 123 more)	**Very low** Due to serious risk of bias, due to very serious imprecision[1]	We are uncertain whether inhaled corticosteroids increase or decrease mortality
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.44 - 1.98) Based on data from 1560 patients in 1 study	**173** per 1000	**163** per 1000 Difference: **10 fewer per 1000** (CI 95% 97 fewer - 170 more)	**Very low** Due to serious risk of bias, due to very serious imprecision[2]	We are uncertain whether inhaled corticosteroids increase or decrease invasive mechanical ventilation
Symptom resolution or improvement[3]	Relative risk: 1.15 (CI 95% 1.08 - 1.24) Based on data from 2425 patients in 6 studies	**606** per 1000	**697** per 1000 Difference: **91 more per 1000** (CI 95% 48 more - 145 more)	**Moderate** Due to serious risk of bias[4]	Inhaled corticosteroids probably increase symptom resolution or improvement
Hospitalizations	Relative risk: 0.85 (CI 95% 0.58 - 1.26) Based on data from 2459 patients in 3 studies	**48** per 1000	**41** per 1000 Difference: **7 fewer per 1000** (CI 95% 20 fewer - 12 more)	**Very low** Due to serious risk of bias, due to very serious imprecision[5]	We are uncertain whether inhaled corticosteroids increase or decrease hospitalizations

1. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. Symptomatic infection in persons at risk or exposed to SARS-COV2
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits , Wide confidence intervals;

Summary of findings Table 19.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Fluvoxamine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Relative risk: 0.69 (CI 95% 0.36 - 1.27) Based on data from 1497 patients in 1 study	**160** per 1000	**110** per 1000 Difference: **50 fewer per 1000** (CI 95% 102 fewer - 43 more)	**Very low** Due to very serious imprecision[1]	There were too few who experienced the mortality, in ordern to determine whether fluvoxamine made a difference
Mechanical ventilation	Relative risk: 0.77 (CI 95% 0.45 - 1.3) Based on data from 1497 patients in 1 study	**160** per 1000	**123** per 1000 Difference: **37 fewer per 1000** (CI 95% 88 fewer - 48 more)	**Very low** Due to very serious imprecision[2]	There were too few who experienced the mortality, in order to determine whether fluvoxamine made a difference
Hospitalizations	Relative risk: 0.77 (CI 95% 0.58 - 1.02) Based on data from 1649 patients in 2 studies	**48** per 1000	**37** per 1000 Difference: **11 fewer per 1000** (CI 95% 20 fewer - 1 more)	**Moderate** Due to serious imprecision[3]	Fluvoxamine probably has little or no difference on hospitalizations
Severe adverse events[4]	Relative risk: 0.81 (CI 95% 0.54 - 1.22) Based on data from 1649 patients in 2 studies	**102** per 1000	**83** per 1000 Difference: **19 fewer per 1000** (CI 95% 47 fewer - 22 more)	**Low** Due to very serious imprecision[5]	Fluvoxamine may not increase severe adverse events

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

Summary of findings Table 20.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Standard of care	Molnupiravir		
Mortality	Relative risk: 0.13 (CI 95% 0.02 - 0.77) Based on data from 1610 patients in 2 studies	**160** per 1000	**21** per 1000 Difference: **139 fewer per 1000** (CI 95% 157 fewer - 37 fewer)	**Very low** Due to very serious imprecision[1]	We are uncertain whether molnupiravir increases or decreases mortality
Hospitalization	Relative risk: 0.56 (CI 95% 0.29 - 1.07) Based on data from 2351 patients in 3 studies	**48** per 1000	**34** per 1000 Difference: **21 fewer per 1000** (CI 95% 34 fewer - 3 more)	**Moderate** Due to serious imprecision[2]	Molnupiravir probably reduces hospitalization
Severe adverse events	Relative risk: 0.49 (CI 95% 0.23 - 1.05) Based on data from 1411 patients in 1 studies Follow up 29	**102** per 1000	**50** per 1000 Difference: **52 fewer per 1000** (CI 95% 79 fewer - 5 more)	**Low** Due to very serious imprecision[3]	Molnupiravir may have little or no difference on severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms, Low number of patients;
2. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
3. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;

Summary of findings Table 21.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Standard of care	Nirmatrelvir-ritonavir		
Mortality	Relative risk: 0.04 (CI 95% 0.0 - 0.68) Based on data from 2085 participants in 1 studies	**160** per 1000	**6** per 1000 Difference: **154 fewer per 1000** (CI 95% 160 fewer - 51 fewer)	**Very low** Due to very serious imprecision[1]	We are uncertain whether nirmatrelvir-ritonavir increases or decreases mortality

Hospitalization	Relative risk: 0.12 (CI 95% 0.06 - 0.25) Based on data from 2085 participants in 1 studies	**48** per 1000 **6** per 1000 Difference: **42 fewer per 1000** (CI 95% 45 fewer - 36 fewer)	**Moderate** Due to serious imprecision[2]	Nirmatrelvir-ritonavir probably decreases hospitalizations
Severe adverse events	Relative risk: 0.49 (CI 95% 0.3 - 0.8) Based on data from 2224 participants in 1 studies Follow up 29	**102** per 1000 **50** per 1000 Difference: **52 fewer per 1000** (CI 95% 71 fewer - 20 fewer)	**Moderate** Due to serious imprecision[3]	Nirmatrelvir-ritonavir probably has little or no difference on severe adverse events

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms, Low number of patients;
2. **Imprecision: serious.** 95%CI includes significant benefits and absence of benefits;
3. **Imprecision: serious.** Low number of events;

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