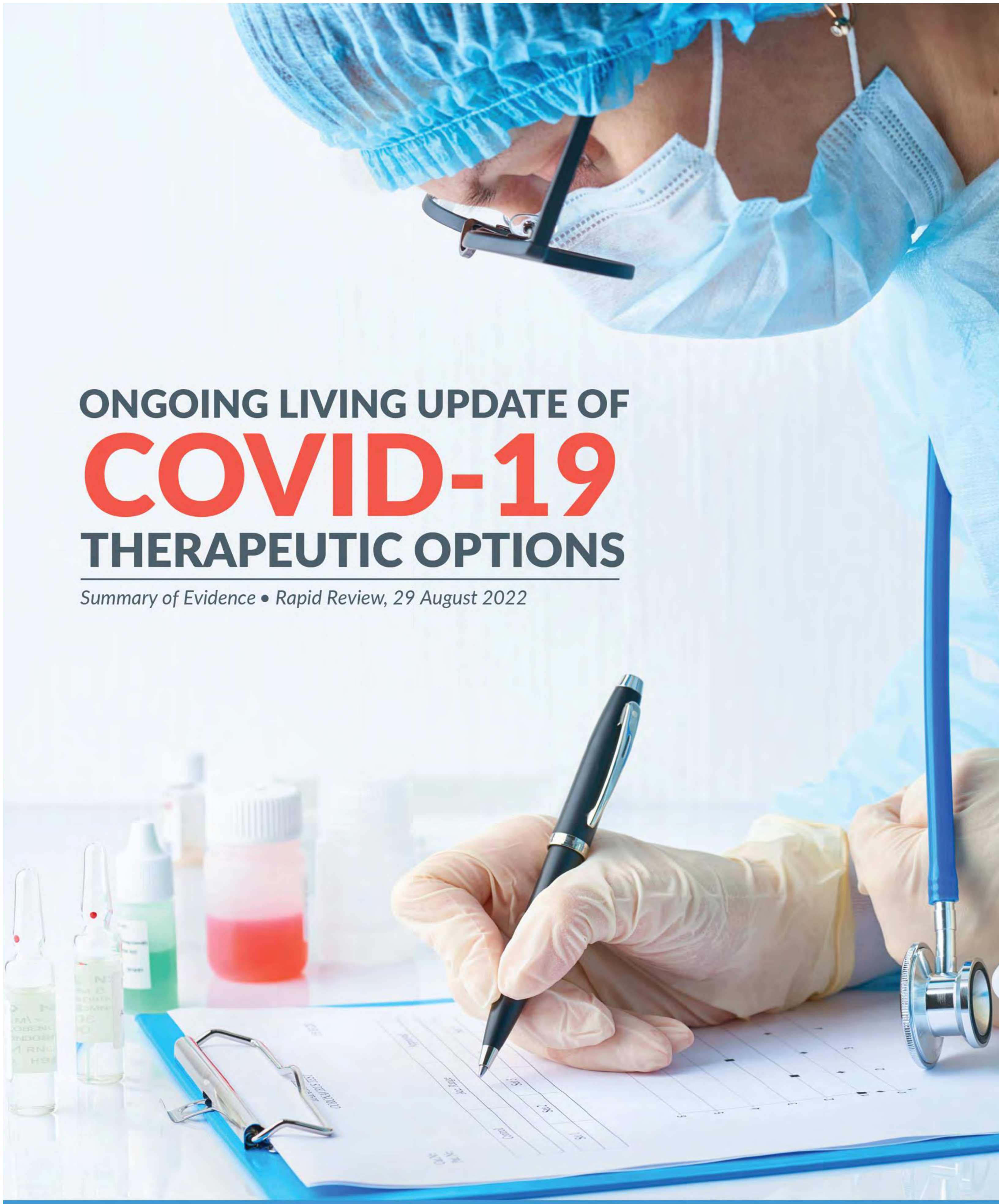


ONGOING LIVING UPDATE OF COVID-19 THERAPEUTIC OPTIONS

Summary of Evidence • Rapid Review, 29 August 2022

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

BE AWARE. PREPARE. ACT.

www.paho.org/coronavirus

Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence, Rapid Review 29 August 2022

PAHO/IMS/EIH/COVID-19/22-0022

© Pan American Health Organization, 2022

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO license (CC BY-NC-SA 3.0 IGO); https://creativecommons.org/licenses/by-nc-sa/3.0/igo.

Under the terms of this license, this work may be copied, redistributed, and adapted for non-commercial purposes, provided the new work is issued using the same or equivalent Creative Commons license and it is appropriately cited. In any use of this work, there should be no suggestion that the Pan American Health Organization (PAHO) endorses any specific organization, product, or service. Use of the PAHO logo is not permitted.

All reasonable precautions have been taken by PAHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall PAHO be liable for damages arising from its use.

Disclaimer

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

Contents

Executive summary
Background
Summary of evidence
Key findings
Changes since previous edition
Concluding remarks
Hallazgos clave
Cambios respecto a la anterior versión
Conclusiones
Systematic review of therapeutic options for treatment of COVID-19
Background
Methods
    Search strategy
    Study selection
    Inclusion criteria
    Living evidence synthesis
Results
    Studies identified and included
    Risk of bias
Main findings
    Full description of included studies
Appendix 1. Summary of findings tables
References

Executive summary

Background

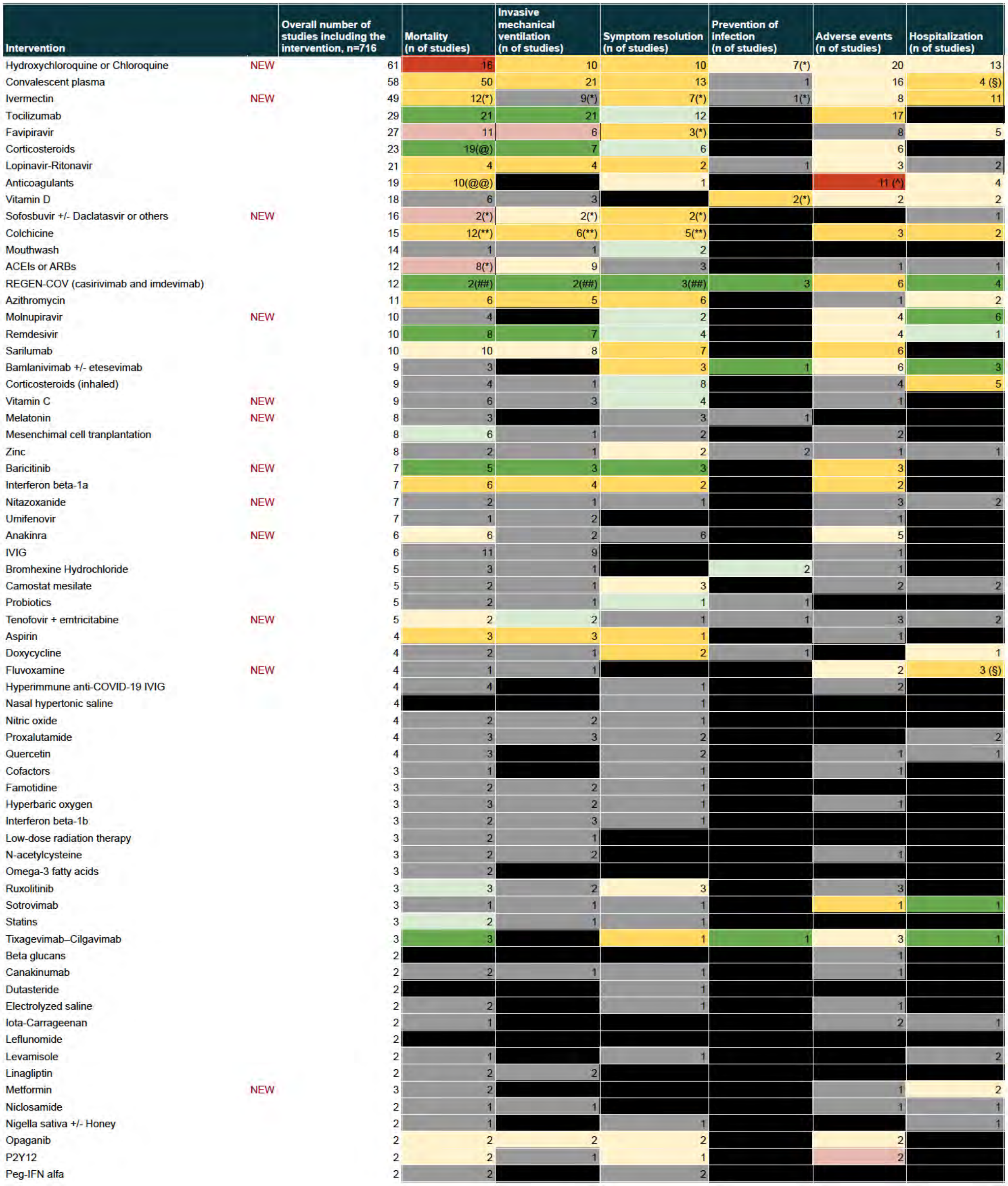
The urgent need for evidence on measures to respond to the COVID-19 pandemic had led to a rapid escalation in numbers of studies testing potential therapeutic options. The vast amount of data generated by these studies must be interpreted quickly so that physicians have the information to make optimal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

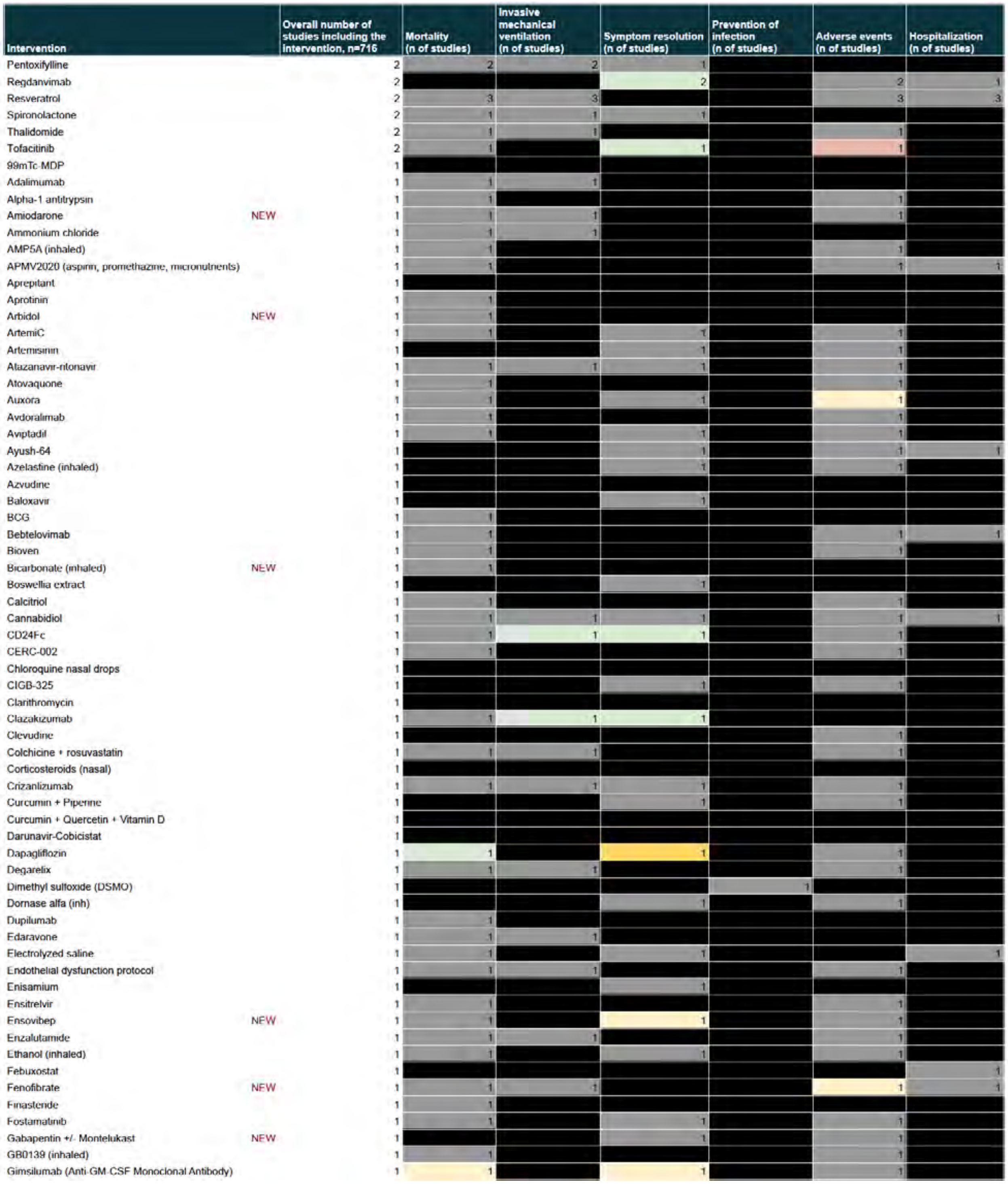
Summary of evidence

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. A living interactive version of Tables 1 and 2 is available here. Table 3 summarizes the status of evidence for the 232 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=716) (interactive online version)

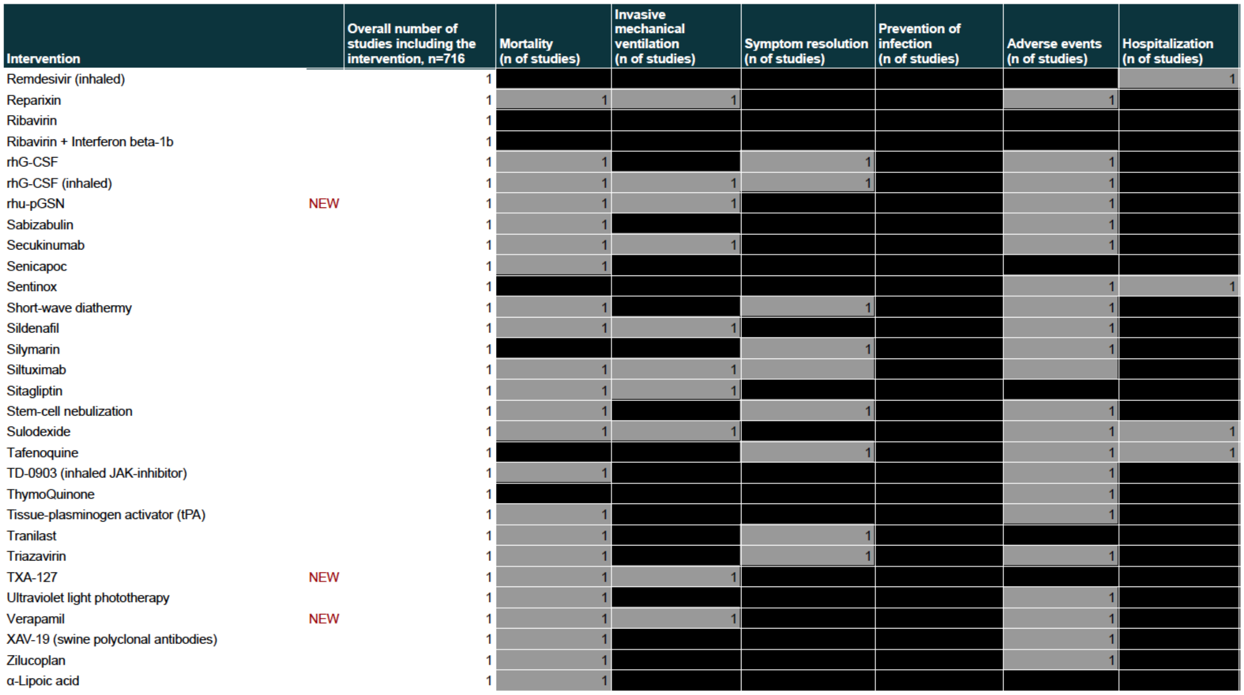


Intervention		Overall number of studies including the intervention, n=716	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Hydroxychloroquine or Chloroquine	NEW	61	16	10	10	7(*)	20	13
Convalescent plasma		58	50	21	13	1	16	4 (§)
Ivermectin	NEW	49	12(*)	9(*)	7(*)	1(*)	8	11
Tocilizumab		29	21	21	12		17	
Favipiravir		27	11	6	3(*)		8	5
Corticosteroids		23	19(@)	7	6		6	
Lopinavir-Ritonavir		21	4	4	2	1	3	2
Anticoagulants		19	10(@@)		1		11 (^)	4
Vitamin D		18	6	3		2(*)	2	2
Sofosbuvir +/- Daclatasvir or others	NEW	16	2(*)	2(*)	2(*)			1
Colchicine		15	12(**)	6(**)	5(**)		3	2
Mouthwash		14	1	1	2			
ACEIs or ARBs		12	8(*)	9	3		1	1
REGEN-COV (casirivimab and imdevimab)		12	2(##)	2(##)	3(##)	3	6	4
Azithromycin		11	6	5	6		1	2
Molnupiravir	NEW	10	4		2		4	6
Remdesivir		10	8	7	4		4	1
Sarilumab		10	10	8	7		6	
Bamlanivimab +/- etesevimab		9	3		3	1	6	3
Corticosteroids (inhaled)		9	4	1	8		4	5
Vitamin C	NEW	9	6	3	4		1	
Melatonin	NEW	8	3		3	1		
Mesenchimal cell tranplantation		8	6	1	2		2	
Zinc		8	2	1	2	2	1	1
Baricitinib	NEW	7	5	3	3		3	
Interferon beta-1a		7	6	4	2		2	
Nitazoxanide	NEW	7	2	1	1		3	2
Umifenovir		7	1	2			1	
Anakinra	NEW	6	6	2	6		5	
IVIG		6	11	9			1	
Bromhexine Hydrochloride		5	3	1		2	1	
Camostat mesilate		5	2	1	3		2	2
Probiotics		5	2	1	1	1		
Tenofovir + emtricitabine	NEW	5	2	2	1	1	3	2
Aspirin		4	3	3	1		1	
Doxycycline		4	2	1	2	1		1
Fluvoxamine	NEW	4	1	1			2	3 (§)
Hyperimmune anti-COVID-19 IVIG		4	4		1		2	
Nasal hypertonic saline		4			1			
Nitric oxide		4	2	2	1			
Proxalutamide		4	3	3	2			2
Quercetin		4	3		2		1	1
Cofactors		3	1		1		1	
Famotidine		3	2	2	1			
Hyperbaric oxygen		3	3	2	1		1	
Interferon beta-1b		3	2	3	1			
Low-dose radiation therapy		3	2	1				
N-acetylcysteine		3	2	2			1	
Omega-3 fatty acids		3	2					
Ruxolitinib		3	3	2	3		3	
Sotrovimab		3	1	1	1		1	1
Statins		3	2	1	1			
Tixagevimab–Cilgavimab		3	3		1	1	3	1
Beta glucans		2					1	
Canakinumab		2	2	1	1		1	
Dutasteride		2			1			
Electrolyzed saline		2	2		1		1	
Iota-Carrageenan		2	1				2	1
Leflunomide		2						
Levamisole		2	1		1			2
Linagliptin		2	2	2				
Metformin	NEW	3	2				1	2
Niclosamide		2	1	1			1	1
Nigella sativa +/- Honey		2	1		1			1
Opaganib		2	2	2	2		2	
P2Y12		2	2	1	1		2	
Peg-IFN alfa		2	2		2			



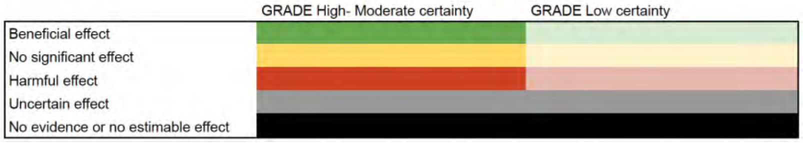
Intervention		Overall number of studies including the intervention, n=716	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Pentoxifylline		2	2	2	1			
Regdanvimab		2			2		2	1
Resveratrol		2	3	3			3	3
Spironolactone		2	1	1	1			
Thalidomide		2	1	1			1	
Tofacitinib		2	1		1		1	
99mTc-MDP		1						
Adalimumab		1	1	1				
Alpha-1 antitrypsin		1	1				1	
Amiodarone	NEW	1	1	1			1	
Ammonium chloride		1	1	1				
AMP5A (inhaled)		1	1				1	
APMV2020 (aspirin, promethazine, micronutrients)		1	1				1	1
Aprepitant		1						
Aprotinin		1	1					
Arbidol	NEW	1	1					
ArtemiC		1	1		1		1	
Artemisinin		1			1		1	
Atazanavir-ritonavir		1	1	1	1		1	
Atovaquone		1	1				1	
Auxora		1	1		1		1	
Avdoralimab		1	1				1	
Aviptadil		1	1		1		1	
Ayush-64		1			1		1	1
Azelastine (inhaled)		1			1		1	
Azvudine		1						
Baloxavir		1			1			
BCG		1	1					
Bebtelovimab		1	1				1	1
Bioven		1	1				1	
Bicarbonate (inhaled)	NEW	1	1					
Boswellia extract		1			1			
Calcitriol		1	1				1	
Cannabidiol		1	1	1	1		1	1
CD24Fc		1	1	1	1		1	
CERC-002		1	1				1	
Chloroquine nasal drops		1						
CIGB-325		1			1		1	
Clarithromycin		1						
Clazakizumab		1	1	1	1			
Clevudine		1					1	
Colchicine + rosuvastatin		1	1	1			1	
Corticosteroids (nasal)		1						
Crizanlizumab		1	1	1	1		1	
Curcumin + Piperine		1			1		1	
Curcumin + Quercetin + Vitamin D		1						
Darunavir-Cobicistat		1						
Dapagliflozin		1	1		1		1	
Degarelix		1	1	1			1	
Dimethyl sulfoxide (DSMO)		1				1		
Dornase alfa (inh)		1			1		1	
Dupilumab		1	1					
Edaravone		1	1	1				
Electrolyzed saline		1	1		1			1
Endothelial dysfunction protocol		1	1	1			1	
Enisamium		1			1			
Ensitrelvir		1	1				1	
Ensovibep	NEW	1	1		1		1	
Enzalutamide		1	1	1			1	
Ethanol (inhaled)		1	1		1		1	
Febuxostat		1						1
Fenofibrate	NEW	1	1	1			1	1
Finasteride		1	1					
Fostamatinib		1	1		1		1	
Gabapentin +/- Montelukast	NEW	1			1		1	
GB0139 (inhaled)		1	1				1	
Gimsilumab (Anti-GM-CSF Monoclonal Antibody)		1	1		1		1	

Intervention		Overall number of studies including the intervention, n=716	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)
Hemadsorption		1	1		1			
Hesperidin		1	1	1	1		1	1
Hypertonic saline (inhaled)	NEW	1	1					
hzVSF-v13		1	1		1		1	
Ibrutinib		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-1a (inhaled)		1	1	1	1		1	
Interferon gamma		1						
Interferon kappa + TFF2		1	1				1	
Interferon-2		1	1		1		1	
Isothymol		1	1					
Itolizumab		1	1	1			1	
Ivermectin (inhaled)		1			1			
Ixekizumab		1	1		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						
Lithium	NEW	1	1				1	
Mavrilimumab		1	1	1	1		1	
Mefenamic acid		1	1				1	1
Metisoprinol		1						
Methylene blue		1	1					
Metoprolol		1	1					
Metronidazole		1			1			
Montelukast		1	1					
Mupadolimab		1					1	
Mycobacterium w		1	1					
N-acetylcysteine (inhaled)	NEW	1	1					
Nafamostat mesylate		1	1				1	
Namilumab		1	1		1		1	
Nano-curcumin		1					1	
Neem (Azadirachta Indica A. Juss)		1				1		
Nicotine patches		1	1				1	
Nirmatrelvir-ritonavir		1	1				1	1
Norelgestromin and Ethinylestradiol		1						
Novaferon		1						
NSAIDS		1	1		1		1	
Nutritional support		1	1	1				
OP-101		1	1	1			1	
Otilimab		1	1				1	
Peg-IFN lambda		1					1	
Pembrolizumab		1	1	1	1		1	
Plitidepsin		1	1	1			1	
PNB001 (CCK-A antagonist)		1	1		1			
Polymerized type I collagen (PT1C)		1						1
Potassium Canrenoate		1	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	
Prostacyclin (inhaled)		1	1					
Pyridostigmine		1	1	1	1		1	
Raloxifene		1	1				1	
Ramipril		1	1			1		
RD-X19 (light therapy)		1			1			



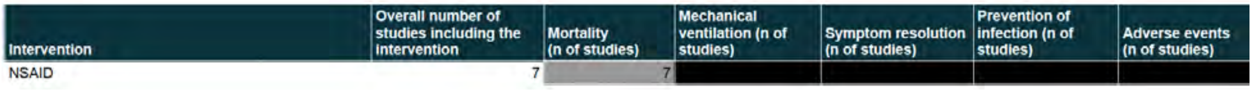
Intervention		Overall number of studies including the intervention, n=716	Mortality (n of studies)	Invasive mechanical ventilation (n of studies)	Symptom resolution (n of studies)	Prevention of infection (n of studies)	Adverse events (n of studies)	Hospitalization (n of studies)
Remdesivir (inhaled)		1	■	■	■	■	■	1
Reparixin		1	1	1	■	■	1	■
Ribavirin		1	■	■	■	■	■	■
Ribavirin + Interferon beta-1b		1	■	■	■	■	■	■
rhG-CSF		1	1	■	1	■	1	■
rhG-CSF (inhaled)		1	1	1	1	■	1	■
rhu-pGSN	NEW	1	1	1	■	■	1	■
Sabizabulin		1	1	■	■	■	1	■
Secukinumab		1	1	1	■	■	1	■
Senicapoc		1	1	■	■	■	■	■
Sentinox		1	■	■	■	■	1	1
Short-wave diathermy		1	1	■	1	■	1	■
Sildenafil		1	1	1	■	■	1	■
Silymarin		1	■	■	1	■	1	■
Siltuximab		1	1	1	▨	■	▨	■
Sitagliptin		1	1	1	■	■	■	■
Stem-cell nebulization		1	1	■	1	■	1	■
Sulodexide		1	1	1	■	■	1	1
Tafenoquine		1	■	■	1	■	1	1
TD-0903 (inhaled JAK-inhibitor)		1	1	■	■	■	1	■
ThymoQuinone		1	■	■	■	■	1	■
Tissue-plasminogen activator (tPA)		1	1	■	■	■	1	■
Tranilast		1	1	■	1	■	■	■
Triazavirin		1	1	■	1	■	1	■
TXA-127	NEW	1	1	1	■	■	■	■
Ultraviolet light phototherapy		1	1	■	■	■	1	■
Verapamil	NEW	1	1	1	■	■	1	■
XAV-19 (swine polyclonal antibodies)		1	1	■	■	■	1	■
Zilucoplan		1	1	■	■	■	1	■
α-Lipoic acid		1	1	■	■	■	■	■

(*) Based on low risk of bias subgroup of studies; (^) Major bleeding or clinically important bleeding; (**) Observed results apply mostly to hospitalized patients with moderate to critical disease. The COLCORONA trial that included patients with recent onset mild disease showed a tendency to less hospitalizations, less mortality and less mechanical ventilation requirements. However the certainty on those potential benefits was low because of very serious imprecision as the number of events was low; (##) Subgroup of seronegative patients; (@) High dose schemes (i.e dexamethasone 12 mg a day) may be more effective than standard dose schemes (i,e dexamethasone 6 mg a day); (@@) Excluding high risk of bias studies; (§) Observed effects would probably be considered important in patients with very high hospitalization risk (>10%).

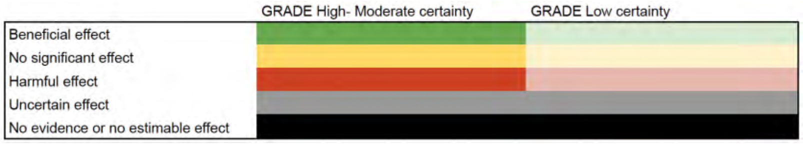


	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect	🟩	🟩
No significant effect	🟨	🟨
Harmful effect	🟥	🟥
Uncertain effect	▨	▨
No evidence or no estimable effect	■	■

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



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=232), as at 29 August 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	**Alpha-1 antitrypsin**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Amiodarone**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Ammonium chloride**	Uncertainty in potential benefits and harms. Further research is needed.
7	**AMP5A (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Anakinra**	Anakinra may not reduce mortality or increase severe adverse events. However, the cerrtainty of the evidence was low because of risk of bias and imprecision. Further research is needed.
9	**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) probably does not decrease mortality in comparison with prophylactic dose (i.e., 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 or reduce hospitalizations.
10	**APMV2020 (aspirin, promethazine, micronutrients)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
11	**Aprepitant**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Aprotinin**	Uncertainty in potential benefits and harms. Further research is needed.
13	**Arbidol**	Uncertainty in potential benefits and harms. Further research is needed.
14	**ArtemiC (artemisinina, curcumina, frankincense, and vitamin C):**	Uncertainty in potential benefits and harms. Further research is needed.
15	**Artemisinin**	Uncertainty in potential benefits and harms. Further research is needed.
16	**Aspirin**	Aspirin probably does not reduce mortality, or mechanical ventilation and probably does not increase symptom resolution or improvement.
17	**Atazanavir/ritonavir**	Uncertainty in potential benefits and harms. Further research is needed.
18	**Atovaquone**	Uncertainty in potential benefits and harms. Further research is needed.
19	**Auxora**	Auxora may not increase severe adverse events. The effects of auxora on other importan outcomes are uncertain. Further research is needed.
20	**Avdoralimab**	Uncertainty in potential benefits and harms. Further research is needed.
21	**Aviptadil**	Uncertainty in potential benefits and harms. Further research is needed.
22	**Ayush-64**	Uncertainty in potential benefits and harms. Further research is needed.
23	**Azelastine**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
24	**Azithromycin**	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
25	**Azvudine**	Uncertainty in potential benefits and harms. Further research is needed.
26	**Baricitinib**	In patients with moderate to critical disease, baricitinib reduces mortality, probably reduces mechanical ventilation requirements, and probably improves time to symptom resolution, without increasing severe adverse events.
27	**Baloxavir**	Uncertainty in potential benefits and harms. Further research is needed.
28	**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.
29	**BCG**	Uncertainty in potential benefits and harms. Further research is needed.
30	**Bebtelovimab**	Uncertainty in potential benefits and harms. Further research is needed.
31	**Beta-glucans**	Uncertainty in potential benefits and harms. Further research is needed.
32	**Bicarbonate (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
33	**Bioven**	Uncertainty in potential benefits and harms. Further research is needed.
34	**Boswellia extract**	Uncertainty in potential benefits and harms. Further research is needed.
35	**Bromhexine hydrochloride**	Bromhexine may reduce symptomatic infections in exposed individuals. Its effects on other clinical important outcomes are uncertain. Further research is needed.
36	**Calcitriol**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
37	**Camostat mesilate**	Camostat mesilate may not improve time to symptom resolution. Further research is needed.
38	**Canakinumab**	Uncertainty in potential benefits and harms. Further research is needed.
39	**Cannabidiol**	Uncertainty in potential benefits and harms. Further research is needed.
40	**CD24Fc (soluble CD24 appended to heavy chains 2 and 3 of human immunoglobulin G1)**	CD24Fc may reduce mechanical ventilation and increase symptom resolution or improvement. However, certainty of the evidence was low for imprecision. Further research is needed.
41	**CERC-002**	Uncertainty in potential benefits and harms. Further research is needed.
42	**Chloroquine nasal drops**	Uncertainty in potential benefits and harms. Further research is needed.
43	**CIGB-325**	Uncertainty in potential benefits and harms. Further research is needed.
44	**Clarithromycin**	Uncertainty in potential benefits and harms. Further research is needed.
45	**Clazakizumab**	Clazakizumab may reduce mechanical ventilation and improve time to symptoms resolution. However, certainty of the evidence was low. Further research is needed.
46	**Clevudine**	Uncertainty in potential benefits and harms. Further research is needed.
47	**Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)**	Uncertainty in potential benefits and harms. Further research is needed.
48	**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.

	Intervention	Summary of findings
49	**Colchicine + rosuvastatin**	Uncertainty in potential benefits and harms. Further research is needed.
50	**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.
51	**Crizanlizumab**	Uncertainty in potential benefits and harms. Further research is needed.
52	**Curcumin + piperine**	Uncertainty in potential benefits and harms. Further research is needed.
53	**Curcumin + quercetin + vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
54	**Dapagliflozin**	Dapagliflozin may reduce mortality but probably does not increase symptom resolution. Further research is needed.
55	**Darunavir-cobicistat**	Uncertainty in potential benefits and harms. Further research is needed.
56	**Degarelix**	Uncertainty in potential benefits and harms. Further research is needed.
57	**Dimethyl sulfoxide (DSMO)**	Uncertainty in potential benefits and harms. Further research is needed.
58	**Dornase alfa (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
59	**Doxycycline**	Doxycycline does not increase symptom resolution or improvement and may not reduce hospitalizations.
60	**Dutasteride**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
61	**Dupilumab**	Uncertainty in potential benefits and harms. Further research is needed.
62	**Edaravone**	Uncertainty in potential benefits and harms. Further research is needed.
63	**Electrolyzed saline**	Uncertainty in potential benefits and harms. Further research is needed.
64	**Endothelial dysfunction protocol**	Uncertainty in potential benefits and harms. Further research is needed.
65	**Enisamium**	Uncertainty in potential benefits and harms. Further research is needed.
66	**Ensovibep**	Uncertainty in potential benefits and harms. Further research is needed.
67	**Ensitrelvir**	Uncertainty in potential benefits and harms. Further research is needed.
68	**Enzalutamide**	Uncertainty in potential benefits and harms. Further research is needed.
69	**Ethanol (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
70	**Famotidine**	Uncertainty in potential benefits and harms. Further research is needed.
71	**Favipiravir**	Favipiravir may increase mortality and mechanical ventilation requirements, it may not reduce hospitalizations and it probably does not improve time to symptom resolution. Further research is needed.
72	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
73	**Fenofibrate**	Fenofibrate may not increase severe adverse events. The effects of fenofibrate on other importan outcomes are uncertain. Further research is needed.

	Intervention	Summary of findings
74	**Finasteride**	Uncertainty in potential benefits and harms. Further research is needed.
75	**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.
76	**Fostamatinib**	Uncertainty in potential benefits and harms. Further research is needed.
77	**Gabapentin +/- montelukast**	Uncertainty in potential benefits and harms. Further research is needed.
78	**GB0139 (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
79	**Gimsilumab (anti-GM-CSF monoclonal antibody)**	Gimsilumab may not reduce mortality nor increase symptom resolution. Further research is needed.
80	**Helium (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
81	**Hemadsorption**	Uncertainty in potential benefits and harms. Further research is needed.
82	**Hesperidin**	Hesperidin may not improve symptom resolution; however, the certainty of the evidence was low. Further research is needed.
83	**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 not have an important effect on the risk of infection and in patients with mild, recent onset disease, and it may not have an important effect on hospitalizations. However, certainty of the evidence is low because of risk of bias and imprecision.
84	**Hyperbaric oxygen**	Uncertainty in potential benefits and harms. Further research is needed.
85	**Hyperimmune anti-COVID-19 intravenous immunoglobulin (C-IVIG)**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
86	**Hypertonic saline (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
87	**hzVSF-v13**	Uncertainty in potential benefits and harms. Further research is needed.
88	**Ibrutinib**	Uncertainty in potential benefits and harms. Further research is needed.
89	**Icatibant/iC1e/K**	Uncertainty in potential benefits and harms. Further research is needed.
90	**Icosapent ethyl**	Uncertainty in potential benefits and harms. Further research is needed.
91	**IFX-1**	Uncertainty in potential benefits and harms. Further research is needed.
92	**Imatinib**	Imatinib may not increase severe adverse events. The effects of imatinib on other importan outcomes are uncertain. Further research is needed.
93	**Indomethacin**	Uncertainty in potential benefits and harms. Further research is needed.
94	**Infliximab**	Uncertainty in potential benefits and harms. Further research is needed.
95	**INM005 (polyclonal fragments of equine antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
96	**Interferon alpha-2b and interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
97	**Interferon beta-1a**	IFN beta-1a probably does not reduce mortality, invasive mechanical ventilation requirements or improve symptom resolution. Further research is needed.

	Intervention	Summary of findings
98	**Interferon beta-1a (inhaled)**	Inhaled interferon beta-1a may improve time to symptom resolution. Further research is needed.
99	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
100	**Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
101	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.
102	**Interleukin-2**	Uncertainty in potential benefits and harms. Further research is needed.
103	**Iota-carrageenan**	Uncertainty in potential benefits and harms. Further research is needed.
104	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
105	**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 reduce mortality or improve time to symptom resolution. In patients with recent onset of the disease, ivermectin probably does not have an important effect on hospitalizations and may not increase severe adverse events. It is uncertain if it reduces symptomatic infections when used as prophylaxis.
106	**Ivermectin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
107	**IVIG (intravenous immunoglobulin)**	Uncertainty in potential benefits and harms. Further research is needed.
108	**Ixekizumab**	Uncertainty in potential benefits and harms. Further research is needed.
109	**KB109**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
110	**L-arginine**	Uncertainty in potential benefits and harms. Further research is needed.
111	***Lactococcus lactis* (intranasal)**	Uncertainty in potential benefits and harms. Further research is needed.
112	**Lactoferrin**	Uncertainty in potential benefits and harms. Further research is needed.
113	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
114	**Lenzilumab**	Lenzilumab may reduce mechanical ventilation requirements and may not increase severe adverse events. The effects of lenzilumab on other importan outcomes are uncertain. Further research is needed.
115	**Levamisole**	Uncertainty in potential benefits and harms. Further research is needed.
116	**Levilimab**	Levilimab may improve time to symptom resolution; however, the certainty of the evidence was low. The effects of levilimab on other important outcomes are uncertain. Further research is needed.
117	**Linagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
118	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.
119	**Lithium**	Uncertainty in potential benefits and harms. Further research is needed.
120	**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.
121	**Low-dose radiation therapy**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
122	**Mavrilimumab**	Uncertainty in potential benefits and harms. Further research is needed.
123	**Mefenamic acid**	Uncertainty in potential benefits and harms. Further research is needed.
124	**Melatonin**	Uncertainty in potential benefits and harms. Further research is needed.
125	**Mesenchymal stem-cell transplantation**	Mesenchymal stem-cell transplantation may reduce mortality. However, the certainty of the evidence is low. Further research is needed.
126	**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.
127	**Methylene blue**	Uncertainty in potential benefits and harms. Further research is needed.
128	**Metisoprinol**	Uncertainty in potential benefits and harms. Further research is needed.
129	**Metoprolol**	Uncertainty in potential benefits and harms. Further research is needed.
130	**Metronidazole**	Uncertainty in potential benefits and harms. Further research is needed.
131	**Molnupiravir**	In patients with recent onset mild COVID-19 molnupiravir reduces hospitalizations, it may improve symptom resolution and may not increase severe adverse events.

	Intervention	**Summary of findings**
132	**Montelukast**	Uncertainty in potential benefits and harms. Further research is needed.
133	**Mouthwash**	Mouthwash may improve time to symptom resolution. Uncertainty in potential benefits and harms on other outcomes. Further research is needed.
134	**Mupadolimab**	Uncertainty in potential benefits and harms. Further research is needed.
135	**Mycobacterium w**	Uncertainty in potential benefits and harms. Further research is needed.
136	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.
137	**N-acetylcysteine (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
138	**Nafamostat mesylate**	Uncertainty in potential benefits and harms. Further research is needed.
139	**Namilumab**	Uncertainty in potential benefits and harms. Further research is needed.
140	**Nano-curcumin**	Uncertainty in potential benefits and harms. Further research is needed.
141	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
142	**Neem (*Azadirachta indica* A. Juss)**	Uncertainty in potential benefits and harms. Further research is needed.
143	**Niclosamide**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
144	**Nicotine patches**	Uncertainty in potential benefits and harms. Further research is needed.
145	***Nigella sativa* +/- honey**	Uncertainty in potential benefits and harms. Further research is needed.
146	**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.
147	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.
148	**Nitric oxide**	Uncertainty in potential benefits and harms. Further research is needed.
149	**Non-steroidal anti-inflammatory drugs (NSAIDs)**	Current best evidence suggests no association between NSAIDs 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.
150	**Norelgestromin and ethinylestradiol**	Uncertainty in potential benefits and harms. Further research is needed.
151	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
152	**Nutritional support**	Uncertainty in potential benefits and harms. Further research is needed.
153	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed
154	**OP-101**	Uncertainty in potential benefits and harms. Further research is needed
155	**Opaganib**	Opaganib may not reduce mortality or mechanical ventilation, it may not increase severe adverse events but it may increase symptom resolution or improvement. Further research is needed.

	Intervention	Summary of findings
156	**Otilimab**	Uncertainty in potential benefits and harms. Further research is needed
157	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
158	**P2Y12 inhibitors**	P2Y12 inhibitors may increase mortality, may not improve time to symptom resolution and may increase severe adverse events. However, certainty of the evidence was low because of imprecision. Further research is needed.
159	**Peg-interferon alfa**	Uncertainty in potential benefits and harms. Further research is needed.
160	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
161	**Pembrolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
162	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.
163	**Plitidepsin**	Uncertainty in potential benefits and harms. Further research is needed.
164	**PNB001 (CCK-A antagonist)**	Uncertainty in potential benefits and harms. Further research is needed.
165	**Polymerized type I collagen (PT1C)**	Uncertainty in potential benefits and harms. Further research is needed.
166	**Potassium canrenoate**	Uncertainty in potential benefits and harms. Further research is needed.
167	**Povidone iodine (nasal spray)**	Uncertainty in potential benefits and harms. Further research is needed.
168	**Probiotics**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
169	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed
170	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed
171	**Propolis**	Uncertainty in potential benefits and harms. Further research is needed
172	**Prostacyclin**	Uncertainty in potential benefits and harms. Further research is needed
173	**Prostacyclin (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed
174	**Proxalutamide**	Uncertainty in potential benefits and harms. Further research is needed
175	**Pyridostigmine**	Uncertainty in potential benefits and harms. Further research is needed
176	**Quercetin**	Uncertainty in potential benefits and harms. Further research is needed
177	**Raloxifene**	Uncertainty in potential benefits and harms. Further research is needed
178	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
179	**RD-X19 (light therapy)**	Uncertainty in potential benefits and harms. Further research is needed.
180	**Recombinant super-compound interferon**	Uncertainty in potential benefits and harms. Further research is needed.
181	**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

	Intervention	Summary of findings
		increasing severe adverse events, and in asymptomatic exposed individuals REGEN-COV reduces symptomatic infections.
182	**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.
183	**Remdesivir**	In hospitalized patients with moderate to critical disease, remdesivir probably reduces mortality and mechanical ventilation, and it may improve time to symptom resolution without increasing 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.
184	**Remdesivir (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
185	**Reparixin**	Uncertainty in potential benefits and harms. Further research is needed.
186	**Resveratrol**	Uncertainty in potential benefits and harms. Further research is needed.
187	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.
188	**rhG-CSF (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
189	**rhu-pGSN**	Uncertainty in potential benefits and harms. Further research is needed.
190	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.
191	**Ribavirin + interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
192	**Ruxolitinib**	Ruxolitinib may reduce mortality; however, the certainty of the evidence was low. Further research is needed.
193	**Sabizabulin**	Uncertainty in potential benefits and harms. Further research is needed.
194	**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.
195	**Secukinumab**	Uncertainty in potential benefits and harms. Further research is needed.
196	**Senicapoc**	Uncertainty in potential benefits and harms. Further research is needed.
197	**Sentinox**	Uncertainty in potential benefits and harms. Further research is needed.
198	**Short-wave diathermy**	Uncertainty in potential benefits and harms. Further research is needed.
199	**Sildenafil**	Uncertainty in potential benefits and harms. Further research is needed.
200	**Siltuximab**	Uncertainty in potential benefits and harms. Further research is needed.
201	**Silymarin**	Uncertainty in potential benefits and harms. Further research is needed.
202	**Sitagliptin**	Uncertainty in potential benefits and harms. Further research is needed.
203	**Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir**	Sofosbuvir with or without daclatasvir or ledipasvir may increase mortality and not reduce mechanical ventilation requirements, and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.
204	**Sotrovimab**	Sotrovimab may probably reduce hospitalizations in patients with recent onset mild COVID-19.

	Intervention	Summary of findings
205	**Spironolactone**	Uncertainty in potential benefits and harms. Further research is needed.
206	**Statins**	Statins may reduce mortality, however certainty of the evidence was low Further research is needed.
207	**Stem-cell nebulization**	Uncertainty in potential benefits and harms. Further research is needed.
208	**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).
209	**Steroids (corticosteroids, inhaled)**	Inhaled corticosteroids may improve time to symptom resolution but probably does not have an important effect on hospitalizations. Its effects on other important outcomes are uncertain. Further research is needed.
210	**Steroids (corticosteroids, nasal)**	Uncertainty in potential benefits and harms. Further research is needed.
211	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
212	**Tafenoquine**	Uncertainty in potential benefits and harms. Further research is needed.
213	**TD-0903 (inhaled JAK-inhibitor)**	Uncertainty in potential benefits and harms. Further research is needed.
214	**Tenofovir + emtricitabine**	Tenofovir + emtricitabine may not reduce mortality but may reduce mechanical ventilation. However, certainty of the evidence was low. Further research is needed.

	Intervention	Summary of findings
215	**Thalidomide**	Uncertainty in potential benefits and harms. Further research is needed.
216	**Thymoquinone**	Uncertainty in potential benefits and harms. Further research is needed.
217	**Tissue-plasminogen activator (tPA)**	Uncertainty in potential benefits and harms. Further research is needed.
218	**Tixagevimab–cilgavimab**	Tixagevimab-cilgavimab probably reduces mortality, hospitalizations, and SARS-COV-2 infections in exposed individuals, and may not increase severe adverse events.
219	**Tocilizumab**	Tocilizumab reduces mortality and reduces mechanical ventilation requirements without possibly increasing severe adverse events.
220	**Tofacitinib**	Tofacitinib may increase symptom resolution or improvement and severe adverse events. Certainty of the evidence was low, further research is needed.
221	**Tranilast**	Uncertainty in potential benefits and harms. Further research is needed.
222	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.
223	**TXA-127**	Uncertainty in potential benefits and harms. Further research is needed.
224	**Ultraviolet light phototherapy**	Uncertainty in potential benefits and harms. Further research is needed.
225	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
226	**Verapamil**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
227	**Vitamin C**	Vitamin C may increase symptom resolution or improvement. Its effects on other clinical important outcomes are uncertain. Further research is needed.
228	**Vitamin D**	Vitamin D probably does no reduce infections in exposed individuals and may not reduce hospitalizations. Vitamin D effect on other important outcomes is uncertain. Further research is needed.
229	**XAV-19 (swine glyco-humanized polyclonal antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
230	**Zilucoplan**	Uncertainty in potential benefits and harms. Further research is needed.
231	**Zinc**	Zinc may not improve symptom resolution. However, the certainty of the evidence was low because of imprecision. Its effects on other clinical important outcomes are uncertain. Further research is needed.
232	**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 232 therapeutic options.

• **Corticosteroids:** The body of evidence on corticosteroids, which includes 24 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:** The results of 10 RCTs, including the final results of the SOLIDARITY trial, show that in hospitalized patients with moderate to critical disease, remdesivir probably reduces mortality and mechanical ventilation, and it may improve time to symptom resolution. Certainty of the evidence was moderate because of imprecision. 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 58 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 on hospitalizations 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.

- **Clazakizumab:** The results of one RCT suggest that, in patients with severe or critical disease, clazakizumab may mechanical ventilation requirements and improve time to symptom resolution. However, certainty of the evidence was low because of imprecision. Further research is needed.

- **Sarilumab:** The results of 10 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 six RCTs assessing anakinra in hospitalized patients with non-severe disease, show inconsistent results on mortality and symptom resolution and suggest that anakinra may not reduce mortality or increase severe adverse events. Certainty of the evidence was low and further research is needed.

- **Tofacitinib:** The results of two RCTs 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 15 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:** Pooled estimates of 49 RCTs 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 subgroup RCTs classified as low risk of bias, ivermectin probably does not reduce mortality or improve time to symptom resolution, and probably does not have an important effect on hospitalizations. Further research is needed to confirm these findings.

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

- **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** Sixteen 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 increase mortality and not reduce mechanical ventilation requirements, and it probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

- **Tenofovir + emtricitabine:** Five RCTs assessed tenofovir + emtricitabine against standard of care or other interventions. Their results suggest that tenofovir + emtricitabine may not reduce mortality and may decrease mechanical ventilation requirements. However, certainty of the evidence was low because of imprecision and risk of bias. Further research is needed to confirm these findings.

- **Baricitinib:** The results of seven RCTs show that, in patients with moderate to critical disease, baricitinib reduces mortality, probably reduces mechanical ventilation requirements, and probably improves time to symptom resolution, without increasing severe adverse events.

- **Ruxolitinib:** The results of three RCTs show that, in patients with moderate to critical disease, ruxolitinib may reduce mortality. However, the certainty of the evidence was low because of imprecision and inconsistency. Further research is needed.

- **CD24Fc (soluble CD24 appended to heavy chains 2 and 3 of human immunoglobulin G1):** The results of one RCT show that in patients with severe disease, CD24Fc may reduce mechanical ventilation and increase symptom resolution. However, the certainty of the evidence was low because of imprecision. Further research is needed.

- **REGEN-COV (casirivimab and imdevimab):** The results of 12 RCTs suggest that, in patients with severe to critical disease, overall REGEN-COV may reduce mortality and 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. 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 RCTs 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 RCTs 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.

- **Tixagevimab–cilgavimab:** The results of three RCTs show that, in individuals with COVID-19, tixagevimab–cilgavimab probably reduces mortality and hospitalizations, and in those exposed to SARS-COV-2 tixagevimab–cilgavimab probably reduces symptomatic infections without increasing severe adverse events.

- **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 eight 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 nine RCTs show that inhaled corticosteroids may improve time to symptom resolution but probably does not have an important effect on hospitalizations. Its effects on other relevant outcomes are uncertain. Further research is needed.

- **Fluvoxamine:** The results of four 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 invasive mechanical ventilation requirements in severe patients without increasing severe adverse events. 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 ten RCTs that compared anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) versus prophylactic dose (i.e., enoxaparin 40 mg a day) showed no differences in mortality with moderate certainty (imprecision). In mild ambulatory patients four RCTs suggest that rivaroxaban or enoxaparin in prophylactic dose may not importantly improve time to symptom resolution or reduce hospitalizations.

- **Aspirin:** Results of four RCTs inform that aspirin probably does not reduce mortality or mechanical ventilation and probably does not increase symptom resolution or improvement.

- **P2Y12 inhibitors:** The results of two RCTs suggest that P2Y12 in combination with anticoagulants in prophylactic or full dose may not reduce mortality, may not improve time to symptom resolution, and may increase severe adverse events. However, the certainty of the evidence was low because of imprecision and the effects on other important outcomes are uncertain. Further research is needed.

- **NSAIDs:** No association between NSAIDs 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 eight 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 10 RCTs show that molnupiravir 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.

- **Vitamin D:** The results of 18 RCTs show that vitamin D probably does not reduce symptomatic infections and may improve reduce hospitalizations. However, the certainty of the evidence was low to moderate because of imprecision and risk of bias. Vitamin D effects on other important outcomes are uncertain. Further research is needed.

- **Vitamin C:** The results of nine RCTs suggest that vitamin C may increase symptom resolution or improvement. However, the certainty of the evidence was low and vitamin C effects on other important outcomes are uncertain. Further research is needed.

- **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 14 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.

- **Camostat mesilate:** The results of five RCTs suggest that camostat mesilate may not improve time to symptom resolution. However, the certainty of the evidence was low because of imprecision and indirectness, furthermore the effects on other important outcomes are uncertain. Further research is needed.

- **Opaganib:** The results of two RCTs suggest that opaganib may not reduce mortality or mechanical ventilation, it may not increase severe adverse events but it may increase symptom resolution or improvement. However, certainty of the evidence was low because of imprecision. Further research is needed.

Changes since previous edition

- **Tenofovir + emtricitabine:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

- **Baricitinib:** New evidence included without significant changes.

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

- **Vitamin C:** New evidence included without significant changes.

- **Molnupiravir:** New evidence included without significant changes.

- **Vitamin D:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

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

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

- **TXA-127:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

- **Gabapentin +/- montelukast:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

- **rhu-pGSN:** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

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

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

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

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

- **N-acetylcysteine (inhaled):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

- **Hypertonic saline (inhaled):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

- **Bicarbonate (inhaled):** New evidence included affecting results interpretation and/or certainty of the evidence judgments.

- **Metformin:** New evidence included without significant changes.

- **Sofosbuvir +/- daclatasvir, ledipasvir, velpatasvir, or ravidasvir:** New evidence included without significant changes.

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

- **Fluvoxamine:** 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 subgroups. 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 232 opciones terapéuticas potenciales.

• **Corticosteroides:** El conjunto de evidencia sobre los corticoesteroides incluye 24 ensayos clínicos controlados aleatorizados (ECCA) y muestra que la administración de dosis bajas y moderadas (la dosis utilizada en el estudio RECOVERY fue de 6 mg diarios de dexametasona 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, 12 mg de dexametasona por día) podrían no resultar más efectivos que los esquemas habituales (por ejemplo, 6 mg de dexametasona por día).

• **Remdesivir:** Los resultados de 10 ECCA, incluyendo los resultados finales del ensayo SOLIDARITY, muestran que en pacientes hospitalizados con enfermedad de moderada a critica, el remdesivir probablemente reduce la mortalidad y la necesidad de ventilación mecánica invasiva, y podría mejorar el tiempo de resolución de los síntomas. La certeza de la evidencia es moderada por imprecisión. En pacientes con enfermedad leve de comienzo reciente, el remdesivir podría reducir las hospitalizaciones, pero la certeza de 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 riesgo bajo de sesgo que evaluaron la hidroxicloroquina en personas expuestas a la COVID-19 sugieren una reducción modesta del riesgo de infección, pero la certeza de la evidencia es baja por inconsistencia (falta de congruencia (*inconsistency*) e imprecisión. Se necesita más información para confirmar estas conclusiones.

• **Antibióticos:** El conjunto de evidencia identificado sobre la azitromicina y la doxiciclina no muestra beneficios significativos en pacientes con COVID-19 de leve a moderada, o grave a crítica.

• **Plasma de convalecientes:** Los resultados de 58 ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19, incluido el estudio RECOVERY que incorpora 11.558 pacientes, no mostraron reducción de la mortalidad, disminución de la necesidad de ventilación mecánica invasiva ni mejoría en el tiempo de resolución de los síntomas con certeza moderada. En pacientes leves, el plasma de convalecientes probablemente no tenga ningún efecto importante sobre las hospitalizaciones con certeza moderada. El plasma de convalecientes podría no asociarse a un aumento de los eventos adversos graves con certeza baja. En un análisis de subgrupo del estudio RECOVERY, no se observó ningún efecto diferencial entre los pacientes tratados con rapidez (menos de 4 días desde el inicio de los síntomas) y los que presentaban 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 de los efectos adversos graves en pacientes con enfermedad grave o crítica.

• **Clazakizumab:** Los resultados de un ECCA sugieren que el clazakizumab 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.

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

• **Anakinra:** Los resultados de seis ECCA que evaluaron la anakinra en pacientes hospitalizados con enfermedad no grave muestran resultados incongruentes en la mortalidad y la resolución de los síntomas y sugieren que anakinra podria no reducir la mortalidad ni aumentar los eventos adversos graves. La certeza de la evidencia es baja y se necesita más información.

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

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

- **Ivermectina:** Los resultados combinados de 49 ECCA indican una reducción de la mortalidad con la ivermectina. Sin embargo, la certeza de la evidencia es muy baja por limitaciones metodológicas y un número de eventos reducido. Con base en la información facilitada por los estudios con riesgo bajo de sesgo, la ivermectina probablemente no reduzca la mortalidad ni 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:** Veintisiete ECCA evaluaron el favipiravir en comparación con la prestación de cuidados estándares u otras intervenciones. Los resultados sugieren que el favipiravir podría aumentar la mortalidad, y la necesidad de ventilación invasiva mecánica, podría no reducir las hospitalizaciones 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:** Dieciséis ECCA evaluaron el 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 de los estudios con un riesgo bajo de sesgo fueron sustancialmente diferentes. Los resultados de los dos estudios clasificados con riesgo bajo de sesgo sugieren que el sofosbuvir solo o en combinación podría aumentar la mortalidad y no reducir 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.

- **Tenofovir y emtricitabina:** Los resultados de cinco ECCA sugieren que el tenofovir y la emtricitabina podrían no reducir la mortalidad, pero probablemente reduzcan la necesidad de ventilación mecánica invasiva. Sin embargo, la certeza de la evidencia es baja por imprecisión y riesgo de sesgo. Se necesita más información para confirmar estas conclusiones.

- **Baricitinib:** Los resultados de siete ECCA muestran que, en pacientes con enfermedad de moderada a crítica, el baricitinib reduce la mortalidad, y probablemente reduce la necesidad de ventilación mecánica invasiva y mejora el tiempo de resolución de síntomas sin aumentar los eventos adversos graves.

- **Ruxolitinib:** Los resultados de tres ECCA sugieren que, en pacientes con enfermedad de moderada a grave, el ruxolitinib podría reducir la mortalidad. Sin embargo, la certeza de la evidencia es baja por inconsistencia (falta de congruencia) e imprecisión. Se necesita más información.

- **CD24Fc (cadenas pesadas 2 y 3 de inmunoglobulina humana G1 anexadas a CD24):** Los resultados de un ECCA muestran que en pacientes con enfermedad grave, el CD24Fc podría reducir la necesidad de ventilación mecánica invasiva y mejorar la resolución de síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

- **REGEN-COV (casirivimab e imdevimab):** Los resultados de 12 ECCA muestran que, en pacientes con enfermedad grave o crítica, el REGEN-COV podría reducir la mortalidad y la necesidad de ventilación mecánica invasiva y mejorar la velocidad de resolución de los síntomas. Sin embargo, la certeza de 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 y la necesidad de ventilación mecánica e incremente la resolución de los 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 de 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 de la evidencia es moderada por imprecisión, pero incluye hallazgos 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 de la evidencia es baja por imprecisión. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información para confirmar o descartar estas conclusiones.

- **Tixagevimab y cilgavimab:** Los resultados de tres ECCA muestran que el tixagevimab y el cilgavimab probablemente reduzcan la mortalidad, las hospitalizaciones y las infecciones sintomáticas en personas expuestas al SARS-CoV-2 y podrían no aumentar los eventos adversos graves.

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

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

- **Trasplante de células madre mesenquimatosas:** Los resultados de ocho 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 de la evidencia es baja por imprecisión. Se necesita más información para confirmar o descartar estas conclusiones.

- **Corticosteroides inhalados:** Los resultados de nueve ECCA muestran que los corticosteroides inhalados podrían mejoran el tiempo de resolución de los síntomas pero probablmente no afecten las hospitalizaciones en forma importante. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

- **Fluvoxamina:** Los resultados de cuatro 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 de 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 necesidad de ventilación mecánica invasiva en pacientes graves sin aumentar los eventos adversos graves. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

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

- **Famotidina:** Por el momento, la certeza de la evidencia sobre los efectos de la famotidina en desenlaces clínicamente importantes es muy baja.

- **Anticoagulantes:** Las complicaciones tromboembólicas en pacientes con COVID-19 son relativamente 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 mejor esquema tromboprofiláctico, excluyendo tres estudios clasificados con riesgo alto de sesgo, los resultados de diez ECCA que compararon los anticoagulantes en dosis intermedias (p. ej., 1 mg/kg de enoxaparina por día) o dosis completas (p. ej., 1 mg/kg de enoxaparina cada 12 h por día) frente a dosis profilácticas (p. ej., 40 mg de enoxaparina por día) no mostraron diferencias en la mortalidad con certeza moderada (imprecisión). Los resultados de cuatro ECCA sugieren que, en pacientes ambulatorios con enfermedad leve, el rivaroxabán o la enoxaparina en dosis profilácticas podría no mejorar el tiempo de resolución de los síntomas de forma considerable ni reducir las hospitalizaciones.

- **Aspirina:** Los resultados de cuatro ECCA informan que la aspirina probablemente no reduzca la mortalidad o la necesidad de ventilación mecánica ni mejore la velocidad de resolución de los síntomas.

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

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

• **IECA y ARB:** Los resultados de ocho 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 de la evidencia es baja, por lo que se necesita más información para confirmar estas conclusiones.

• **Molnupiravir:** Los resultados de diez ECCA muestran que el tratamiento con molnupiravir reduzce las hospitalizaciones y podría no aumentar los eventos adversos graves en pacientes con enfermedad de leve a moderada de comienzo reciente.

• **Nirmatrelvir y ritonavir:** Los resultados de un ECCA muestran que el tratamiento con nirmatrelvir y ritonavir probablemente reduzca las hospitalizaciones y no aumente los eventos adversos graves en pacientes con enfermedad de leve a moderada de comienzo reciente.

• **Vitamina D:** Los resultados de 18 ECCA muestran que el tratamiento con vitamina D probablemente no reduzca las infecciones y podría no reducir las hospitalizaciones. Sin embargo, la certeza de la evidencia es baja por imprecisión y riesgo de sesgo. Los efectos de la vitamina D sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Vitamina C:** Los resultados de nueve ECCA sugieren que el tratamiento con vitamina C podría mejorar la resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja y el efecto sobre otros desenlaces importantes es incierto. Se necesita más información.

• **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 de la evidencia es baja por imprecisión y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Enjuague bucal:** Los resultados de 14 ECCA sugieren que el tratamiento con enjuagues bucales podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

• **Mesilato de camostat:** Los resultados de cinco ECCA sugieren que el tratamiento con mesilato de camostat podría no mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión e información indirecta, y los efectos sobre otros desenlaces importantes son inciertos. Se necesita más información.

- **Opaganib:** Los resultados de dos ECCA sugieren que el opaganib podría no reducir la mortalidad ni la necesidad de ventilación mecánica invasiva y probablemente no incremente los eventos adversos graves, pero podría mejorar el tiempo de resolución de los síntomas. Sin embargo, la certeza de la evidencia es baja por imprecisión. Se necesita más información.

Cambios respecto a la versión anterior

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

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

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

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

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

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

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

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

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

- **TXA-127:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

- **Gabapentina con o sin montelukast:** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

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

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

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

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

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

- **N-acetilcisteína (inhalada):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

- **Solucion salina hipertónica (inhalada):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

- **Bicarbonato (inhalado):** La evidencia nueva incluida modifica la interpretación de los resultados o la certeza de la evidencia.

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

- **Sofosbuvir con o sin daclatasvir, ledipasvir, velpatasvir o ravidasvir:** 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.

- **Fluvoxamina:** 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 latest 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 29 August 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, +/- 1.9%; 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.

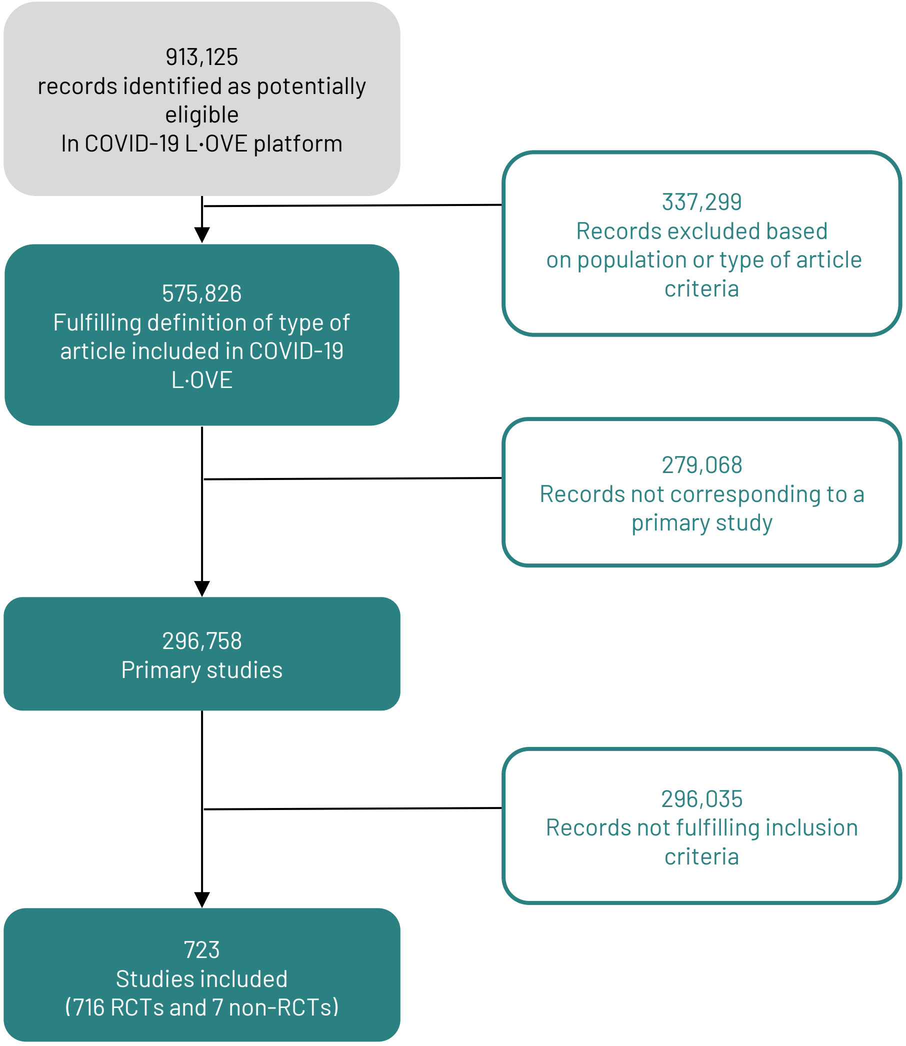
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in Figure 1. A total of 723 studies were selected for inclusion, 716 RCTs and 7 non-RCTs. A list of excluded studies is available upon request.

Figure 1. Study identification and selection process


913,125
records identified as potentially eligible
In COVID-19 L·OVE platform
337,299
Records excluded based on population or type of article criteria
575,826
Fulfilling definition of type of article included in COVID-19 L·OVE
279,068
Records not corresponding to a primary study
296,758
Primary studies
296,035
Records not fulfilling inclusion criteria
723
Studies included
(716 RCTs and 7 non-RCTs)

Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs resulted in high risk of bias due to suboptimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). Most RCTs were also very small in size and had small event numbers. The methods were very poor overall, and the reporting was suboptimal. For the observational studies, we had concerns with the representativeness of study groups (selection bias) and imbalance of the known and unknown prognostic factors (confounding). Many studies are also at risk of being confounded by indication. Most are not prospective in nature and the outcome measures are mainly heterogeneous with wide variation in reporting across the included studies. In general, follow-up was short and as mentioned, confounded potentially by the severity of disease, comorbidities, and previous or concomitant COVID-19 treatment. The risk of bias assessment of each RCT is presented in Table 4.

Table 4. Risk of bias of included RCTs

Study	Risk-of-bias arising from randomization process	Risk-of-bias due to deviations from the intended interventions	Risk-of-bias due to missing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result	**Overall Risk-of-bias judgement**	
						Mortality and Invasive mechanical ventilation	**Symptoms, infection and adverse events**
RECOVERY - 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 Department	High	Low	Low	Low	Low	High	High
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khamis F et al	High	Some Concerns	Low	Some Concerns	Low	High	High
BLAZE-1	High	Low	Low	Low	Low	High	High
PETAL	Low	Low	Low	Low	Low	Low	Low
Lanzoni G et al	High	Low	Low	Low	Low	High	High
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
Cairns DM et al	Low	Low	Low	Low	Low	Low	Low
PHYDRA	Low	Low	Low	Low	Low	Low	Low
Nekoukar Z et al	Low	Low	Low	Low	Low	Low	Low
RAAS-COVID-19	High	Some Concerns	Low	Some Concerns	Low	High	High
SpiroCOVID19	Low	Low	Low	Low	Low	Low	Low
CR216-21	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EPICOS	Low	Low	Low	Low	Low	Low	Low
COPERNICO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PROTECT-Patient trial	High	Some Concerns	Low	Some Concerns	Low	High	High
Singh H et al	Low	Low	Low	Low	Low	Low	Low
Barzin Tond S et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY	High	Some Concerns	Low	Some Concerns	Low	High	High

RUXCOVID-DEVENT	Low	Low	Low	Low	Low	Low	Low
SAC-COVID	Low	Low	Low	Low	Low	Low	Low
V323Oct2020	Low	Low	Low	Low	Low	Low	Low
Ghafoori M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORTIVID	Low	Low	Low	Low	Low	Low	Low
COVERAGE	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Hassaniazad M et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BREATHE	Low	Low	Low	Low	Low	Low	Low
Karonova TL et al	High	Some Concerns	Low	Some Concerns	Low	High	High
MeCOVID	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
COVID-VIT-D	High	Some Concerns	Low	Some Concerns	Low	High	High
TOGHETER - Ivermectin	Low	Low	Low	Low	Low	Low	Low
FLARE	Low	Low	Low	Low	Low	Low	Low
Brennan CM et al	Low	Low	Some Concerns	Low	Low	High	High
IRB 3305	Low	Low	Low	Low	Low	Low	Low
Tabarsi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Fathi-Kazerooni M et al	High	Low	Low	Low	Low	High	High
Rebelatto CK et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
LIFESAVER	Low	Low	Low	Low	Low	Low	Low
RECOVER	Low	Low	Low	Low	Low	Low	Low
LACCPT	Low	Low	Low	Low	Low	Low	Low
CPC-SARS	Low	Low	Low	Low	Low	Low	Low
Herrick J et al	Low	Low	Low	Low	Low	Low	Low
Tatem G et al	Low	Low	Low	Low	Low	Low	Low
Chowdhury FR et al	Low	Low	Low	Low	Low	Low	Low
PLACO-COVID	Low	Low	Low	Low	Low	Low	Low
ASCOT	Low	Low	Low	Low	Low	Low	Low
Co-CLARITY	Low	Low	Low	Low	Low	Low	Low
Rego EM et al	Low	Low	Low	Low	Low	Low	Low
PERUCONPLASMA	Low	Low	Low	Low	Low	Low	Low
CP-COVID-19	Low	Low	Low	Low	Low	Low	Low
CONFIDENT	Low	Low	Low	Low	Low	Low	Low
PC/COVID-19	Low	Low	Low	Low	Low	Low	Low
COP-COVID-19	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
CCAP	Low	Low	Low	Low	Low	Low	Low
COOPCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
REMAP-CAP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COPE – Coalition V	Low	Low	Low	Low	Low	Low	Low
AlQahtani M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Omehecatl	High	Some Concerns	Low	Some Concerns	Low	High	High
CORONAVIT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Seo H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Gorial FI et al	High	Some Concerns	Low	Some Concerns	Low	High	High
IMpaCt-RT	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIPOC	High	Some Concerns	Low	Some Concerns	Low	High	High
SafeDrop	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
Redondo-Calvo FJ et al	Low	Low	Some Concerns	Low	Low	High	High
CANDLE	Low	Low	Low	Low	Low	Low	Low
COVID-Compromise	Low	Low	Low	Low	Low	Low	Low
HITCH	Low	Low	Low	Low	Low	Low	Low
Kumar D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19-HBO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVASE	High	Some Concerns	Low	Some Concerns	Low	High	High
RCT-MP-COVID-19	Low	Low	Low	Low	Low	Low	Low
COPLA-II	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Coppock D et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Badavi M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PROVENT	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Pahwani S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Mostafaie A et al						NA	NA
SILVERBULLET						NA	NA
R-2020-785-176						NA	NA
GS-US-553-9020						NA	NA
DAWn-AZITHRO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
DW-MSC	Low	Low	Low	Low	Low	Low	Low
CoVIP	Low	Low	Low	High	High	High	High
Alizadeh N et al	Some Concerns	Low	Low	Low	Low	Some Concerns	Some Concerns
Thllo	Low	Low	Low	Low	Low	Low	Low
ACTT-4	Low	Low	Low	Low	Low	Low	Low
Nicastri E et al	Low	Low	Low	Low	Low	Low	Low
PROTHROMCOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
COVID-HEP	Low	Some Concerns	Low	Some Concerns	Low	Low	High
STU-2020-0707	Low	Low	Low	Low	Low	Low	Low
MANTICO	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CSSC-001	Low	Low	Low	Low	Low	Low	Low
Mukae H et al	Low	Low	Low	Low	Low	Low	Low
ZILU-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Rahman SMA et al	High	Low	Low	Low	Low	High	High
TACTIC-COVID	Low	Low	Low	Low	Low	Low	Low
iNSPIRE	Low	Low	Low	Low	Low	Low	Low
MGC-006	Low	Low	Low	Low	Low	Low	Low
REPAVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
NO COV-ED	High	Some Concerns	Low	Some Concerns	Low	High	High
Villasis-Keever MA et al	High	Low	High	Low	Low	High	High
CARED-TRIAL	Low	Low	Low	Low	Low	Low	Low
Lonze BE et al	Low	Low	Low	Low	Low	Low	Low
STRUCK	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV-6	Low	Low	Low	Low	Low	Low	Low
Rezai_Mild	Low	Low	Low	Low	Low	Low	Low
Rezai_Severe	Low	Low	Some Concerns	Low	Low	High	High
Angkasekwinai_Treat	Low	Low	Low	Low	Low	Low	Low
Angkasekwinai_Prev	Low	Low	Low	Low	Low	Low	Low

Mirahmadizadeh et al	Low	Low	Low	Low	Low	Low	Low
George et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Rojas et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Bargay-Lleonart et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ETHIC	High	Some Concerns	Low	Some Concerns	Low	High	High
OVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mukae H et al	Low	Low	Low	Low	Low	Low	Low
Khan et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Moslemi et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Stambouli et al	Low	Low	Low	Low	Low	Low	Low
Stambouli et al	Low	Low	Low	Low	Low	Low	Low
Alemany et al	Low	Low	Low	Low	Low	Low	Low
McMahon et al	Low	Low	Low	Low	Low	Low	Low
Karampitsakos et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Carvalho Neuenschwander et al	Low	Low	Low	Low	Low	Low	Low
Amoushahi et al	High	Low	Low	Low	Low	High	High
Castro-Rodriguez et al	High	Some Concerns	High	Some Concerns	Low	High	High
Terada et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Medhat et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Prasenohadi et al	Low	Low	Low	Low	Low	Low	Low
TACKLE	Low	Low	Low	Low	Low	Low	Low
TICO	Low	Low	Low	Low	Low	Low	Low
Labro et al	Low	Low	Low	Low	Low	Low	Low
Askari rt al	Low	Low	Low	Low	Low	Low	Low
Dow et al	High	Low	Low	Low	Low	High	High
Cecconi et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Tirupakuzhi et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Lau et al	Low	Low	Low	Low	Low	Low	Low
COVIT-TRIAL	High	Some Concerns	Low	Some Concerns	Low	High	High
Karonova	High	Some Concerns	Low	Some Concerns	Low	High	High
Bencheqroun	Low	Low	Low	Low	Low	Low	Low
Panatto	High	Some Concerns	Low	Some Concerns	Low	High	High
UW 20-535	High	Some Concerns	Low	Some Concerns	Low	High	High
Barnette	High	Low	Low	Low	Low	High	High
Saviano	High	Some Concerns	Low	Some Concerns	Low	High	High
Tobback	Low	Low	Low	Low	Low	Low	Low
Barrueco	Low	Low	Low	Low	Low	Low	Low
Zeyad	High	Some Concerns	Low	Some Concerns	Low	High	High
Self	Low	Low	Low	Low	Low	Low	Low
Kumar	High	Some Concerns	Low	Some Concerns	Low	High	High
Zou	High	Some Concerns	Low	Some Concerns	Low	High	High
Tandon	Low	Low	Low	Low	Low	Low	Low
COVIDICUS	Low	Low	Low	Low	Low	Low	Low
Dastenae	High	Some Concerns	Low	Some Concerns	Low	High	High
Rabbani	High	Some Concerns	Low	Some Concerns	Low	High	High
Bharti	Low	Low	Some Concerns	Low	High	High	High
Ojeda	High	Low	Low	Low	Low	High	High
Bozorgmehr R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Romero-Ibarguengoitia	High	Some Concerns	Low	Some Concerns	Low	High	High
ACTIV-6 - Fluticazone	Low	Low	Low	Low	Low	Low	Low
BLAZE-4	Low	Low	Low	Low	Low	Low	Low
PRANA	Low	Low	Low	Low	Low	Low	Low
Aryan	High	Low	Low	Low	Low	High	High
Cervero	High	Some Concerns	Low	Some Concerns	Low	High	High
Abroug	High	Low	Low	Low	Low	High	High
PLATCOV - Iver	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PLATCOV - Regen	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Fogleman C et al	Low	Low	Low	Low	Low	Low	Low
PanCOVID19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AGILE	Low	Low	Low	Low	Low	Low	Low
D-COVID	High	Low	Low	Low	Low	High	High
IRICT	Low	Low	Low	Low	Low	Low	Low
Choudhary R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Khodashahi R et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AAAT0535	Low	Low	Low	Low	Low	Low	Low
ACTIV-3/TICO	Low	Low	Low	Low	Low	Low	Low
Soltani R et al	High	Some Concerns	Low	Some Concerns	Low	High	High
ANACONDA	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BTI-202	Low	Low	Low	Low	Low	Low	Low
ReCOVery-SIRIO	High	Some Concerns	Low	Some Concerns	Low	High	High
MOVe-IN	Low	Low	Low	Low	Low	Low	Low
MOVe-OUT - ph2	Low	Low	Low	Low	Low	Low	Low
FERMIN	Low	Low	Low	Low	Low	Low	Low
Nimitvilai S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Spuch C et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Delić N et al	High	Some Concerns	Low	Some Concerns	Low	High	High
DMMETCOV19-2	Low	Low	Low	Low	Low	Low	Low
COVER HCW	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
COVID-OUT	Low	Low	Low	Low	Low	Low	Low

Main findings

Corticosteroids

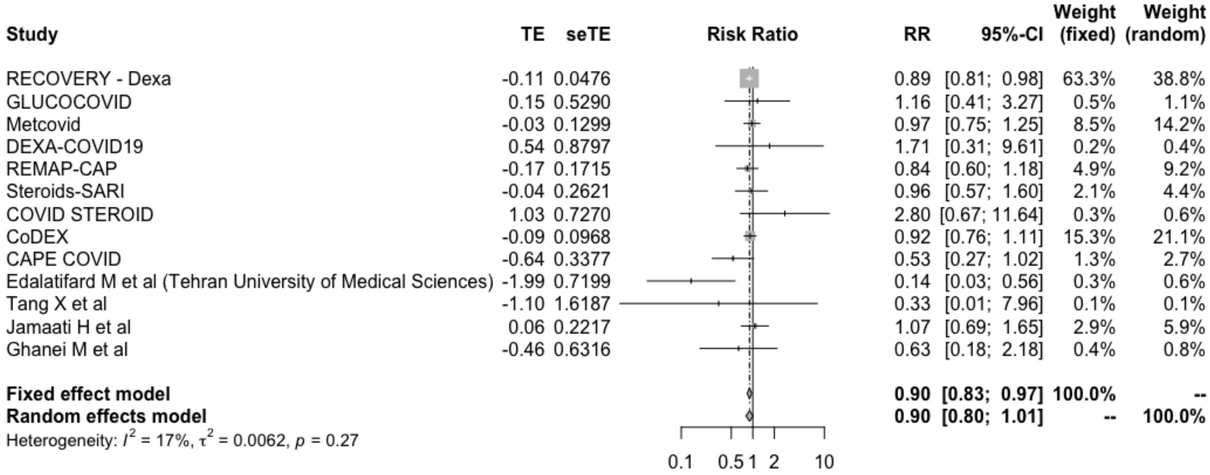
See Summary of findings Table 1, Appendix 1

We identified 17 RCTs including 9,485 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. Sixteen 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%, and one study included hospitalized patients without respiratory failure. 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 eight studies including 2,490 patients in which different corticosteroid dosage schemes were compared and one study including 42 patients in which high dose steroids were compared to tocilizumab. 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 0.97 (95%CI 0.78 to 1.21); RD -0.5% (95%CI -3.5% to 3.4%); Low certainty ⊕⊕○○ (Figure 5) (based on low risk of bias studies)
- It is uncertain if high-dose corticosteroids (i.e., dexamethasone 12 mg a day) increase or reduce mechanical ventilation compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.94 (95%CI 0.41 to 2.11); RD -1% (95%CI -10.2% to 19.2%); Very low certainty ⊕○○○

- High-dose corticosteroids (i.e., dexamethasone 12 mg a day) may not increase symptom resolution or improvement compared to standard-dose corticosteroids (i.e., dexamethasone 6 mg a day), RR 0.99 (95%CI 0.9 to 1.08); RD -0.6% (95%CI -5.5% to 4.9%); Low certainty ⊕⊕○○
- 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 0.82 (95%CI 0.6 to 1.11); RD -1.8% (95%CI -4.1% to 1.1%); Low certainty ⊕⊕○○

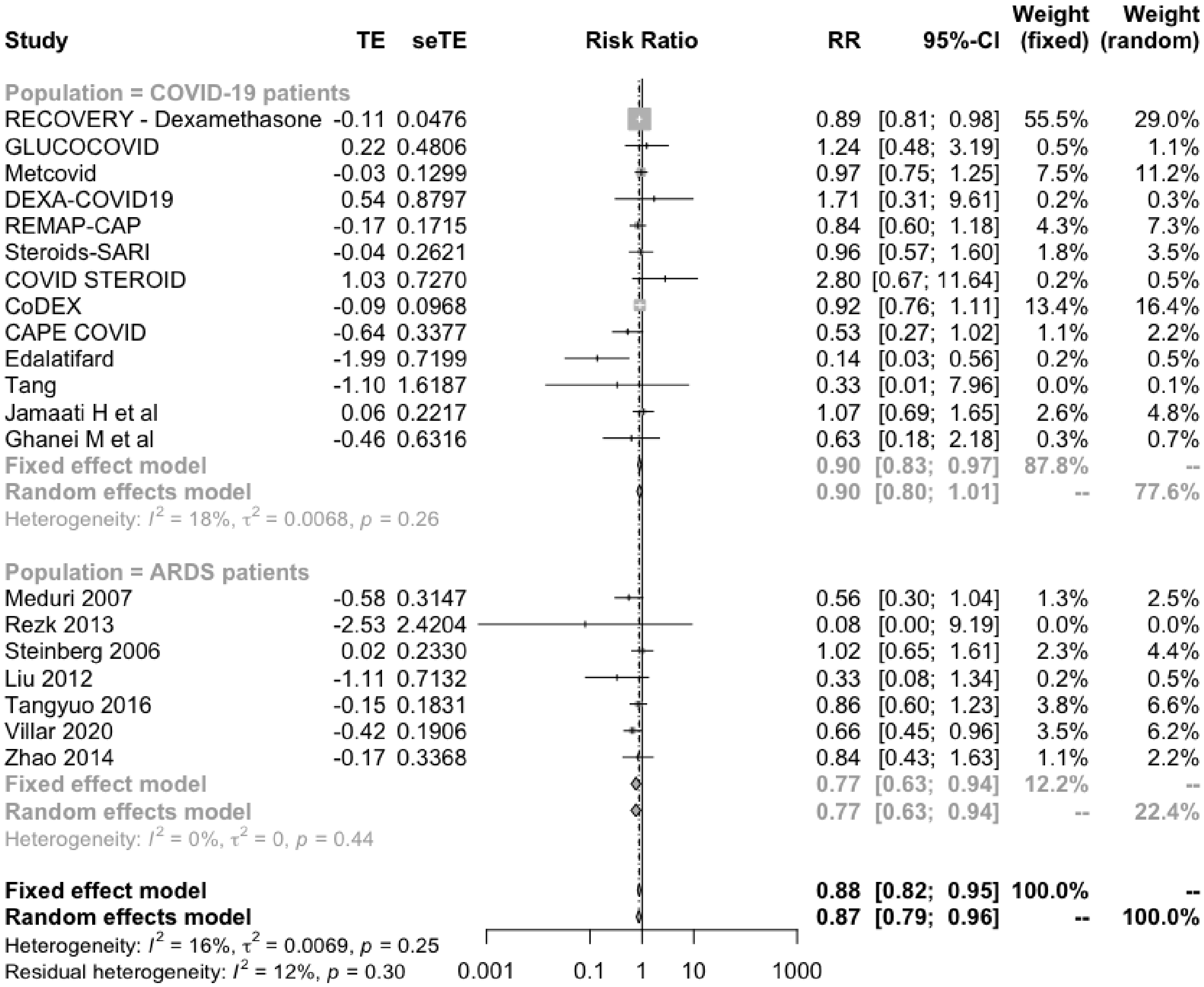
Figure 2. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
RECOVERY - Dexa	-0.11	0.0476	0.89	[0.81; 0.98]	63.3%	38.8%
GLUCOCOVID	0.15	0.5290	1.16	[0.41; 3.27]	0.5%	1.1%
Metcovid	-0.03	0.1299	0.97	[0.75; 1.25]	8.5%	14.2%
DEXA-COVID19	0.54	0.8797	1.71	[0.31; 9.61]	0.2%	0.4%
REMAP-CAP	-0.17	0.1715	0.84	[0.60; 1.18]	4.9%	9.2%
Steroids-SARI	-0.04	0.2621	0.96	[0.57; 1.60]	2.1%	4.4%
COVID STEROID	1.03	0.7270	2.80	[0.67; 11.64]	0.3%	0.6%
CoDEX	-0.09	0.0968	0.92	[0.76; 1.11]	15.3%	21.1%
CAPE COVID	-0.64	0.3377	0.53	[0.27; 1.02]	1.3%	2.7%
Edalatifard M et al (Tehran University of Medical Sciences)	-1.99	0.7199	0.14	[0.03; 0.56]	0.3%	0.6%
Tang X et al	-1.10	1.6187	0.33	[0.01; 7.96]	0.1%	0.1%
Jamaati H et al	0.06	0.2217	1.07	[0.69; 1.65]	2.9%	5.9%
Ghanei M et al	-0.46	0.6316	0.63	[0.18; 2.18]	0.4%	0.8%
Fixed effect model			**0.90**	**[0.83; 0.97]**	**100.0%**	**--**
Random effects model			**0.90**	**[0.80; 1.01]**	**--**	**100.0%**

Heterogeneity: $I^2 = 17\%$, $\tau^2 = 0.0062$, $p = 0.27$

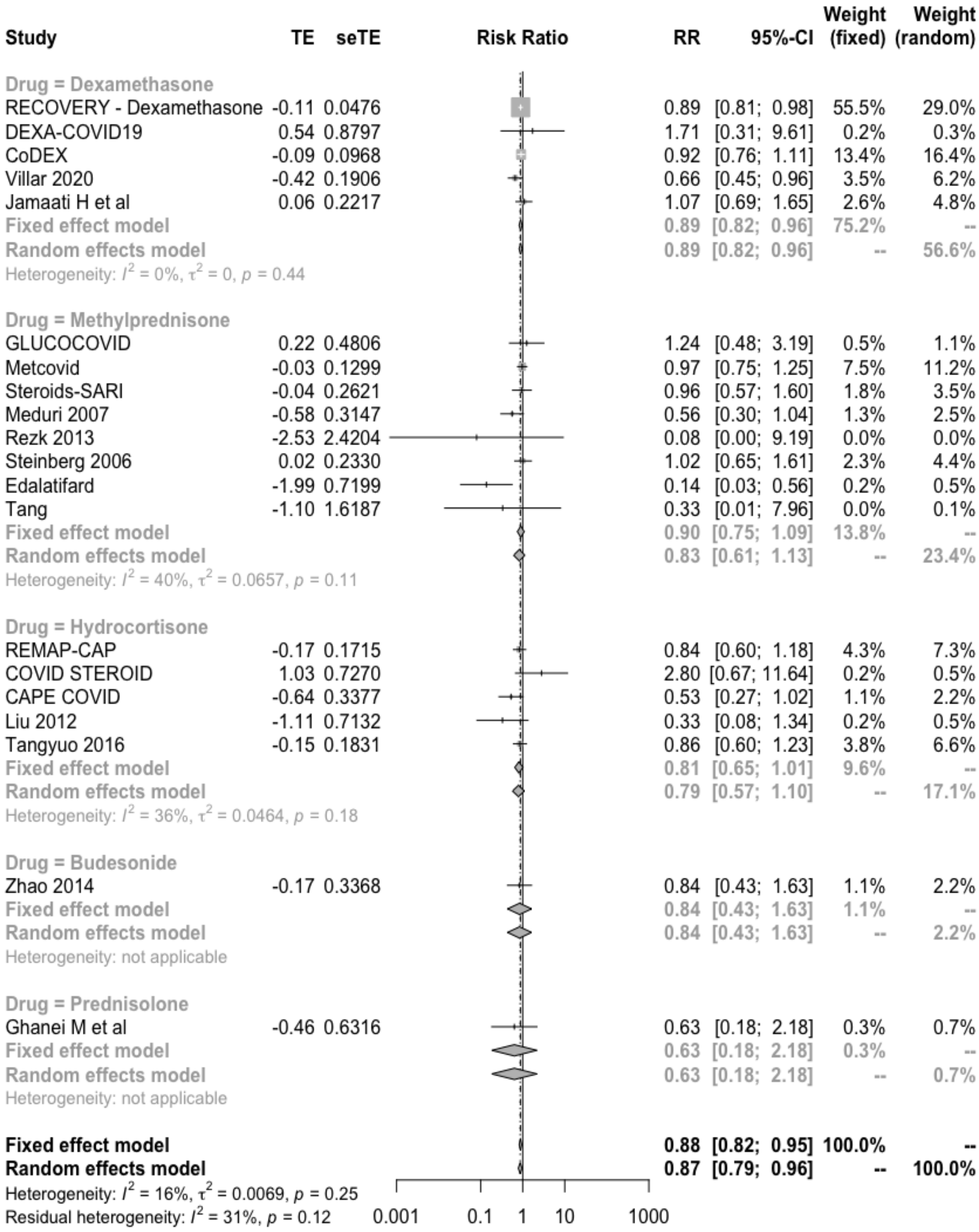
Figure 3. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19



Study	TE	seTE	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: $I^2 = 18\%$, $\tau^2 = 0.0068$, $p = 0.26$						
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: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.44$						
Fixed effect model			**0.88**	**[0.82; 0.95]**	**100.0%**	**--**
Random effects model			**0.87**	**[0.79; 0.96]**	**--**	**100.0%**

Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0.0069$, $p = 0.25$
Residual heterogeneity: $I^2 = 12\%$, $p = 0.30$

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

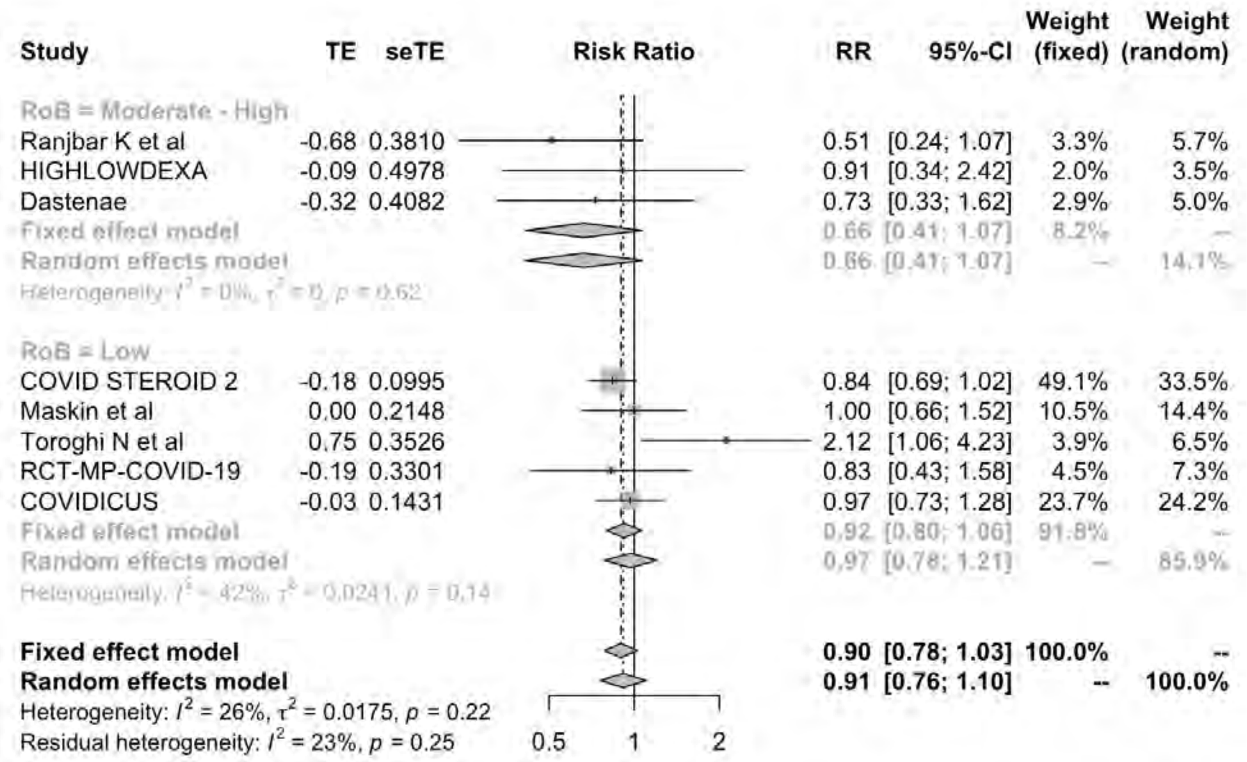


Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
Drug = Dexamethasone						
RECOVERY - Dexamethasone	-0.11	0.0476	0.89	[0.81; 0.98]	55.5%	29.0%
DEXA-COVID19	0.54	0.8797	1.71	[0.31; 9.61]	0.2%	0.3%
CoDEX	-0.09	0.0968	0.92	[0.76; 1.11]	13.4%	16.4%
Villar 2020	-0.42	0.1906	0.66	[0.45; 0.96]	3.5%	6.2%
Jamaati H et al	0.06	0.2217	1.07	[0.69; 1.65]	2.6%	4.8%
Fixed effect model			0.89	[0.82; 0.96]	75.2%	--
Random effects model			0.89	[0.82; 0.96]	--	56.6%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.44$						
Drug = Methylprednisone						
GLUCOCOVID	0.22	0.4806	1.24	[0.48; 3.19]	0.5%	1.1%
Metcovid	-0.03	0.1299	0.97	[0.75; 1.25]	7.5%	11.2%
Steroids-SARI	-0.04	0.2621	0.96	[0.57; 1.60]	1.8%	3.5%
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%
Edalatifard	-1.99	0.7199	0.14	[0.03; 0.56]	0.2%	0.5%
Tang	-1.10	1.6187	0.33	[0.01; 7.96]	0.0%	0.1%
Fixed effect model			0.90	[0.75; 1.09]	13.8%	--
Random effects model			0.83	[0.61; 1.13]	--	23.4%
Heterogeneity: $I^2 = 40\%$, $\tau^2 = 0.0657$, $p = 0.11$						
Drug = Hydrocortisone						
REMAP-CAP	-0.17	0.1715	0.84	[0.60; 1.18]	4.3%	7.3%
COVID STEROID	1.03	0.7270	2.80	[0.67; 11.64]	0.2%	0.5%
CAPE COVID	-0.64	0.3377	0.53	[0.27; 1.02]	1.1%	2.2%
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%
Fixed effect model			0.81	[0.65; 1.01]	9.6%	--
Random effects model			0.79	[0.57; 1.10]	--	17.1%
Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.0464$, $p = 0.18$						
Drug = Budesonide						
Zhao 2014	-0.17	0.3368	0.84	[0.43; 1.63]	1.1%	2.2%
Fixed effect model			0.84	[0.43; 1.63]	1.1%	--
Random effects model			0.84	[0.43; 1.63]	--	2.2%
Heterogeneity: not applicable						
Drug = Prednisolone						
Ghanei M et al	-0.46	0.6316	0.63	[0.18; 2.18]	0.3%	0.7%
Fixed effect model			0.63	[0.18; 2.18]	0.3%	--
Random effects model			0.63	[0.18; 2.18]	--	0.7%
Heterogeneity: not applicable						
Fixed effect model			**0.88**	**[0.82; 0.95]**	**100.0%**	**--**
Random effects model			**0.87**	**[0.79; 0.96]**	**--**	**100.0%**

Heterogeneity: $I^2 = 16\%$, $\tau^2 = 0.0069$, $p = 0.25$

Residual heterogeneity: $I^2 = 31\%$, $p = 0.12$

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



In addition, one study that compared high dose corticosteroids (dexamethasone 20 mg 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 11,814 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 4,146 patients assigned to remdesivir and 4,129 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% or less mortality in the control arm. Our results showed:

- Remdesivir probably reduces mortality, RR 0.93 (95%CI 0.89 to 1.03); RD -1.1% (95%CI -1.8% to 0.5%); Moderate certainty ⊕⊕⊕○ (Figure 6)

- Remdesivir probably reduces invasive mechanical ventilation requirement, RR 0.76 (95%CI 0.56 to 1.04); RD -4.2% (95%CI -7.6% to 0.7%); Moderate 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

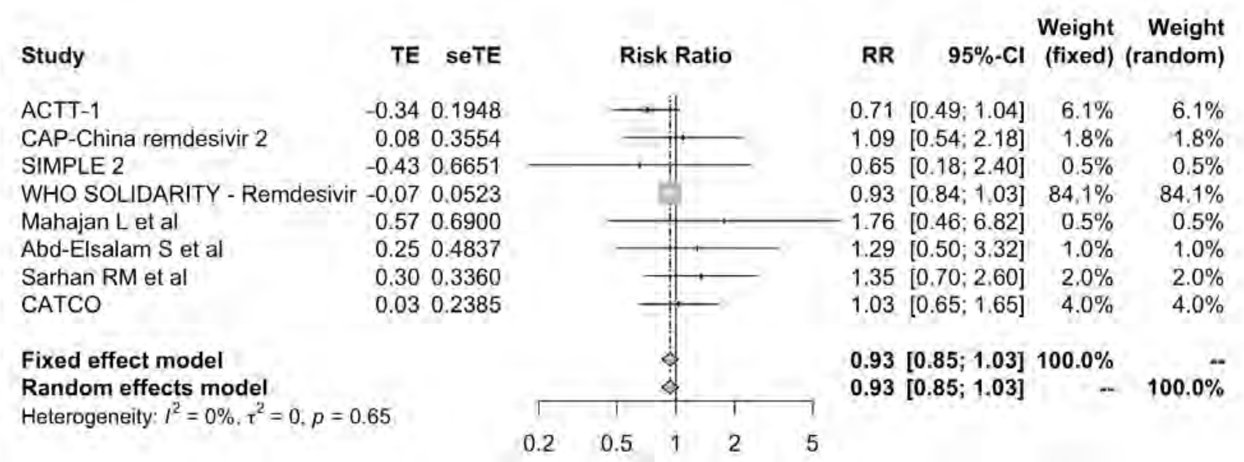


Figure 7. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

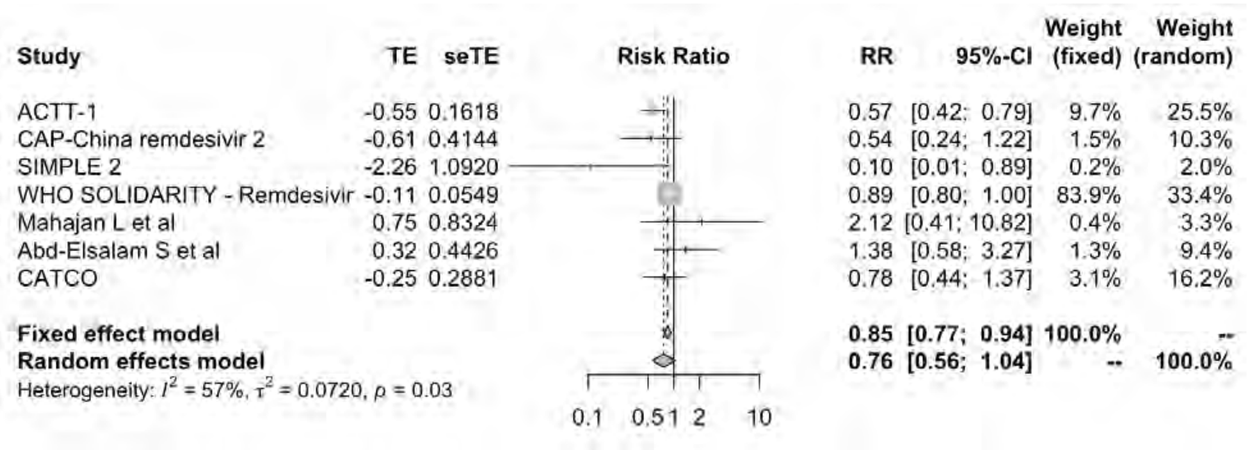
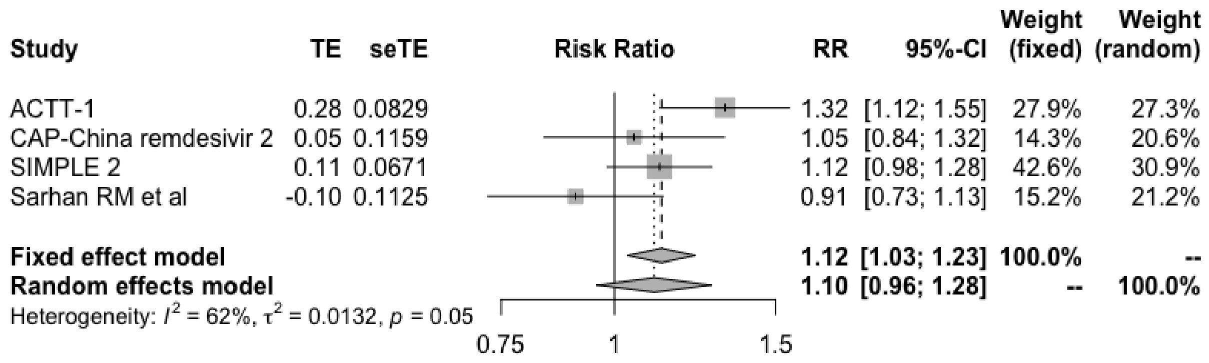


Figure 8. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

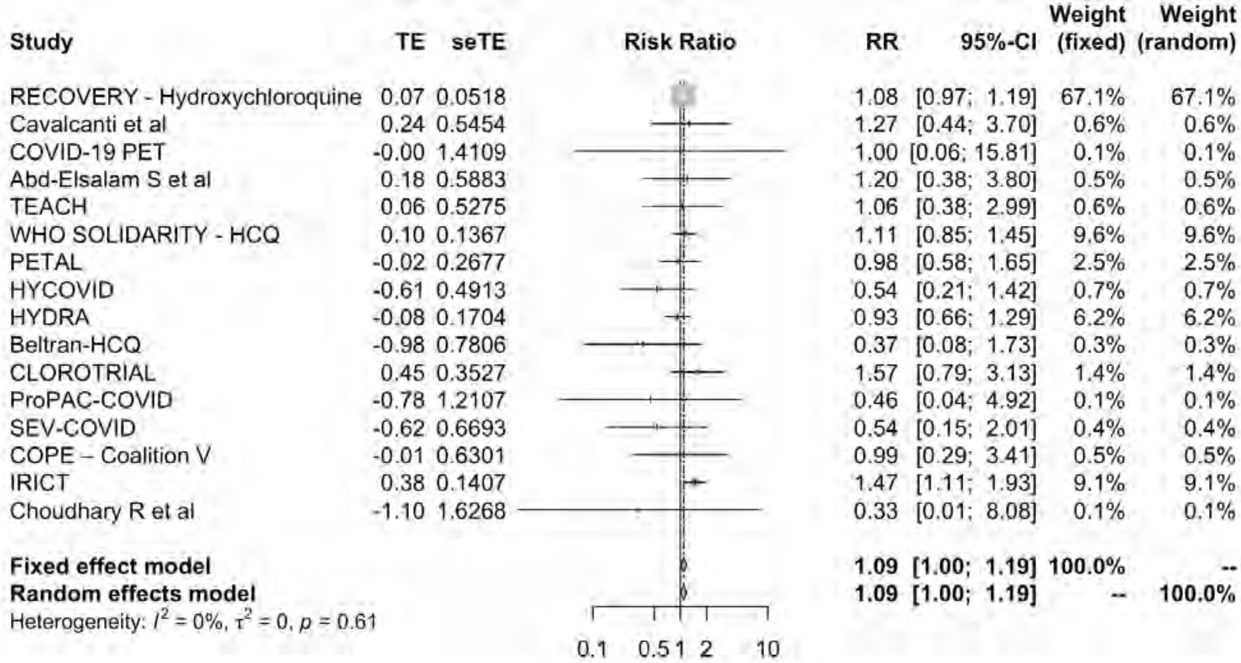
See Summary of findings Table 3, Appendix 1

We identified 61 RCTs including 25,977 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 does not increase mortality, RR 1.09 (95%CI 1 to 1.19); RD 1.4% (95%CI 0% to 3%); Moderate certainty ⊕⊕⊕○ (Figure 9)
- Hydroxychloroquine or chloroquine probably does not reduce invasive mechanical ventilation requirement; RR 1.08 (95%CI 0.93 to 1.25); RD 1.4% (95%CI -1.2% to 4.3%); 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 not have an important effect on 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 0.90 (95%CI 0.66 to 1.22); RD -1% (95%CI -3.5% to 2.2%); Low certainty ⊕⊕○○
- Hydroxychloroquine or chloroquine may not have an important effect on hospitalizations in patients with mild COVID-19, RR 0.82 (95%CI 0.61 to 1.1); RD -0.9% (95%CI -1.9% to 0.5%); Low certainty ⊕⊕○○

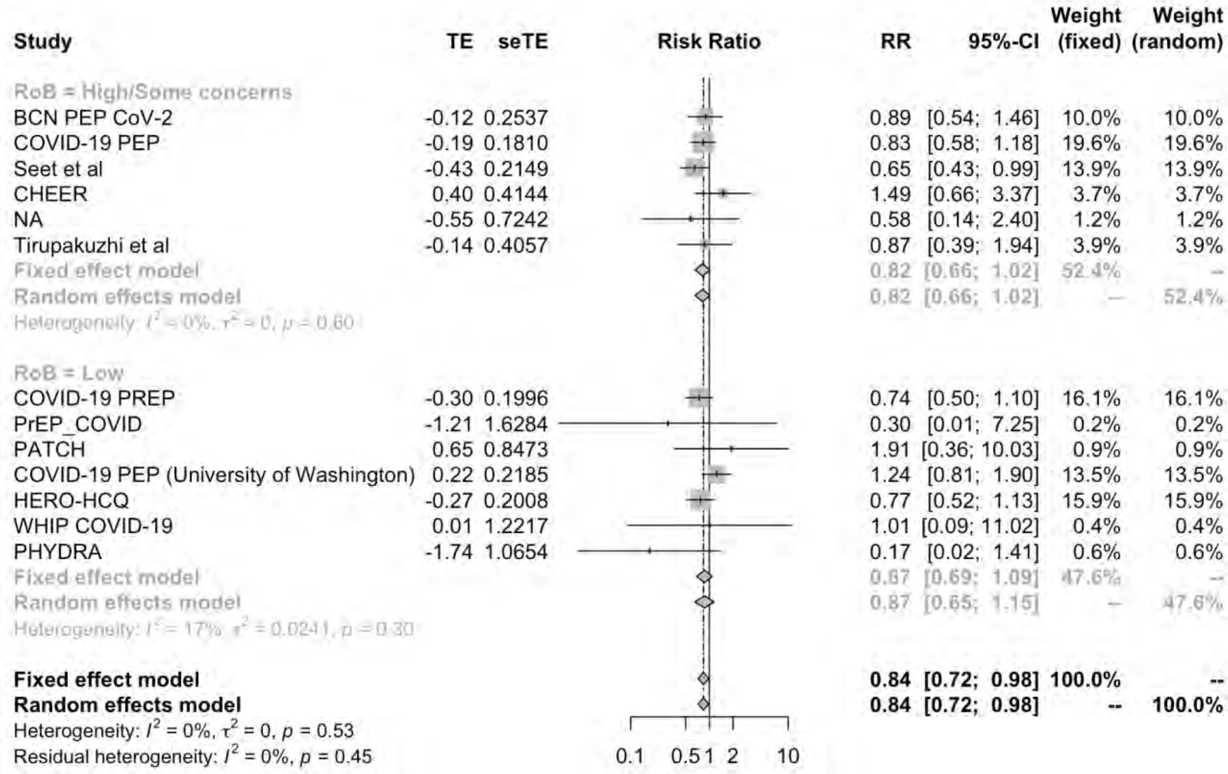
Figure 9. All-cause mortality in RCTs comparing hydroxychloroquine or chloroquine with standard of care in patients with COVID-19



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
RECOVERY - Hydroxychloroquine	0.07	0.0518	1.08	[0.97; 1.19]	67.1%	67.1%
Cavalcanti et al	0.24	0.5454	1.27	[0.44; 3.70]	0.6%	0.6%
COVID-19 PET	-0.00	1.4109	1.00	[0.06; 15.81]	0.1%	0.1%
Abd-Elsalam S et al	0.18	0.5883	1.20	[0.38; 3.80]	0.5%	0.5%
TEACH	0.06	0.5275	1.06	[0.38; 2.99]	0.6%	0.6%
WHO SOLIDARITY - HCQ	0.10	0.1367	1.11	[0.85; 1.45]	9.6%	9.6%
PETAL	-0.02	0.2677	0.98	[0.58; 1.65]	2.5%	2.5%
HYCOVID	-0.61	0.4913	0.54	[0.21; 1.42]	0.7%	0.7%
HYDRA	-0.08	0.1704	0.93	[0.66; 1.29]	6.2%	6.2%
Beltran-HCQ	-0.98	0.7806	0.37	[0.08; 1.73]	0.3%	0.3%
CLOROTRIAL	0.45	0.3527	1.57	[0.79; 3.13]	1.4%	1.4%
ProPAC-COVID	-0.78	1.2107	0.46	[0.04; 4.92]	0.1%	0.1%
SEV-COVID	-0.62	0.6693	0.54	[0.15; 2.01]	0.4%	0.4%
COPE – Coalition V	-0.01	0.6301	0.99	[0.29; 3.41]	0.5%	0.5%
IRICT	0.38	0.1407	1.47	[1.11; 1.93]	9.1%	9.1%
Choudhary R et al	-1.10	1.6268	0.33	[0.01; 8.08]	0.1%	0.1%
Fixed effect model			**1.09**	**[1.00; 1.19]**	**100.0%**	**--**
Random effects model			**1.09**	**[1.00; 1.19]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$

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

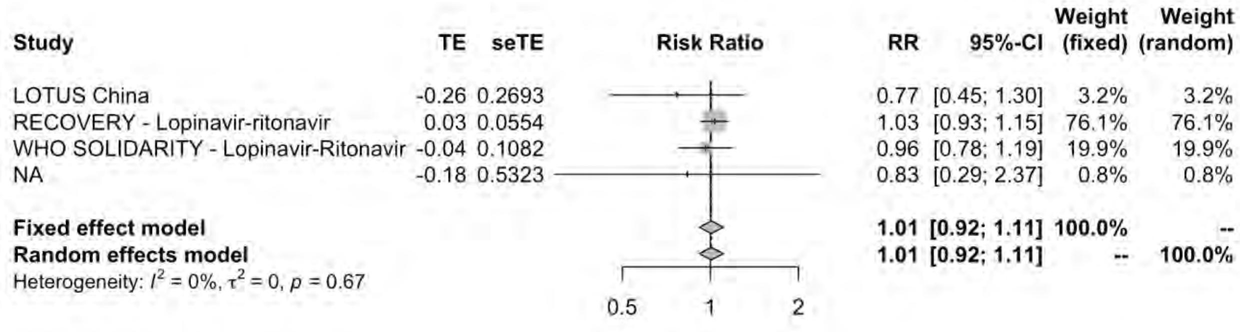
See Summary of findings Table 4, Appendix 1

We identified 21 RCTs including 10,697 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 1.22 (95%CI 0.61 to 2.47); RD 1.1% (95%CI -1.9% to -7.1%); 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

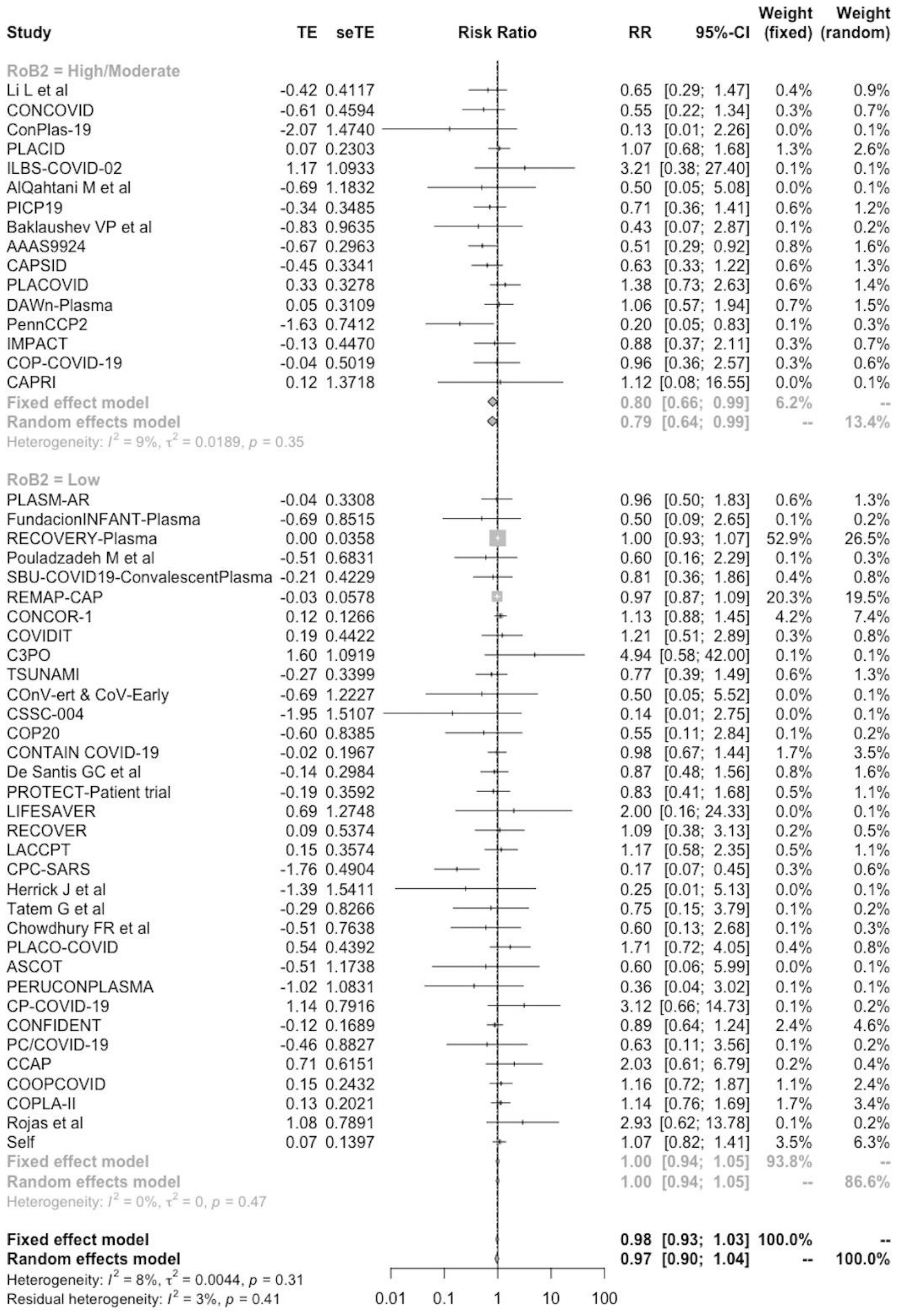
[*See summary of findings Table 5 in appendix 1*]

We identified 58 RCTs including 24,753 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 (52/58) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 5.5% to 53%. The remaining studies included patients with recent onset symptoms and reported a control-arm mortality rate of 0.4% to 6.6%, or non-infected exposed individuals. 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 0.98 (95%CI 0.93 to 1.03); RD -0.3% (95%CI -1.1% to 0.5%); High certainty ⊕⊕⊕⊕ (Figure 12)
- Convalescent plasma does not significantly reduce invasive mechanical ventilation requirements, RR 1.02 (95% CI 0.94 to 1.11); RD 0.3% (95%CI -1% to 1.9%); High certainty ⊕⊕⊕⊕
- Convalescent plasma probably does not improve symptom resolution or improvement, RR 0.99 (95% CI 0.95 to 1.02); RD -0.6% (95%CI -3% to 1.2); High certainty ⊕⊕⊕⊕

- It is uncertain if convalescent plasma reduces symptomatic infections in exposed individuals, RR 0.92 (95% CI 0.32 to 2.62); RD -1.4% (95%CI -11.8% to 28.2); Very low certainty ⊕○○○
- Convalescent plasma may not increase severe adverse events, RR 1.03 (95% CI 0.88 to 1.21); RD 0.3% (95%CI -1.2% to 2.1%); Low certainty ⊕⊕○○
- Convalescent plasma probably has no important effect on hospitalizations, RR 0.77 (95% CI 0.57 to 1.03); RD -1.1% (95%CI -2.1% to 0.1%); Moderate certainty ⊕⊕⊕○ (Figure 13). The observed effect would probably be considered important in patients with very high hospitalization risk.

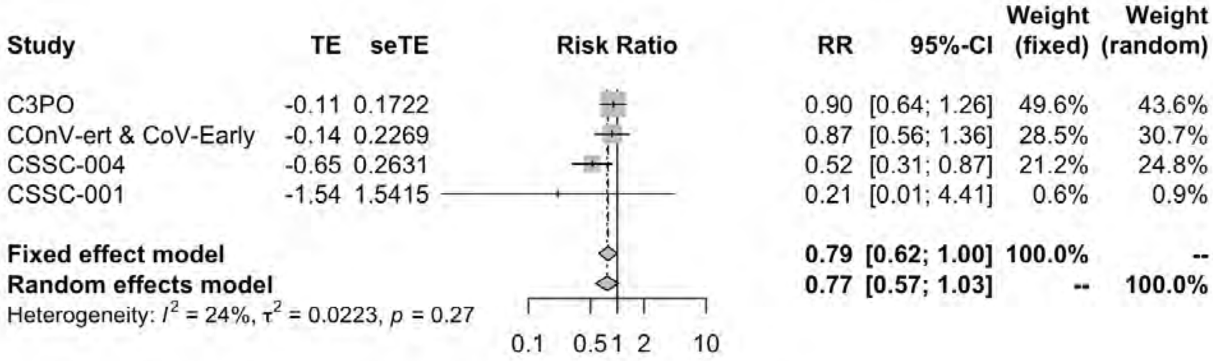
Figure 12. All-cause mortality in RCTs comparing convalescent plasma with standard of care for treatment of patients with COVID-19



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
RoB2 = High/Moderate						
Li L et al	-0.42	0.4117	0.65	[0.29; 1.47]	0.4%	0.9%
CONCOVID	-0.61	0.4594	0.55	[0.22; 1.34]	0.3%	0.7%
ConPlas-19	-2.07	1.4740	0.13	[0.01; 2.26]	0.0%	0.1%
PLACID	0.07	0.2303	1.07	[0.68; 1.68]	1.3%	2.6%
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]	0.0%	0.1%
PICP19	-0.34	0.3485	0.71	[0.36; 1.41]	0.6%	1.2%
Baklaushev VP et al	-0.83	0.9635	0.43	[0.07; 2.87]	0.1%	0.2%
AAAS9924	-0.67	0.2963	0.51	[0.29; 0.92]	0.8%	1.6%
CAPSID	-0.45	0.3341	0.63	[0.33; 1.22]	0.6%	1.3%
PLACOVID	0.33	0.3278	1.38	[0.73; 2.63]	0.6%	1.4%
DAWn-Plasma	0.05	0.3109	1.06	[0.57; 1.94]	0.7%	1.5%
PennCCP2	-1.63	0.7412	0.20	[0.05; 0.83]	0.1%	0.3%
IMPACT	-0.13	0.4470	0.88	[0.37; 2.11]	0.3%	0.7%
COP-COVID-19	-0.04	0.5019	0.96	[0.36; 2.57]	0.3%	0.6%
CAPRI	0.12	1.3718	1.12	[0.08; 16.55]	0.0%	0.1%
Fixed effect model			0.80	[0.66; 0.99]	6.2%	--
Random effects model			0.79	[0.64; 0.99]	--	13.4%
Heterogeneity: $I^2 = 9\%$, $\tau^2 = 0.0189$, $p = 0.35$						
RoB2 = Low						
PLASM-AR	-0.04	0.3308	0.96	[0.50; 1.83]	0.6%	1.3%
FundacionINFANT-Plasma	-0.69	0.8515	0.50	[0.09; 2.65]	0.1%	0.2%
RECOVERY-Plasma	0.00	0.0358	1.00	[0.93; 1.07]	52.9%	26.5%
Pouladzadeh M et al	-0.51	0.6831	0.60	[0.16; 2.29]	0.1%	0.3%
SBU-COVID19-ConvalescentPlasma	-0.21	0.4229	0.81	[0.36; 1.86]	0.4%	0.8%
REMAP-CAP	-0.03	0.0578	0.97	[0.87; 1.09]	20.3%	19.5%
CONCOR-1	0.12	0.1266	1.13	[0.88; 1.45]	4.2%	7.4%
COVIDIT	0.19	0.4422	1.21	[0.51; 2.89]	0.3%	0.8%
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]	0.6%	1.3%
COnV-ert & CoV-Early	-0.69	1.2227	0.50	[0.05; 5.52]	0.0%	0.1%
CSSC-004	-1.95	1.5107	0.14	[0.01; 2.75]	0.0%	0.1%
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]	1.7%	3.5%
De Santis GC et al	-0.14	0.2984	0.87	[0.48; 1.56]	0.8%	1.6%
PROTECT-Patient trial	-0.19	0.3592	0.83	[0.41; 1.68]	0.5%	1.1%
LIFESAVER	0.69	1.2748	2.00	[0.16; 24.33]	0.0%	0.1%
RECOVER	0.09	0.5374	1.09	[0.38; 3.13]	0.2%	0.5%
LACCPT	0.15	0.3574	1.17	[0.58; 2.35]	0.5%	1.1%
CPC-SARS	-1.76	0.4904	0.17	[0.07; 0.45]	0.3%	0.6%
Herrick J et al	-1.39	1.5411	0.25	[0.01; 5.13]	0.0%	0.1%
Tatem G et al	-0.29	0.8266	0.75	[0.15; 3.79]	0.1%	0.2%
Chowdhury FR et al	-0.51	0.7638	0.60	[0.13; 2.68]	0.1%	0.3%
PLACO-COVID	0.54	0.4392	1.71	[0.72; 4.05]	0.4%	0.8%
ASCOT	-0.51	1.1738	0.60	[0.06; 5.99]	0.0%	0.1%
PERUCONPLASMA	-1.02	1.0831	0.36	[0.04; 3.02]	0.1%	0.1%
CP-COVID-19	1.14	0.7916	3.12	[0.66; 14.73]	0.1%	0.2%
CONFIDENT	-0.12	0.1689	0.89	[0.64; 1.24]	2.4%	4.6%
PC/COVID-19	-0.46	0.8827	0.63	[0.11; 3.56]	0.1%	0.2%
CCAP	0.71	0.6151	2.03	[0.61; 6.79]	0.2%	0.4%
COOPCOVID	0.15	0.2432	1.16	[0.72; 1.87]	1.1%	2.4%
COPLA-II	0.13	0.2021	1.14	[0.76; 1.69]	1.7%	3.4%
Rojas et al	1.08	0.7891	2.93	[0.62; 13.78]	0.1%	0.2%
Self	0.07	0.1397	1.07	[0.82; 1.41]	3.5%	6.3%
Fixed effect model			1.00	[0.94; 1.05]	93.8%	--
Random effects model			1.00	[0.94; 1.05]	--	86.6%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$						
Fixed effect model			**0.98**	**[0.93; 1.03]**	**100.0%**	**--**
Random effects model			**0.97**	**[0.90; 1.04]**	**--**	**100.0%**

Heterogeneity: $I^2 = 8\%$, $\tau^2 = 0.0044$, $p = 0.31$
Residual heterogeneity: $I^2 = 3\%$, $p = 0.41$

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) or 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.

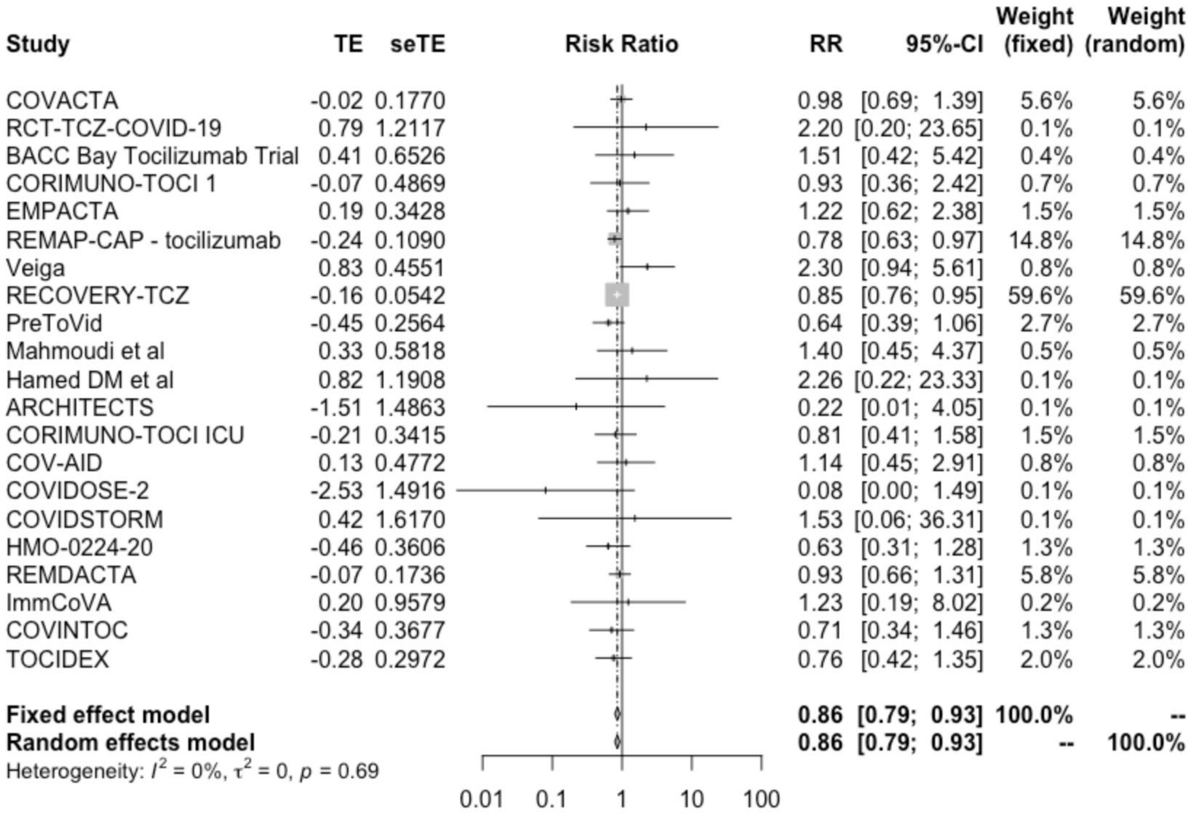
Tocilizumab

See Summary of findings Table 6 in Appendix 1

We identified 29 RCTs including 9,466 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 0.86 (95%CI 0.79 to 93); RD -2.2% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕ (Figure 14)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.84 (95%CI 0.79 to 0.91); RD -2.8% (95%CI -3.6% to -1.6%); High certainty ⊕⊕⊕⊕ (Figure 15)
- Tocilizumab may improve time to symptom resolution, RR 1.08 (95%CI 1.02 to 1.14); RD 4.8% (95%CI 1.2% to 8.5%); Low certainty ⊕⊕○○
- Tocilizumab probably does not significantly increase severe adverse events at 28-30 days, RR 0.95 (95%CI 0.87 to 1.04); RD -0.5% (95%CI -1.3% to 0.4%); Moderate certainty ⊕⊕⊕○

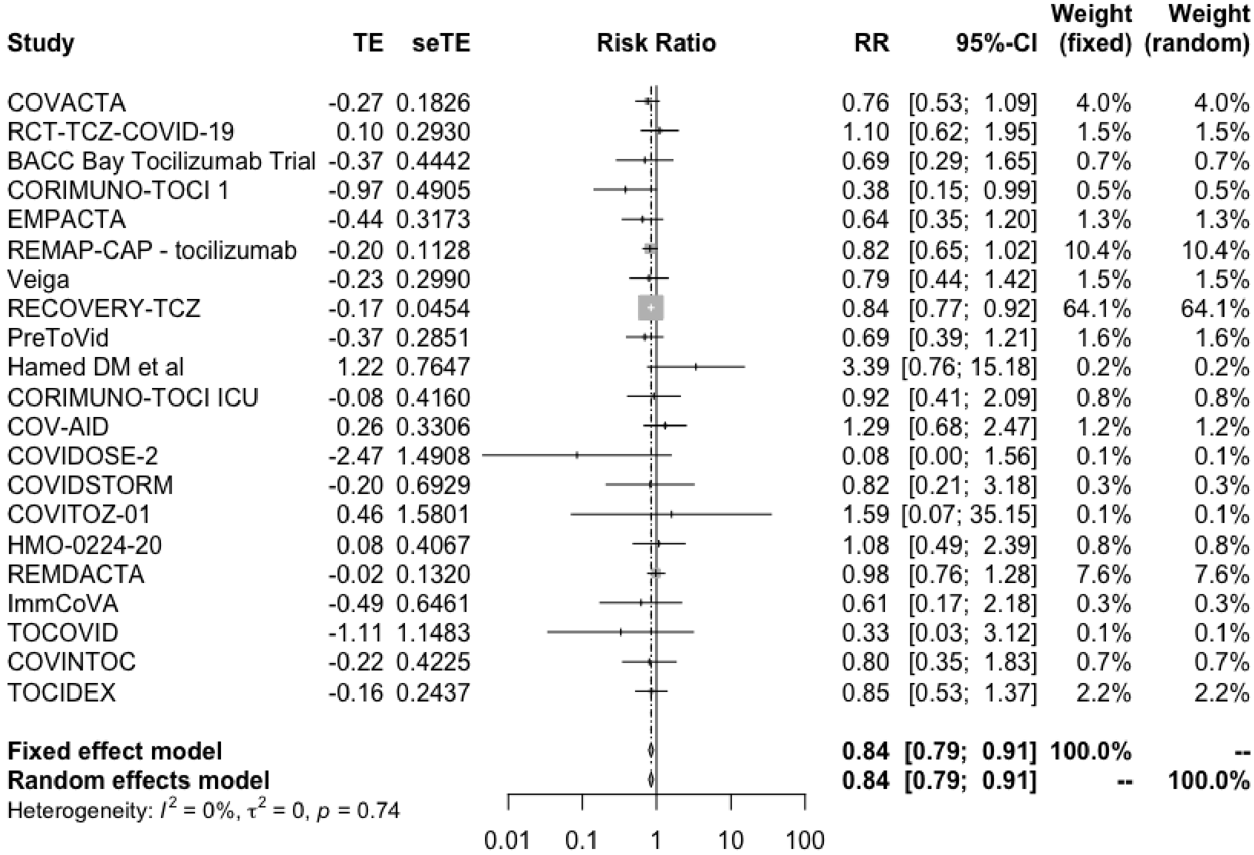
Figure 14. All-cause mortality in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
COVACTA	-0.02	0.1770	0.98	[0.69; 1.39]	5.6%	5.6%
RCT-TCZ-COVID-19	0.79	1.2117	2.20	[0.20; 23.65]	0.1%	0.1%
BACC Bay Tocilizumab Trial	0.41	0.6526	1.51	[0.42; 5.42]	0.4%	0.4%
CORIMUNO-TOCI 1	-0.07	0.4869	0.93	[0.36; 2.42]	0.7%	0.7%
EMPACTA	0.19	0.3428	1.22	[0.62; 2.38]	1.5%	1.5%
REMAP-CAP - tocilizumab	-0.24	0.1090	0.78	[0.63; 0.97]	14.8%	14.8%
Veiga	0.83	0.4551	2.30	[0.94; 5.61]	0.8%	0.8%
RECOVERY-TCZ	-0.16	0.0542	0.85	[0.76; 0.95]	59.6%	59.6%
PreToVid	-0.45	0.2564	0.64	[0.39; 1.06]	2.7%	2.7%
Mahmoudi et al	0.33	0.5818	1.40	[0.45; 4.37]	0.5%	0.5%
Hamed DM et al	0.82	1.1908	2.26	[0.22; 23.33]	0.1%	0.1%
ARCHITECTS	-1.51	1.4863	0.22	[0.01; 4.05]	0.1%	0.1%
CORIMUNO-TOCI ICU	-0.21	0.3415	0.81	[0.41; 1.58]	1.5%	1.5%
COV-AID	0.13	0.4772	1.14	[0.45; 2.91]	0.8%	0.8%
COVIDOSE-2	-2.53	1.4916	0.08	[0.00; 1.49]	0.1%	0.1%
COVIDSTORM	0.42	1.6170	1.53	[0.06; 36.31]	0.1%	0.1%
HMO-0224-20	-0.46	0.3606	0.63	[0.31; 1.28]	1.3%	1.3%
REMDACTA	-0.07	0.1736	0.93	[0.66; 1.31]	5.8%	5.8%
ImmCoVA	0.20	0.9579	1.23	[0.19; 8.02]	0.2%	0.2%
COVINTOC	-0.34	0.3677	0.71	[0.34; 1.46]	1.3%	1.3%
TOCIDEX	-0.28	0.2972	0.76	[0.42; 1.35]	2.0%	2.0%
Fixed effect model			**0.86**	**[0.79; 0.93]**	**100.0%**	**--**
Random effects model			**0.86**	**[0.79; 0.93]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.69$

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 and one study that compared baricitinib versus tocilizumab reported no significant differences in mortality or mechanical ventilation. However, the certainty of the evidence was low because of imprecision.

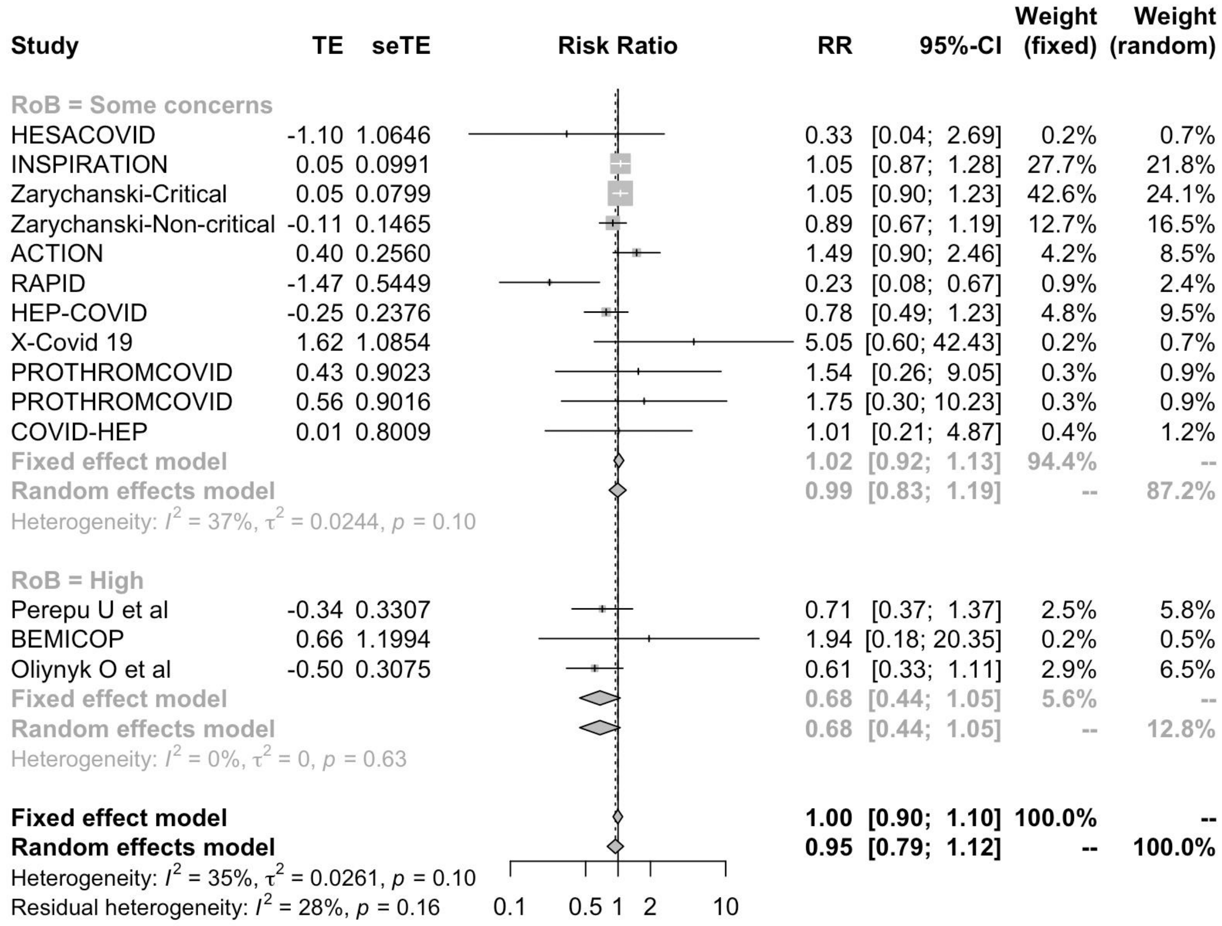
Anticoagulants

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 19 RCTs including 8,121 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. In addition we identified one study that compared rivaroxaban and enoxaparin in hospitalized patients. 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 0.99 (95%CI 0.83 to 1.19); RD -0.2% (95%CI -2.7% to 3%); Moderate 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 0.43 to 1.59); RD -1.3% (95%CI -4% to 4.1%); 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 0.71); RD -3.1% (95%CI -3.9% to -2%); High certainty ⊕⊕⊕⊕
- In moderate to critical patients, anticoagulants in intermediate dose or full dose probably increase major bleeding in comparison with prophylactic dose, RR 1.56 (95%CI 1.08 to 2.25); RD 1.1% (95%CI 0.2% to 2.4%); 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, anticoagulants in prophylactic dose may not reduce hospitalizations, RR 0.94 (95%CI 0.55 to 1.59); RD -0.3% (95%CI -2.2% to 2.8%); 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



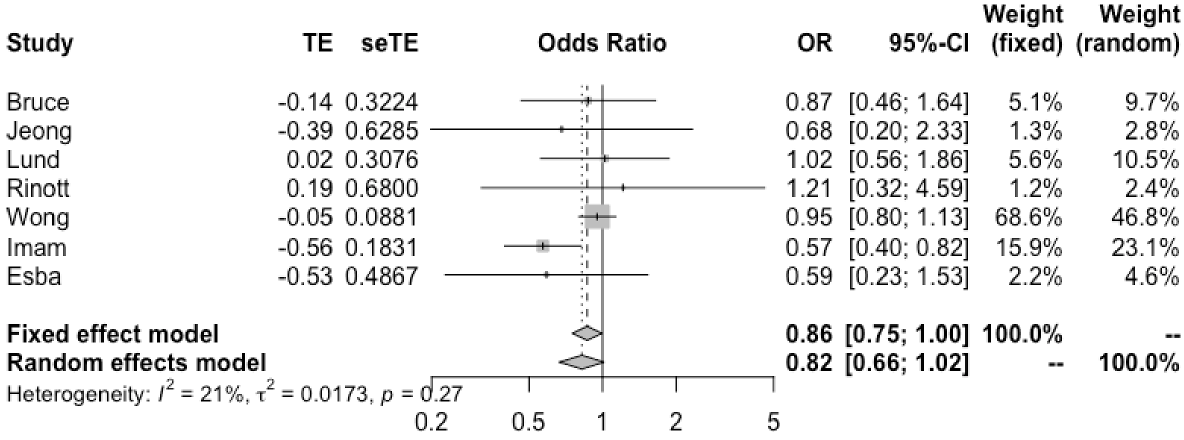
NSAIDs

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



Study	TE	seTE	OR	95%-CI	Weight (fixed)	Weight (random)
Bruce	-0.14	0.3224	0.87	[0.46; 1.64]	5.1%	9.7%
Jeong	-0.39	0.6285	0.68	[0.20; 2.33]	1.3%	2.8%
Lund	0.02	0.3076	1.02	[0.56; 1.86]	5.6%	10.5%
Rinott	0.19	0.6800	1.21	[0.32; 4.59]	1.2%	2.4%
Wong	-0.05	0.0881	0.95	[0.80; 1.13]	68.6%	46.8%
Imam	-0.56	0.1831	0.57	[0.40; 0.82]	15.9%	23.1%
Esba	-0.53	0.4867	0.59	[0.23; 1.53]	2.2%	4.6%
Fixed effect model			**0.86**	**[0.75; 1.00]**	**100.0%**	**--**
Random effects model			**0.82**	**[0.66; 1.02]**	**--**	**100.0%**

Heterogeneity: $I^2 = 21\%$, $\tau^2 = 0.0173$, $p = 0.27$

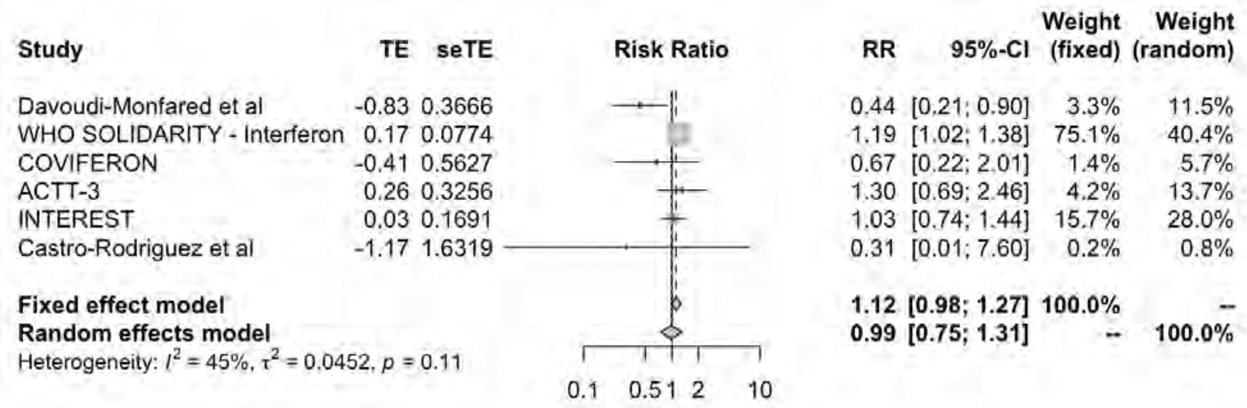
Interferon Beta-1a

See Summary of findings Table 9, Appendix 1

We identified seven RCTs including 7,017 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 2,144 patients assigned to intervention and 2,147 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 0.99 (95%CI 0.75 to 1.31); RD -0.2% (95%CI -4% to 5%); Moderate certainty ⊕⊕⊕○ (Figure 18)
- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 1.01 (95%CI 0.87 to 1.18); RD 0.2% (95%CI -2.2% to 3.1%); 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



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
Davoudi-Monfared et al	-0.83	0.3666	0.44	[0.21; 0.90]	3.3%	11.5%
WHO SOLIDARITY - Interferon	0.17	0.0774	1.19	[1.02; 1.38]	75.1%	40.4%
COVIFERON	-0.41	0.5627	0.67	[0.22; 2.01]	1.4%	5.7%
ACTT-3	0.26	0.3256	1.30	[0.69; 2.46]	4.2%	13.7%
INTEREST	0.03	0.1691	1.03	[0.74; 1.44]	15.7%	28.0%
Castro-Rodriguez et al	-1.17	1.6319	0.31	[0.01; 7.60]	0.2%	0.8%
Fixed effect model			**1.12**	**[0.98; 1.27]**	**100.0%**	**--**
Random effects model			**0.99**	**[0.75; 1.31]**	**--**	**100.0%**

Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0452$, $p = 0.11$

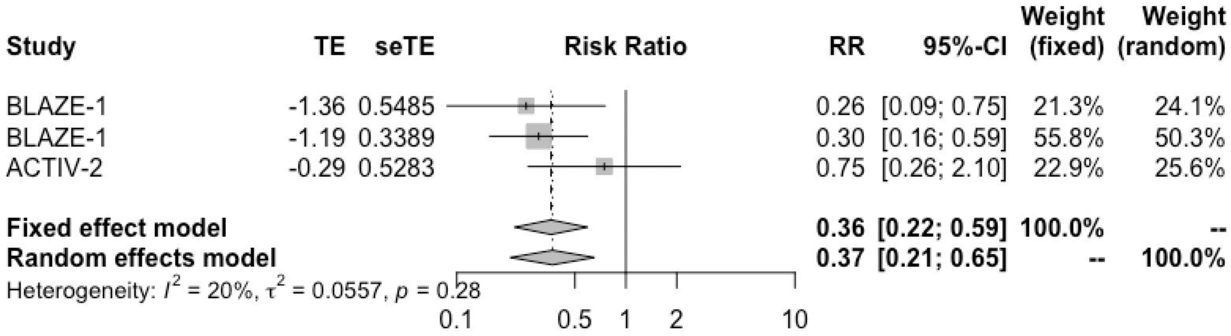
Bamlanivimab +/- etesevimab (monoclonal antibody)

See Summary of findings Table 10, Appendix 1

We identified nine RCTs including 5,939 patients in which bamlanivimab was compared against standard of care or other treatments. Eight 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 not 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.

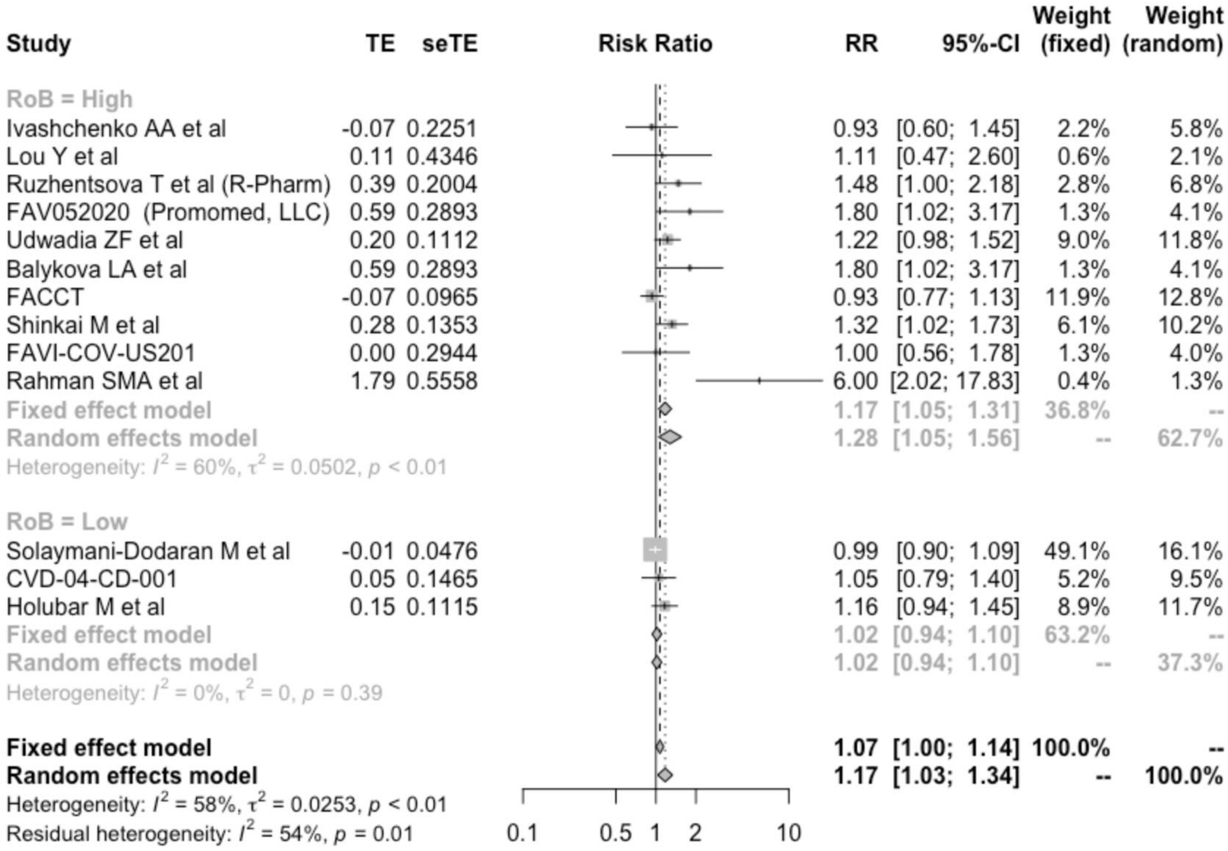
Favipiravir

See Summary of findings Table 11, Appendix 1

We identified 27 RCTs including 4,344 patients in which favipiravir was compared against standard of care or other treatments. Fifteen studies reported on favipiravir with or without HCQ versus standard of care, two studies reported on favipiravir vs HCQ or CQ, two 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 1.09 (95%CI 0.78 to 1.52); RD 1.4% (95%CI -3.6% to 8.3); 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 0.87 (95%CI 0.48 to 1.58); RD -1.3% (95%CI -5.3% to 5.9%); Very low certainty ⊕○○○
- Favipiravir may not reduce hospitalizations in patients with non-severe disease; RR 1.33 (95%CI 0.64 to 1.78); RD 1.6% (95%CI -1.7% to 3.7; 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

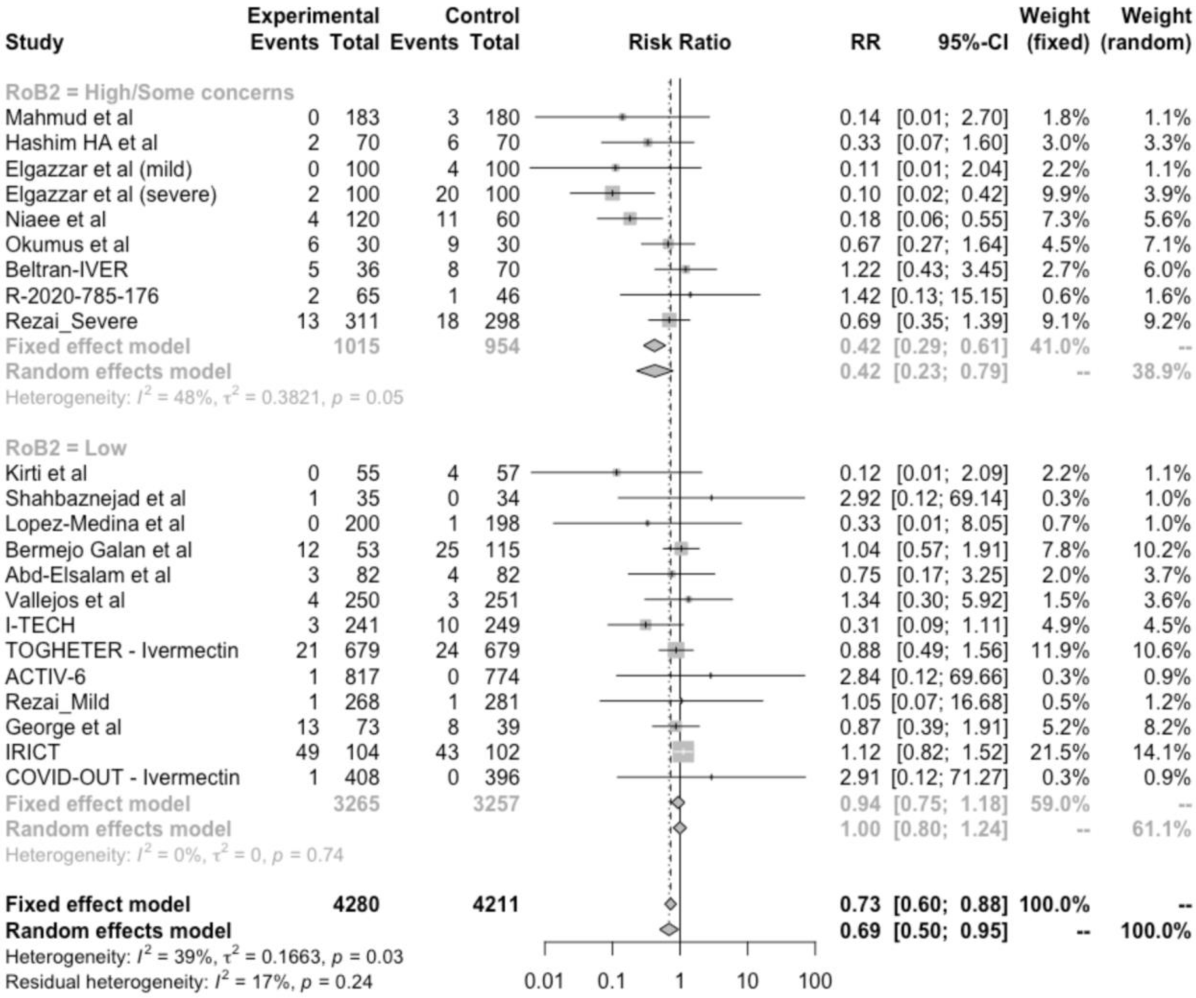
See Summary of findings Table 12, Appendix 1

We identified 49 RCTs including 13,326 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 42%. Most studies did not report on clinical important outcomes and most of the ones that did have important methodological limitations including inappropriate randomization process and lack or unclear report of allocation concealment. Our results showed:

- Ivermectin probably does not reduce mortality, RR 1 (95%CI 0.8 to 1.24); RD -0% (95%CI -3.2% to 3.8%); Moderate certainty ⊕⊕⊕○ (Figure 21) (based on low risk of bias studies)
- It is uncertain if ivermectin affects mechanical ventilation, RR 0.82 (95%CI 0.58 to 1.17); RD -3.1% (95%CI -7.3% to 2.9%); Very low certainty ⊕○○○ (based on low risk of bias studies)

- Ivermectin probably does not improve symptom resolution or improvement, RR 1.04 (95%CI 0.98 to 1.1); RD 2.4% (95%CI -1.2% to 6%); Moderate certainty ⊕⊕⊕◯ (Figure 22) (based on low risk of bias studies).
- It is uncertain if ivermectin affects symptomatic infection, RR 1.01 (95%CI 0.54 to 1.89); RD 0.2% (95%CI -8% to 15.5%); Very low certainty ⊕◯◯◯ (based on low risk of bias studies)
- Ivermectin may not increase severe adverse events, RR 1.05 (95%CI 0.69 to 1.62); RD 0.5% (95%CI -3.2% to 6.3%); Low certainty ⊕⊕◯◯
- Ivermectin probably does not have an important effect on hospitalizations in patients with recent onset non-severe disease, RR 0.90 (95%CI 0.74 to 1.1); RD -0.5% (95%CI -1.2% to 0.5%); Moderate certainty ⊕⊕⊕◯ (based on low risk of bias studies). The observed effect would probably be considered important in patients with very high hospitalization risk (>10%).

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

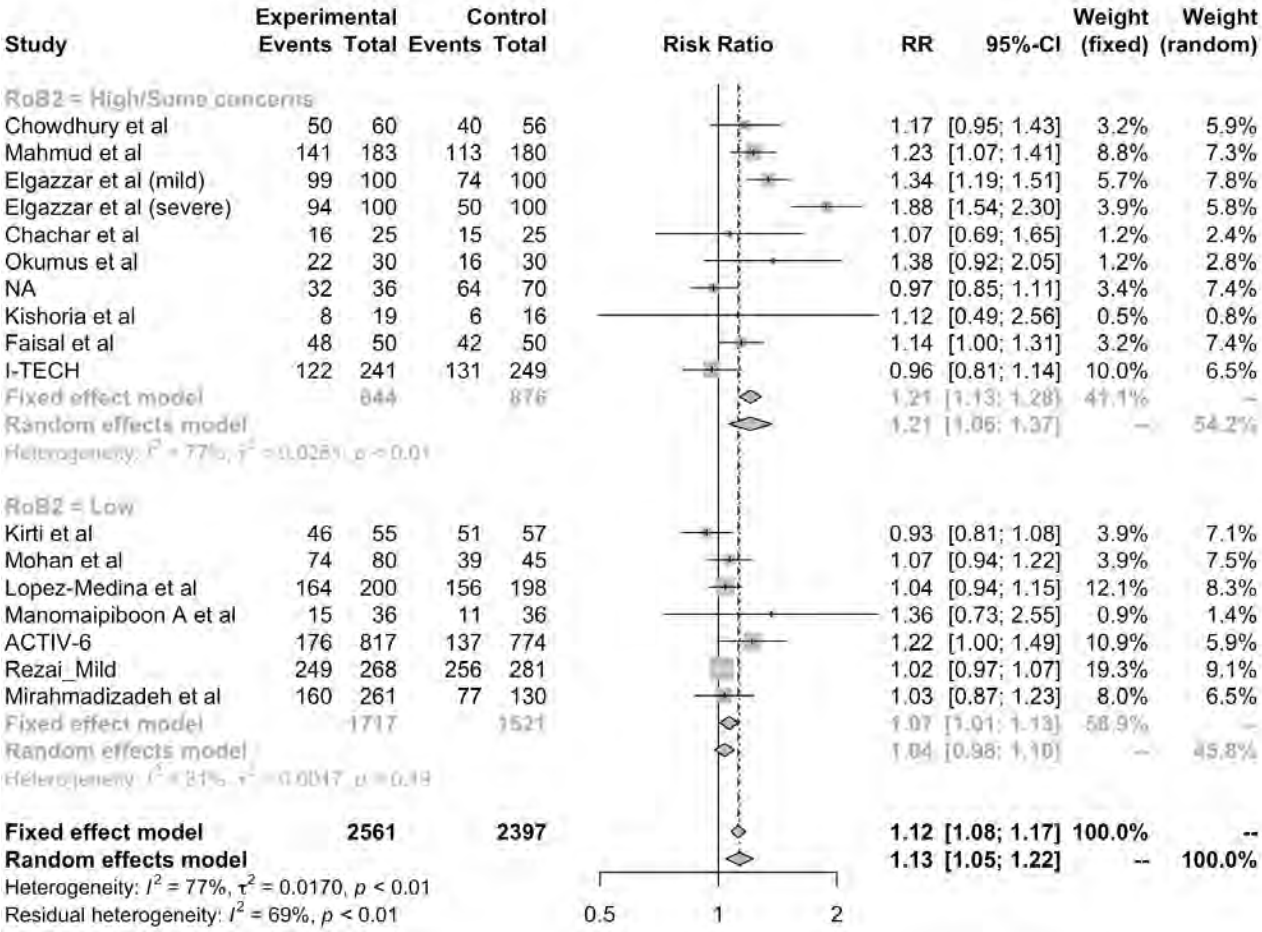


Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%-CI	Weight (fixed)	Weight (random)
RoB2 = High/Some concerns								
Mahmud et al	0	183	3	180	0.14	[0.01; 2.70]	1.8%	1.1%
Hashim HA et al	2	70	6	70	0.33	[0.07; 1.60]	3.0%	3.3%
Elgazzar et al (mild)	0	100	4	100	0.11	[0.01; 2.04]	2.2%	1.1%
Elgazzar et al (severe)	2	100	20	100	0.10	[0.02; 0.42]	9.9%	3.9%
Niaee et al	4	120	11	60	0.18	[0.06; 0.55]	7.3%	5.6%
Okumus et al	6	30	9	30	0.67	[0.27; 1.64]	4.5%	7.1%
Beltran-IVER	5	36	8	70	1.22	[0.43; 3.45]	2.7%	6.0%
R-2020-785-176	2	65	1	46	1.42	[0.13; 15.15]	0.6%	1.6%
Rezai_Severe	13	311	18	298	0.69	[0.35; 1.39]	9.1%	9.2%
Fixed effect model		1015		954	0.42	[0.29; 0.61]	41.0%	--
Random effects model					0.42	[0.23; 0.79]	--	38.9%
Heterogeneity: $I^2 = 48\%$, $\tau^2 = 0.3821$, $p = 0.05$								
RoB2 = Low								
Kirti et al	0	55	4	57	0.12	[0.01; 2.09]	2.2%	1.1%
Shahbaznejad et al	1	35	0	34	2.92	[0.12; 69.14]	0.3%	1.0%
Lopez-Medina et al	0	200	1	198	0.33	[0.01; 8.05]	0.7%	1.0%
Bermejo Galan et al	12	53	25	115	1.04	[0.57; 1.91]	7.8%	10.2%
Abd-Elsalam et al	3	82	4	82	0.75	[0.17; 3.25]	2.0%	3.7%
Vallejos et al	4	250	3	251	1.34	[0.30; 5.92]	1.5%	3.6%
I-TECH	3	241	10	249	0.31	[0.09; 1.11]	4.9%	4.5%
TOGHETER - Ivermectin	21	679	24	679	0.88	[0.49; 1.56]	11.9%	10.6%
ACTIV-6	1	817	0	774	2.84	[0.12; 69.66]	0.3%	0.9%
Rezai_Mild	1	268	1	281	1.05	[0.07; 16.68]	0.5%	1.2%
George et al	13	73	8	39	0.87	[0.39; 1.91]	5.2%	8.2%
IRICT	49	104	43	102	1.12	[0.82; 1.52]	21.5%	14.1%
COVID-OUT - Ivermectin	1	408	0	396	2.91	[0.12; 71.27]	0.3%	0.9%
Fixed effect model		3265		3257	0.94	[0.75; 1.18]	59.0%	--
Random effects model					1.00	[0.80; 1.24]	--	61.1%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.74$								
Fixed effect model		**4280**		**4211**	**0.73**	**[0.60; 0.88]**	**100.0%**	**--**
Random effects model					**0.69**	**[0.50; 0.95]**	**--**	**100.0%**

Heterogeneity: $I^2 = 39\%$, $\tau^2 = 0.1663$, $p = 0.03$

Residual heterogeneity: $I^2 = 17\%$, $p = 0.24$

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.

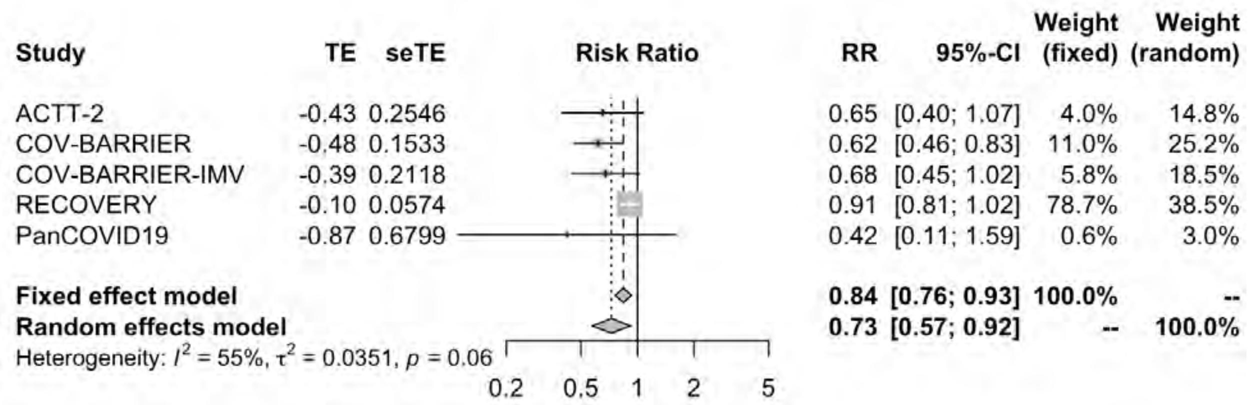
Baricitinib

See Summary of findings Table 13, Appendix 1

We identified seven RCTs including 12,363 patients in which baricitinib was compared against standard of care or other treatments. All studies included moderate to severe hospitalized patients. Critical patients were excluded. Our results showed:

- Baricitinib reduces mortality, RR 0.73 (95%CI 0.57 to 0.92); RD -4.3% (95%CI -6.9% to -1.3%); High certainty ⊕⊕⊕⊕ (Figure 23)
- Baricitinib probably reduces mechanical ventilation, RR 0.83 (95%CI 0.66 to 1.04); RD -2.9% (95%CI -5.9% to 0.7%); Moderate certainty ⊕⊕⊕○
- Baricitinib probably improves time to symptom resolution, RR 1.27 (95%CI 1.13 to 1.42); RD 16.4% (95%CI 7.9% to 25.5%); Moderate certainty ⊕⊕⊕○
- Baricitinib probably does not increase severe adverse events, RR 0.78 (95%CI 0.64 to 0.95); RD -2.2% (95%CI -3.7% to -0.5%); Moderate certainty ⊕⊕⊕○

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



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
ACTT-2	-0.43	0.2546	0.65	[0.40; 1.07]	4.0%	14.8%
COV-BARRIER	-0.48	0.1533	0.62	[0.46; 0.83]	11.0%	25.2%
COV-BARRIER-IMV	-0.39	0.2118	0.68	[0.45; 1.02]	5.8%	18.5%
RECOVERY	-0.10	0.0574	0.91	[0.81; 1.02]	78.7%	38.5%
PanCOVID19	-0.87	0.6799	0.42	[0.11; 1.59]	0.6%	3.0%
Fixed effect model			**0.84**	**[0.76; 0.93]**	**100.0%**	**--**
Random effects model			**0.73**	**[0.57; 0.92]**	**--**	**100.0%**

Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.0351$, $p = 0.06$

In addition one study that compared baricitinib versus tocilizumab reported no significant differences in mortality or mechanical ventilation. However, the certainty of the evidence was low because of imprecision.

Azithromycin

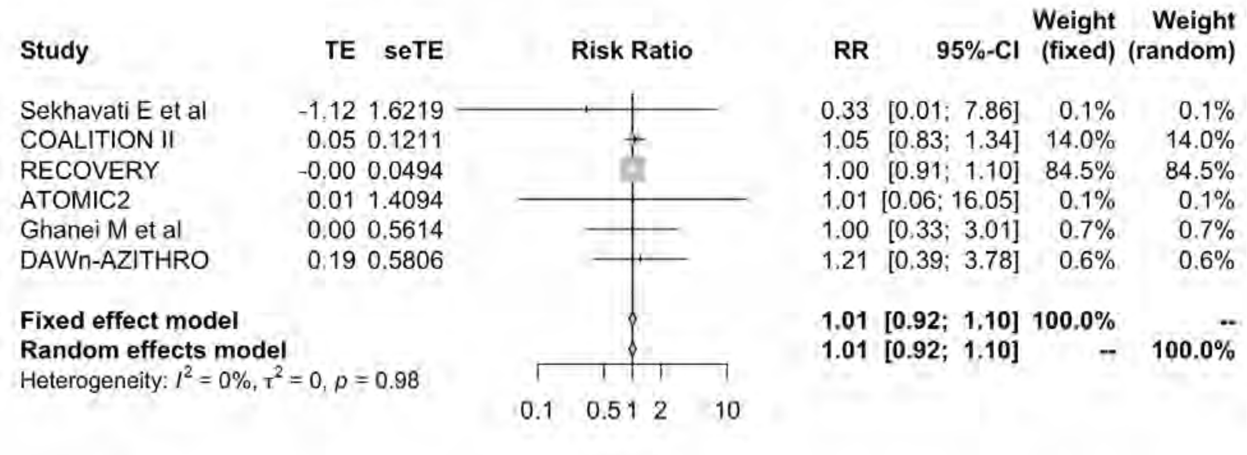
See Summary of findings Table 14, Appendix 1

We identified 11 RCTs including 10,612 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 0.92 (95%CI 0.77 to 1.1); RD -1.4% (95%CI -4% to 1.7%); 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



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
Sekhavati E et al	-1.12	1.6219	0.33	[0.01; 7.86]	0.1%	0.1%
COALITION II	0.05	0.1211	1.05	[0.83; 1.34]	14.0%	14.0%
RECOVERY	-0.00	0.0494	1.00	[0.91; 1.10]	84.5%	84.5%
ATOMIC2	0.01	1.4094	1.01	[0.06; 16.05]	0.1%	0.1%
Ghanei M et al	0.00	0.5614	1.00	[0.33; 3.01]	0.7%	0.7%
DAWn-AZITHRO	0.19	0.5806	1.21	[0.39; 3.78]	0.6%	0.6%
Fixed effect model			**1.01**	**[0.92; 1.10]**	**100.0%**	**--**
Random effects model			**1.01**	**[0.92; 1.10]**	**--**	**100.0%**

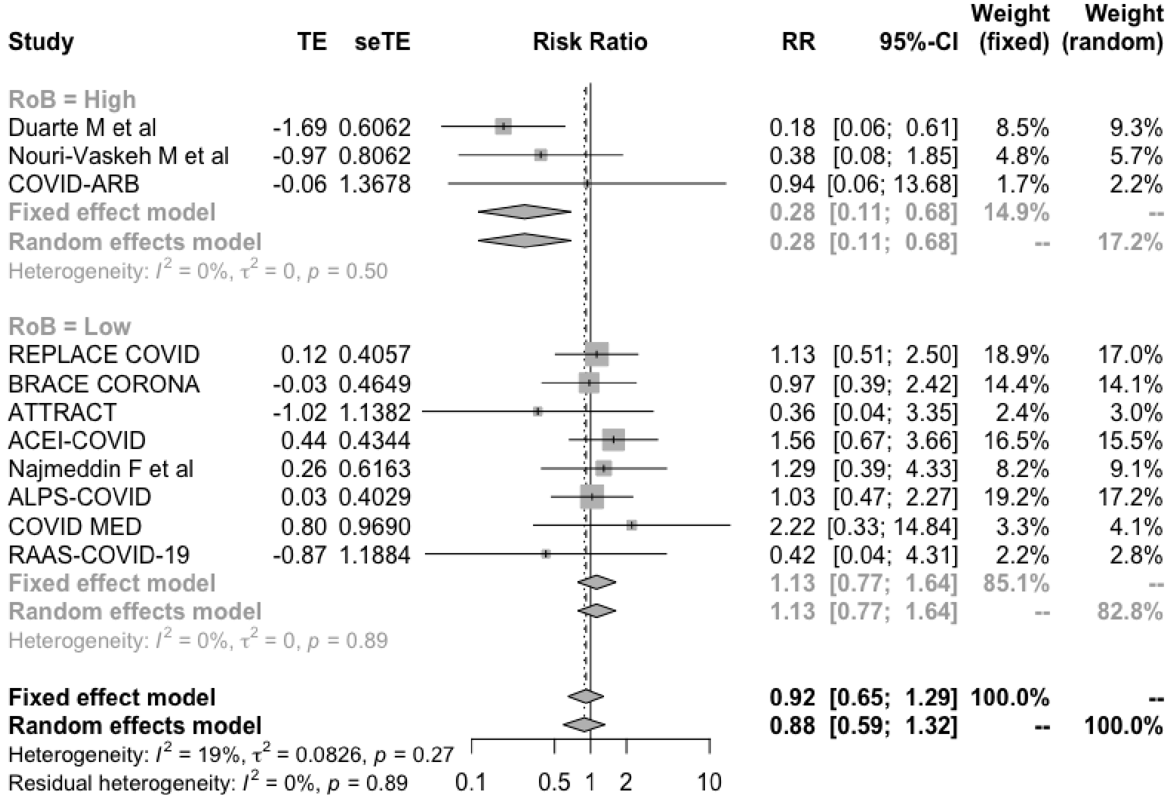
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$

ACEI/ARB initiation or continuation

We identified 12 RCTs including 1,812 patients in which patients with COVID-19 were randomized to initiate or continue ACEI/ARB treatment and compared to standard of care or discontinue ACEI/ARB. Our results showed:

- ACEI/ARB initiation or continuation may increase mortality, RR 1.13 (95%CI 0.77 to 1.64); RD 2.1% (95%CI -3.7% to 10.2%); 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 15 RCTs including 18,605 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 0.92 to 1.05); RD -0.2% (95%CI -1.3% to 0.8%); Moderate certainty ⊕⊕⊕○ (Figure 26)
- Colchicine probably does not reduce mechanical ventilation requirements, RR 0.98 (95%CI 0.89 to 1.07); RD -0.3% (95%CI -1.9% to 1.2%); Moderate certainty ⊕⊕⊕○ (Figure 27)
- Colchicine does not increase symptom resolution or improvement, RR 1 (95%CI 0.98 to 1.02); RD 0% (95%CI -1.2% to 1.2%); High certainty ⊕⊕⊕⊕

- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕
- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕○○○
- Colchicine 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

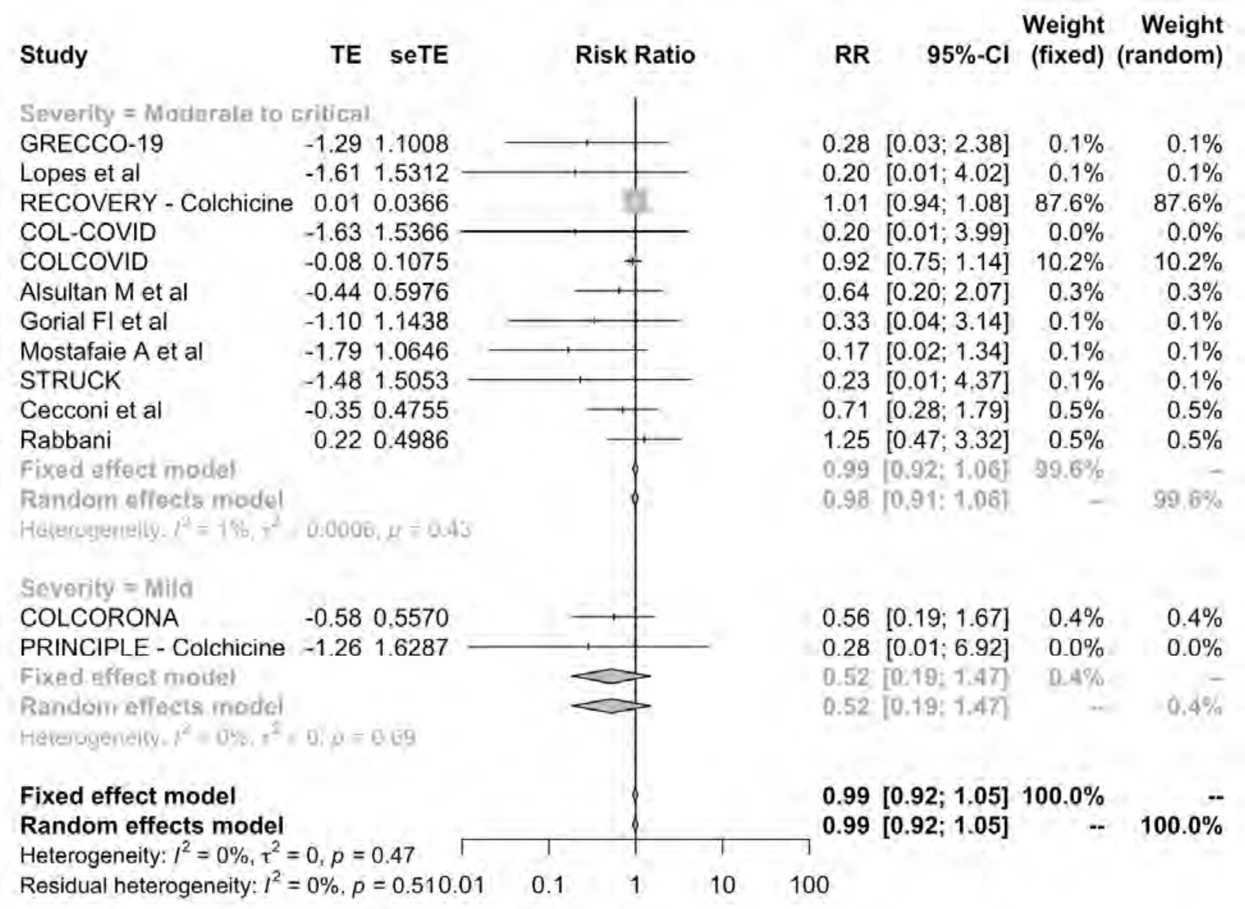
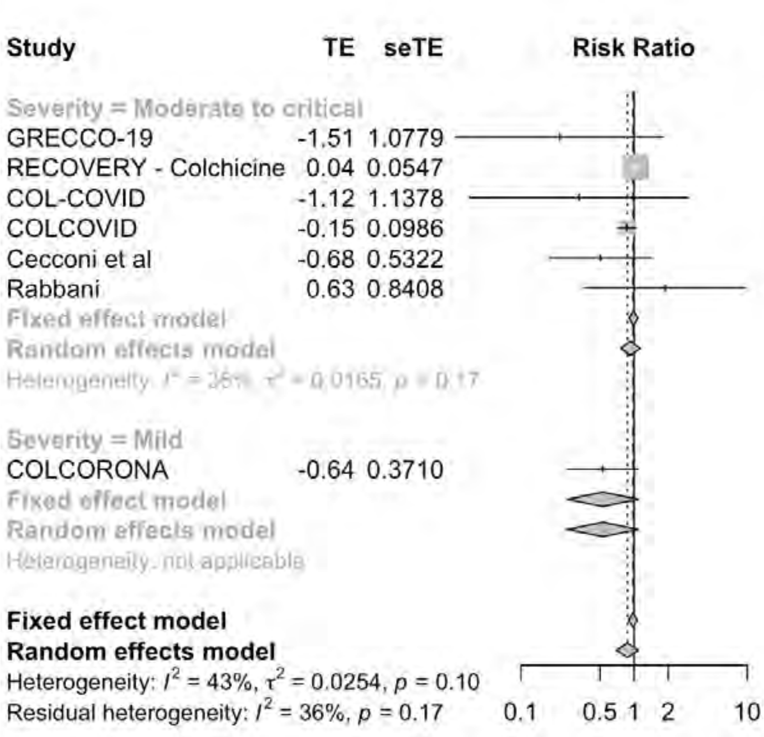


Figure 27. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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.

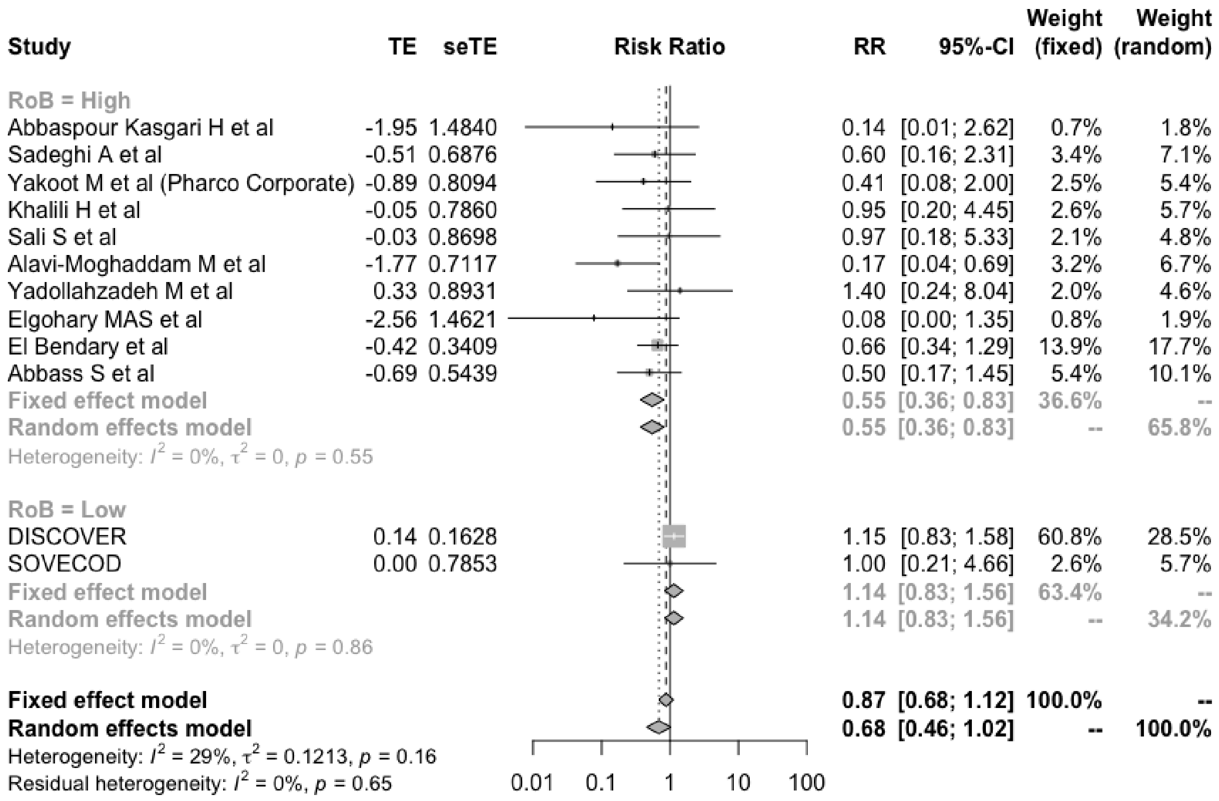
Sofosbuvir +/- daclatasvir, ledipasvir, or velpatasvir

See Summary of findings Table 16, Appendix 1

We identified 16 RCTs including 3,061 patients in which sofosbuvir alone or in combination with daclatasvir or ledipasvir was compared against standard of care or other treatments. Two studies compared sofosbuvir alone vs. standard of care, one study compared sofosbuvir alone vs. lopinavir-ritonavir, seven studies compared sofosbuvir + daclatasvir vs. standard of care, three studies compared sofosbuvir + daclatasvir vs. lopinavir-ritonavir, and three 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 increase 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%); 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)
- It is uncertain if sofosbuvir +/- daclatasvir or ledipasvir affects symptomatic infections in exposed individuals, RR 0.52 (95%CI 0.30 to 0.89); RD -8.3% (95%CI -12.1% to -1.9%); Very low certainty ⊕◯◯◯
- It is uncertain if sofosbuvir +/- daclatasvir or ledipasvir increases severe adverse events, RR 0.35 (95%CI 0.06 to 2.19); RD -6.6% (95%CI -9.6% to 12.1%); Very low certainty ⊕◯◯◯

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



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
RoB = High						
Abbaspour Kasgari H et al	-1.95	1.4840	0.14	[0.01; 2.62]	0.7%	1.8%
Sadeghi A et al	-0.51	0.6876	0.60	[0.16; 2.31]	3.4%	7.1%
Yakoot M et al (Pharco Corporate)	-0.89	0.8094	0.41	[0.08; 2.00]	2.5%	5.4%
Khalili H et al	-0.05	0.7860	0.95	[0.20; 4.45]	2.6%	5.7%
Sali S et al	-0.03	0.8698	0.97	[0.18; 5.33]	2.1%	4.8%
Alavi-Moghaddam M et al	-1.77	0.7117	0.17	[0.04; 0.69]	3.2%	6.7%
Yadollahzadeh M et al	0.33	0.8931	1.40	[0.24; 8.04]	2.0%	4.6%
Elgohary MAS et al	-2.56	1.4621	0.08	[0.00; 1.35]	0.8%	1.9%
El Bendary et al	-0.42	0.3409	0.66	[0.34; 1.29]	13.9%	17.7%
Abbass S et al	-0.69	0.5439	0.50	[0.17; 1.45]	5.4%	10.1%
Fixed effect model			0.55	[0.36; 0.83]	36.6%	--
Random effects model			0.55	[0.36; 0.83]	--	65.8%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.55$						
RoB = Low						
DISCOVER	0.14	0.1628	1.15	[0.83; 1.58]	60.8%	28.5%
SOVECOD	0.00	0.7853	1.00	[0.21; 4.66]	2.6%	5.7%
Fixed effect model			1.14	[0.83; 1.56]	63.4%	--
Random effects model			1.14	[0.83; 1.56]	--	34.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$						
Fixed effect model			**0.87**	**[0.68; 1.12]**	**100.0%**	**--**
Random effects model			**0.68**	**[0.46; 1.02]**	**--**	**100.0%**

Heterogeneity: $I^2 = 29\%$, $\tau^2 = 0.1213$, $p = 0.16$
Residual heterogeneity: $I^2 = 0\%$, $p = 0.65$

REGEN-COV (casirivimab and imdevimab)

See Summary of findings Table 17, Appendix 1

We identified 12 RCTs including 25,207 patients in which REGEN-COV (casirivimab and imdevimab) was compared against standard of care, or other treatments, in patients with recent onset COVID-19. The 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 0.63 to 1.09); RD -2.7% (95%CI -5.9% to 1.4%); 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 0.24 (95%CI 0.08 to 0.76); RD -13.2% (95%CI -16% to -4.2%); High certainty ⊕⊕⊕⊕
- REGEN-COV probably does not increase severe adverse events, RR 0.51 (95%CI 0.38 to 0.67); RD -5% (95%CI -6.3% to -3.4%); Moderate certainty ⊕⊕⊕○
- REGEN-COV probably reduces hospitalization, RR 0.28 (95%CI 0.19 to 0.42); RD -3.5% (95%CI -3.9% to -2.8%); Moderate certainty ⊕⊕⊕○ (Figure 30)

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

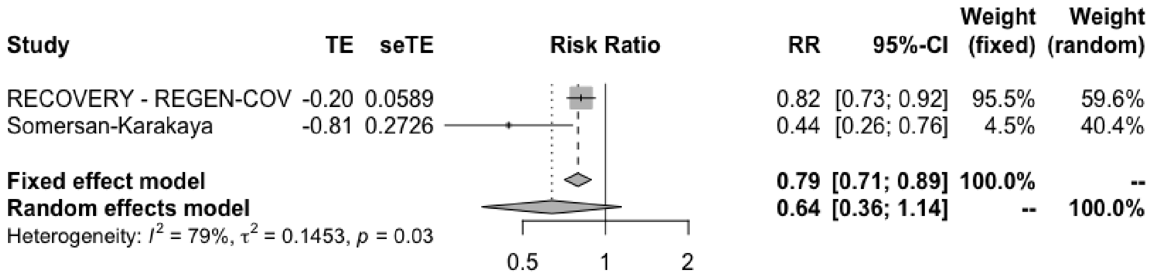
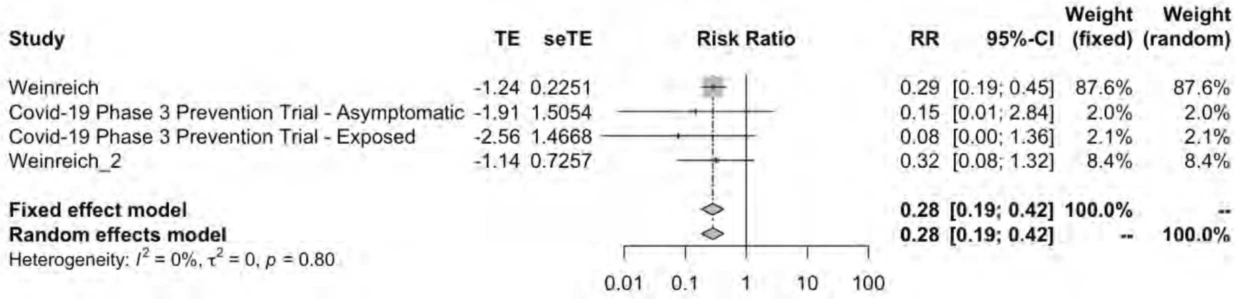


Figure 30. Hospitalization in randomized studies comparing REGEN-COV vs standard of care in patients with COVID-19



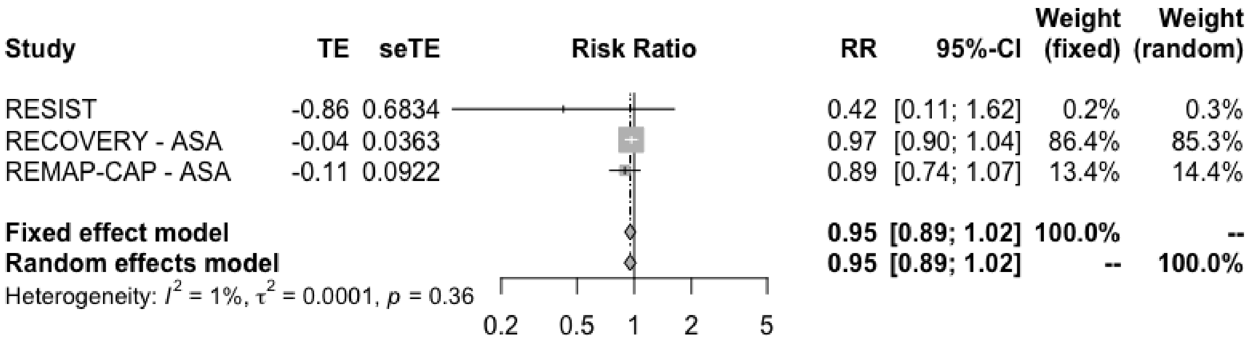
In addition, two studies that compared REGEN-COV (casirivimab and imdevimab) against bamlanivimab +/- etesevimab and sotrovimab in non-severe patients with risk factors for severity reported no important differences in hospitalizations.

Aspirin

We identified four RCTs including 16,696 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 0.95 (95%CI 0.89 to 1.02); RD -0.8% (95%CI -1.8% to 0.3; Moderate certainty ⊕⊕⊕○ (Figure 31)
- Aspirin probably does not reduce mechanical ventilation, RR 0.94 (95%CI 0.84 to 1.05); RD -1% (95%CI -2.8% 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

See Summary of findings Table 18, Appendix 1

We identified three RCTs including 4,934 patients with recent onset mild COVID-19 and risk factors for severe disease, in which sotrovimab was compared against standard of care or other interventions. Our results showed:

- Sotrovimab probably reduces hospitalizations, RR 0.20 (95%CI 0.08 to 0.48); RD -3.8% (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 0.34 (95%CI 0.16 to 0.68); RD -6.7% (95%CI -8.6% to -3.3%); Moderate certainty ⊕⊕⊕○

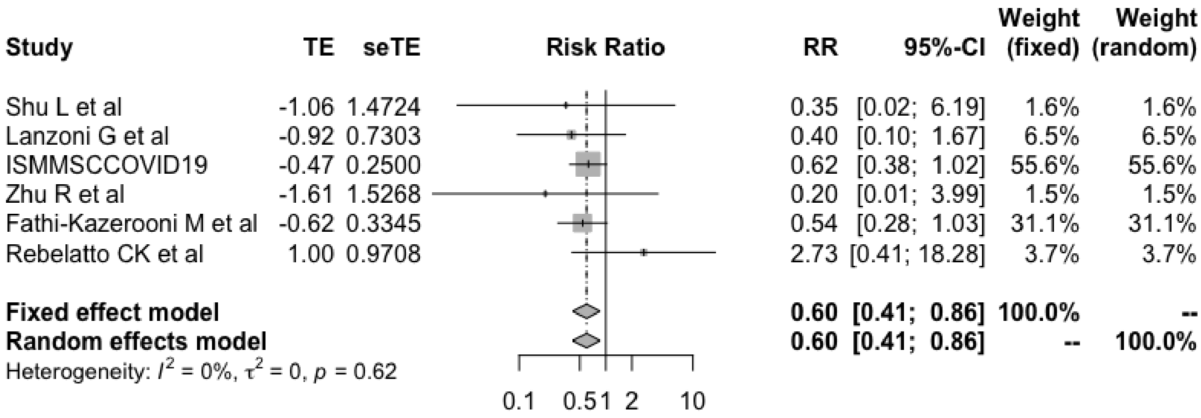
One study that compared REGEN-COV and sotrovimab in mild to moderate patients showed similar hospitalization rates (RR 0.93 95%CI, 0.77 to 1.13)

Mesenchymal stem-cell transplantation

We identified eight RCTs including 315 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 0.6 (95%CI 0.41 to 0.86); RD -6.4% (95%CI -9.4% to -2.2%); Low certainty ⊕⊕○○ (Figure 32)

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



Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
Shu L et al	-1.06	1.4724	0.35	[0.02; 6.19]	1.6%	1.6%
Lanzoni G et al	-0.92	0.7303	0.40	[0.10; 1.67]	6.5%	6.5%
ISMMSCCOVID19	-0.47	0.2500	0.62	[0.38; 1.02]	55.6%	55.6%
Zhu R et al	-1.61	1.5268	0.20	[0.01; 3.99]	1.5%	1.5%
Fathi-Kazerooni M et al	-0.62	0.3345	0.54	[0.28; 1.03]	31.1%	31.1%
Rebelatto CK et al	1.00	0.9708	2.73	[0.41; 18.28]	3.7%	3.7%
Fixed effect model			**0.60**	**[0.41; 0.86]**	**100.0%**	**--**
Random effects model			**0.60**	**[0.41; 0.86]**	**--**	**100.0%**

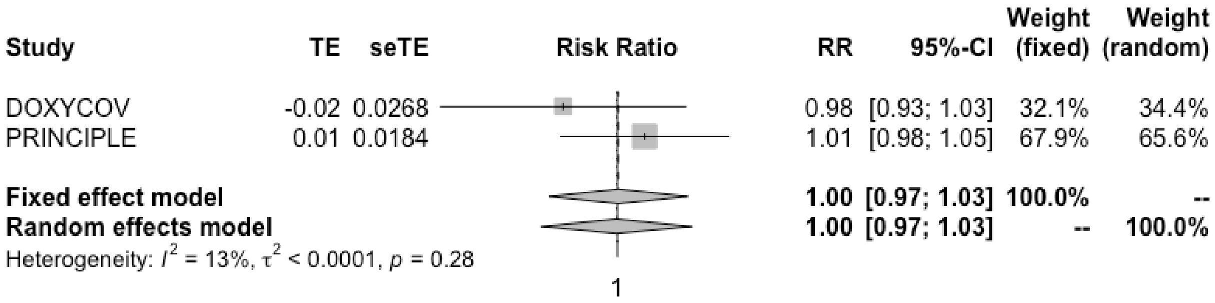
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.62$

Doxycycline

We identified four RCTs including 2,415 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 1.16 (95%CI 0.76 to 1.76); RD 0.7% (95%CI -1.1% 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



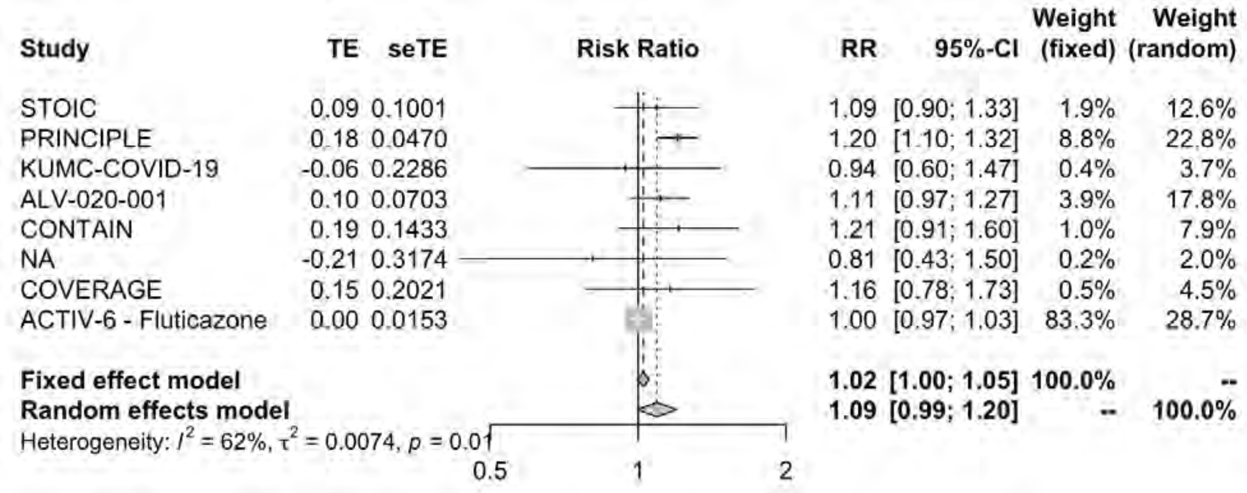
Inhaled corticosteroids

See Summary of findings Table 19, Appendix 1

We identified nine RCTs including 4,309 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 0.82 (95%CI 0.44 to 1.53); RD -2.8% (95%CI -9% to 8.5%); 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 1.09 (95%CI 0.99 to 1.2); RD 5.5% (95%CI -0.6% to 12.1%); Low certainty ⊕⊕○○ (Figure 34)
- Inhaled corticosteroids probably does not have an important effect on hospitalizations, RR 0.9 (95%CI 0.7 to 1.15); RD -0.5% (95%CI -1.4% to 0.7%); Moderate certainty ⊕⊕⊕○
- It is uncertain if inhaled corticosteroids reduce or increase severe adverse events, RR 0.5 (95%CI 0.23 to 1.12); RD -5.1% (95%CI -7.9% 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



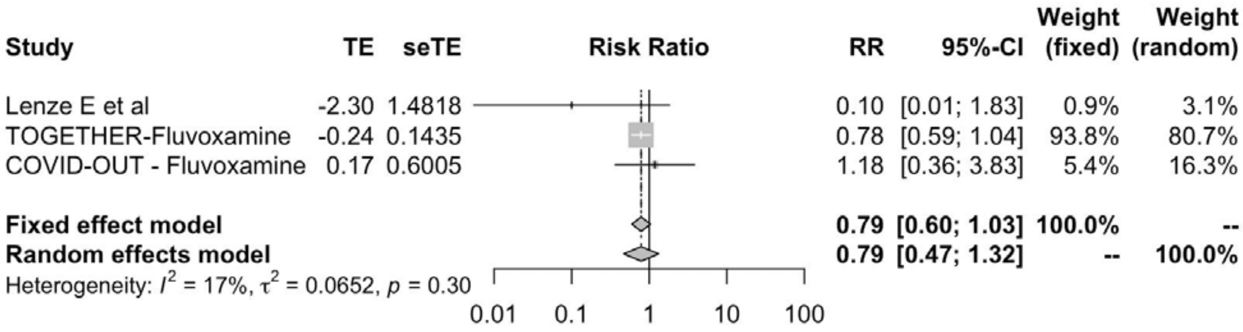
Fluvoxamine

[***See Summary of findings Table 20, Appendix 1***]

We identified four RCTs including 2,356 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 0.79 (95%CI 0.6 to 1.03); RD -1% (95%CI -1.9% 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



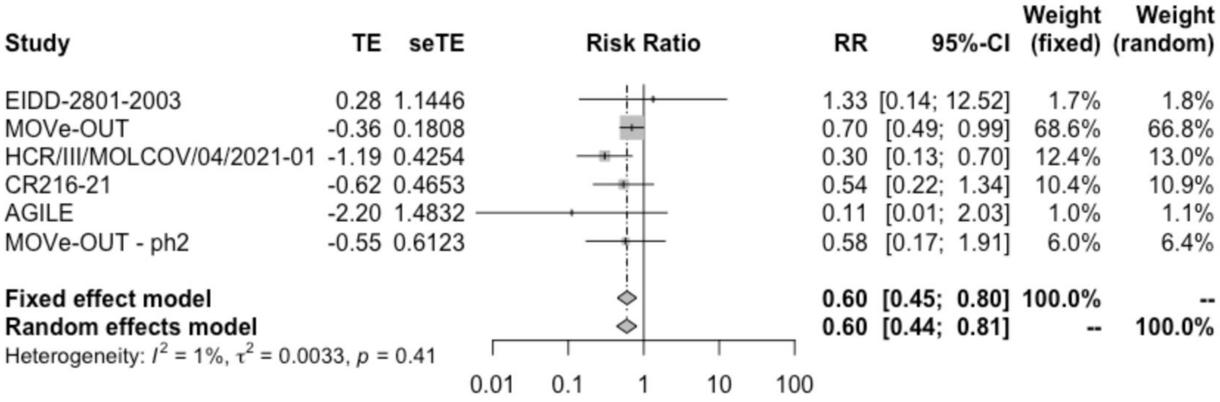
Molnupiravir

See Summary of findings Table 21, Appendix 1

We identified ten RCTs including 4,532 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 0.35 (95%CI 0.06 to 2.19); RD -1.4% (95%CI -15% to 19.4%); Very low certainty ⊕○○○
- It is uncertain if molnupiravir reduces or mechanical ventilation, RR 0.36 (95%CI 0.11 to 1.12); RD -11.1% (95%CI -15.4% to 2.1%); Very low certainty ⊕○○○
- Molnupiravir reduces hospitalizations in patients with recent onset disease, RR 0.6 (95%CI 0.44 to 0.81); RD -1.9% (95%CI -2.7% to -0.9%); High certainty ⊕⊕⊕⊕ (Figure 36)
- Molnupiravir may increase symptom resolution, RR 1.17 (95%CI 1.1 to 1.3); RD 10.3% (95%CI 3.6% to -18.2%); Low certainty ⊕⊕○○
- Molnupiravir may not increase severe adverse events, RR 0.75 (95%CI 0.48 to 1.19); RD -2.6% (95%CI -5.3% to -1.9%); 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 22, Appendix 1

We identified one RCT including 2,085 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 ⊕⊕⊕○

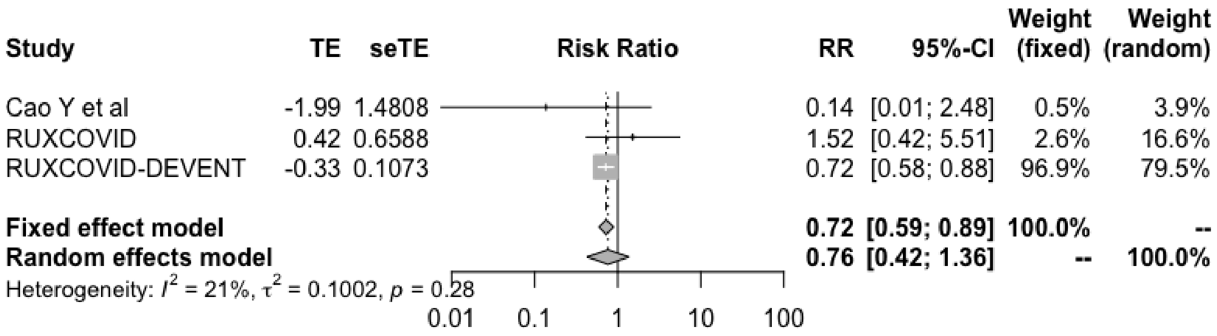
Ruxolitinib

See Summary of findings Table 23, Appendix 1

We identified three RCTs including 686 patients with COVID-19, in which ruxolitinib was compared against standard of care. RUXOCOVID-DEVENT was the biggest trial including 211 patients with critical COVID-19. Our results showed:

- Ruxolitinb may reduce mortality, RR 0.72 (95%CI 0.59 to 0.89); RD -4.5% (95%CI -6.5% to -1.7%); Low certainty ⊕⊕○○ (Figure 37)
- It is uncertain if ruxolitinib increases or decreses mechanical ventilation, RR 0.99 (95%CI 0.49 to 1.99); RD -0.1% (95%CI -8.8% to 17.%); Very low certainty ⊕○○○
- Ruxolitinib may not improve time to symptom resolution, RR 1.05 (95%CI 0.89 to 1.24); RD 3% (95%CI -6.7% to 14.5%); Low certainty ⊕⊕○○
- It is uncertain if ruxolitinib increses or decreases severe adverse events, RR 1.12 (95%CI 0.69 to 1.82); RD 1.2% (95%CI -3.7% to 8.4%); Very low certainty ⊕○○○

Figure 37. Mortality in randomized studies comparing ruxolitinib vs standard of care in patients with COVID-19



CD24Fc

See Summary of findings Table 24, Appendix 1

We identified one RCT including 234 patients with COVID-19, in which CD24Fc was compared against standard of care. Our results showed:

- It is uncertain if CD24Fc reduces or increases mortality, RR 0.9 (95%CI 0.49 to 1.69); RD -1.5% (95%CI -8.2% to 11%); Very low certainty ⊕○○○
- CD24Fc may decrease mechanical ventilation, RR 0.57 (95%CI 0.34 to 0.96); RD -7.4% (95%CI -11.4% to -0.7%); Low certainty ⊕⊕○○
- CD24Fc may increase symptom resolution, RR 1.18 (95%CI 1 to 1.39); RD 10.7% (95%CI -0.2% to 23.4%); Low certainty ⊕⊕○○
- It is uncertain if CD24Fc increases or decreases severe adverse events, RR 0.98 (95%CI 0.61 to 1.57); RD -0.2% (95%CI -4% to 5.8%); Very low certainty ⊕○○○

Vitamin D

See Summary of findings Table 25, Appendix 1

We identified 18 RCTs including 8,593 patients with COVID-19, in which Vitamin D was compared against standard of care or other treatments. Our results showed:

- It is uncertain if vitamin D reduces or increases mortality, RR 1.24 (95%CI 0.8 to 1.91); RD 3.8% (95%CI -3.2% to 14.4%); Very low certainty ⊕○○○
- It is uncertain if vitamin D reduces or increases mechanical ventilation, RR 0.5 (95%CI 0.25 to 1); RD -8.6% (95%CI -13% to 0%); Very low certainty ⊕○○○
- It is uncertain if vitamin D reduces or increases symptom resolution or improvement, RR 1.78 (95%CI 1.1 to 2.94); RD 39.4.6% (95%CI 4.6% to 39.4%); Very low certainty ⊕○○○
- Vitamin D probably does not reduce symptomatic infections in exposed individuals, RR 1.25 (95%CI 0.93 to 1.67); RD 4.3% (95%CI -1.2% to 11.7%); Moderate certainty ⊕⊕⊕○ (excluding high risk of bias studies)

- Vitamin D may not reduce hospitalizations, RR 1.26 (95%CI 0.84 to 1.89); RD 1.2% (95%CI -0.8% to 4.3%); Low certainty ⊕⊕○○
- Vitamin D may not increase severe adverse events, RR 1.03 (95%CI 0.84 to 1.26); RD 0.3% (95%CI -1.6% to 2.7%); Low certainty ⊕⊕○○

In addition one study that compared high dose vitamin D supplementation (cholecalciferol 400,000 IU) versus standard dose (cholecalciferol 50,000 IU) reported no significant differences in mortality at 28 days (HR 0.7 95%CI 0.36 to 1.36) in patients hospitalized for COVID-19.

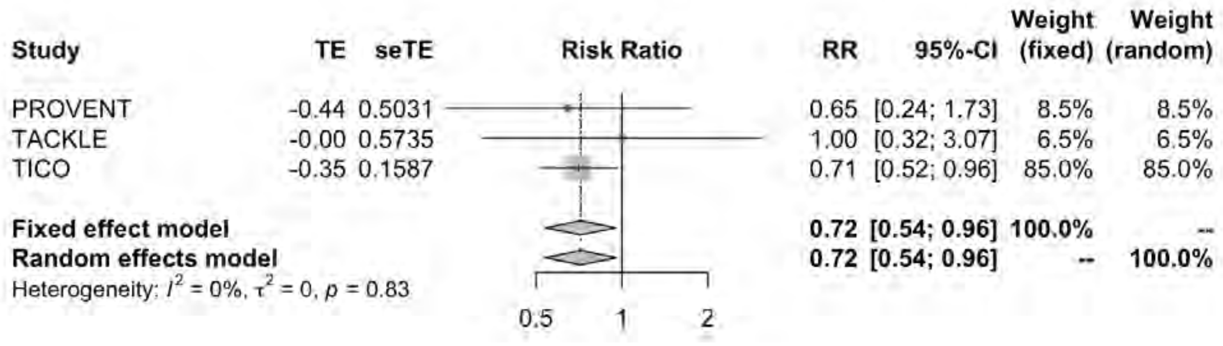
Tixagevimab–Cilgavimab

See Summary of findings Table 26, Appendix 1

We identified three RCT including 7,492 individuals with COVID-19 or exposed to SARS-COV-2, in which Tixagevimab–cilgavimab was compared against standard of care. Our results showed:

- Tixagevimab–cilgavimab probably reduces mortality, RR 0.72 (95%CI 0.54 to 0.96); RD -4.5% (95%CI -7.4% to -0.6%); Moderate certainty ⊕⊕⊕○
- Tixagevimab–cilgavimab probably does not increase symptom resolution or improvement, RR 1.03 (95%CI 0.99 to 1.08); RD 2% (95%CI -0.6% to 4.7%); Moderate certainty ⊕⊕⊕○
- Tixagevimab–cilgavimab probably reduces symptomatic infections in exposed individuals, RR 0.18 (95%CI 0.09 to 0.35); RD -14.2% (95%CI -15.8% to -11.2%); Moderate certainty ⊕⊕⊕○
- Tixagevimab–cilgavimab may not increase severe adverse events, RR 0.95 (95%CI 0.69 to 1.31); RD -0.5% (95%CI -3.2% to 3.2%); Low certainty ⊕⊕○○
- Tixagevimab–cilgavimab probably reduces mortality, RR 0.42 (95%CI 0.24 to 0.74); RD -2.8% (95%CI -3.6% to 1.3%); Moderate certainty ⊕⊕⊕○

Figure 37. Mortality in randomized studies comparing Tixagevimab–cilgavimab vs standard of care in patients with COVID-19



Full description of included studies

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

Table 5. Description of included studies and interventions effects

99mTc-MDP **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Yuan et al;[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

Alpha-1 antitrypsin

Uncertainty in potential benefits and harms. Further research 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					
McElvaney et al;[17] peer reviewed; 2021	Patients with critical COVID-19 infection. 25 assigned to alpha-1 antitrypsin 120 mg/kg once a week and 11 assigned to SOC	Mean age 58.4 ± , male 61.1%, hypertension 44.4%, diabetes 27.7%, COPD 30.5%, CHD 16.6%, CKD 27.7%, obesity 66.6%	Corticosteroids 72.2%, remdesivir 0%, hydroxychloroquine 0%, tocilizumab 0%,	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
Amiodarone **Uncertainty in potential benefits and harms. Further research 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					
ReCOVery-SIRIO trial;[18] Navarese et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 71 assigned to amiodarone 200 to 400 mg a day and 72 assigned to SOC	Median age 61.3 , male 62.3%, diabetes 23.7%, COPD 6.5%, cancer 7%,	Remdesivir 1.9%, hydroxychloroquine 2.3%, azithromycin 6%, convalescent plasma 1.9%	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 probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕⊕○○ **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;[19] 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;[20] 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

Anakinra may not reduce mortality or increase severe adverse events. However the cerrtainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CORIMUNO-ANA-1 trial;[21] 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:** RR 0.96 (95%CI 0.57 to 1.6); RD -0.6% (95%CI -6.9% to 9.6%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection**
SAVE-MORE trial;[22] 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;[23] Declercq et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 112 assigned to anakinra 100 mg 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.	**(prophylaxis studies):** No information **Adverse events:** RR 0.98 (95%CI 0.78 to 1.24); RD -0.2% (95%CI -2.2% to 2.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Kharazmi et al;[24] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 15 assigned to anakinra 100 mg 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.	
Zeyad et al;[25] preprint; 2022	Patients with severe to critical COVID-19 infection. 40 assigned to Anakinra 200 mg a day for 3 days and 40 assigned to SOC	Mean age 49.9 ± 11.7, male 82.5%, diabetes 43.8%, COPD 1.3%, CHD 8.8%, CKD 1.3%	Corticosteroids 100%, remdesivir 83.8%, azithromycin 78.8%, convalescent plasma 67.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
ANACONDA trial;[26] Audemard-Verger et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 36 assigned to anakinra 400 mg a day for 3 days followed by 200 mg a day for 7 days and 34 assigned to SOC	Mean age 70.6 , male 73.2%, hypertension 49.3%, diabetes 21.1%, COPD 9.9%, asthma 4.2%, CHD 12.7%, CKD 9.9%	Corticosteroids 63.4%, hydroxychloroquine 1.5%, azithromycin 12.6%	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.	

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;[27] Cohen et al; Peer reviewed; 2020	Patients with mild to severe COVID-19 previously treated with ACEI/ARB. 75 assigned to continuation of ACEI/ARB and 77 assigned to discontinuation of ACEI/ARB	Mean age 62 ± 12, male 55.5%, hypertension 100%, diabetes 37%, COPD 17%, asthma %, CHD 12%,	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.13 (95%CI 0.77 to 1.64); RD 2.1% (95%CI -3.7% to 10.2%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.89 (95%CI 0.66 to 1.22); RD -1.9% (95%CI -5.9% to 3.8%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty
BRACE CORONA trial;[28] Lopes et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB	Median age 55.5 ± 19, male 59.6%, hypertension 100%, diabetes 31.9%, COPD %, asthma 3.9%, CHD 4.6%, CKD 1.4%, cancer 1.5%,	Corticosteroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection, and adverse events Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.	

ACEI-COVID trial;[29] 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;[30] 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;[31] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan 50 mg a day for 14 days and 39 assigned to Amlodipine 5 mg a day for 14 days	Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
SURG-2020-28683 trial;[32] 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;[33] 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;[34] 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;[35] peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to continuation of ACEI/ARB and 29 assigned to discontinuation of ACEI/ARB	Mean age 66.3 ± 9.9, male 46.9%, diabetes 50%, COPD 1.6%, CHD 25%, CKD 1.6%, cancer 4.7%,	Corticosteroids 42.2%, remdesivir 10.9%, , azithromycin 9.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events Notes: 10.9% lost to follow-up	
ALPS-COVID trial;[36] Puskarich et al; peer reviewed; 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;[37] 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	
RAAS-COVID-19 trial;[38] Sharma et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 25 assigned to continuation of ACEI/ARB and 21 assigned to discontinuation of ACEI/ARB	Mean age 71.5 ± 12.9, male 56.5%, hypertension 100%, diabetes 43.5%, COPD 4.4%, CKD 19.6%, cerebrovascular disease 6.5%, cancer 6.5%,	Corticosteroids 47.8%,	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.	

Anticoagulants

There are specific recommendations on the use of antithrombotic agents[8] for thromboprophylaxis in hospitalized patients with COVID-19. Regarding the best thromboprophylactic scheme, anticoagulants in intermediate (i.e., enoxaparin 1 mg/kg a day) or full dose (i.e., enoxaparin 1 mg/kg twice a day) probably do not decrease mortality in comparison with prophylactic dose (i.e., enoxaparin 40 mg a day). Anticoagulants in intermediate or full dose 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;[39] 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 events outcomes results.	**Mortality:** RR 0.99 (95%CI 0.83 to 1.19); RD -0.2% (95%CI -2.7% to 3%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** No information **Symptom**

REMAP-CAP, ACTIV-4a, ATTACC trial;[40] 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.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Venous thromboembolic events (intermediate dose):** RR 0.82 (95%CI 0.43 to 1.59); RD -1.3% (95%CI -4% to 4.1%); Low ⊕⊕◯◯ **Venous thromboembolic events (therapeutic dose):** RR 0.56 (95%CI 0.44 to 0.71); RD -3.1% (95%CI -3.9% to -2%); High ⊕⊕⊕⊕ **Major bleeding:** RR 1.56 (95%CI 1.08 to 2.25); RD 1.1% (95%CI 0.2% to 2.4%); Moderate ⊕⊕⊕◯ **Hospitalization:** No information
INSPIRATION trial;[41] 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;[42] preprint; 2021	Patients with severe to critical COVID-19 infection. 87 assigned to low molecular weight heparin intermediate dose (i.e., enoxaparin 1 mg/kg a day) and 86 assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	Median age 64 ± 62, male 56%, hypertension 60%, diabetes 37%, COPD 23%, CHD 31%, cancer 12%, obesity 49%	Corticosteroids 75%, remdesivir 61%, azithromycin 21%, convalescent plasma 27%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
REMAP-CAP, ACTIV-4a, ATTACC trial;[43] Zarychanski et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 1171 assigned to enoxaparin 1 mg/kg twice a day and 1048	Mean age 59 ± 14, male 58.7%, hypertension 51.8%, diabetes 29.7%, COPD 21.7%, CHD 10.6%, CKD 6.9%, immunosuppressive	Corticosteroids 61.7%, remdesivir 36.4%, tocilizumab 0.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse	

	assigned to low molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day)	therapy 9.7%		events Notes: Open-label study but outcome assessors were blinded.	
ACTION trial;[44] 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;[45] 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;[46] Spyropoulos et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 129 assigned to enoxaparin 1 mg/kg twice a day and 124 assigned to low molecular weight	Mean age 66.7 ± 14, male 53.8%, hypertension 59.9%, diabetes 37.3%, COPD 6.7%, CHD 8.7%, CKD 3.6%, cerebrovascular disease 3.2%, cancer 2%	Corticosteroids 81%, remdesivir 70.6%,	Some concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection, and adverse events	

	heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose				
BEMICOP trial;[47] 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;[48] 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;[49] Morici et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91 assigned to enoxaparin 40 mg twice a day and 92 assigned to low	Mean age 59 ± 21, male 62.8%, hypertension 36.1%, diabetes 13.7%, COPD 5.5%, CKD 1.6%, cerebrovascular disease 2.7%	Corticosteroids 45.9%, remdesivir 21.8%, tocilizumab 1.1%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	

	molecular weight heparin prophylactic dose (i.e., enoxaparin 40 mg a day) or unfractionated heparin prophylactic dose			study which might have introduced bias to symptoms and adverse events outcomes results.	
PROTHROMCOVID trial;[50] Muñoz-Rivas et al; preprint; 2021	Patients with severe COVID-19 infection. 103 assigned to tinzaparin 175 IU/kg once daily, 91 assigned to tinzaparin 100 IU/kg once daily and 106 assigned to tinzaparin 4500 IU once daily	Mean age 56.3, male 60.6%, hypertension 33%, diabetes 16.7%, COPD 4%, CHD 3.3%, CKD 2%, cerebrovascular disease 1.3%	Corticosteroids 89.3%, remdesivir 18%, tocilizumab 15%; Vaccinated 23%	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.	
COVID-HEP trial;[51] Blondon et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 79 assigned to enoxaparin 1 mg/kg twice daily and 80 assigned to enoxaparin 20 to 60 mg once daily. Critically ill patients received enoxaparin 40 mg twice daily.	Mean age 62 ± 12, male 66%, hypertension 36.5%, diabetes 18.9%, COPD 11.9%, CHD 9.4%, cancer 6.3%	Corticosteroids 94.3%, tocilizumab 11.9%	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.	
Kumar et al;[52] peer reviewed ; 2021	Patients with moderate COVID-19 infection. 115 assigned to rivaroxaban 10 to 15 mg a day and 113 assigned to LMWH-P	Mean age 53 ± , male 71.3%, hypertension 26.6%, diabetes 30.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

ACTIV-4B trial;[53] Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 278 assigned to apixaban 2.5 to 5 mg 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 ⊕◯◯◯ **Hospitalization:** RR 0.94 (95%CI 0.55 to 1.59); RD -0.3% (95%CI -2.2% to 2.8%); Low ⊕⊕◯◯
Gates MRI RESPOND-1 trial;[54] Ananworanich et al; peer reviewed; 2021	Patients with mild covid-19 and risk factors for severity. 222 assigned to rivaroxaban 10 mg 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	
OVID trial;[55] Barco et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 234 assigned to LMWH-P enoxaparin 40 mg a day for 14 days and 238 assigned to SOC	Mean age 56.5 ± , male 54%, hypertension 24.4%, diabetes 8%, COPD 2%, asthma %, CHD %, CKD %, cerebrovascular disease %, immunosuppresive therapy %, cancer %, obesity %	Corticosteroids 1.7%, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 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.	
ETHIC trial;[56] Cools et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 105 assigned to enoxaparin 40 mg a day for 21 days and 114 assigned to SOC	Mean age 59 ± , male 55.7%, hypertension 70.4%, diabetes 30.8%, COPD 12.3%, cerebrovascular disease 1.8%, immunosuppression 2.5%, cancer 1.2%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

APMV2020 (aspirin, promethazine and micronutrients)

Uncertainty in potential benefits and harms. Further research 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					
Kumar et al;[57] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 99 assigned to APMV2020 (aspirin 150 mg, promethazine 5 mg, vit D 2000 IU, vit C 750 mg, niacinamide 80 mg, zinc 15 mg , potassium 100 micrograms, sodioum selenate 82.5 micrograms) twice a day for 10 days and 93 assigned to SOC	Mean age 37 ± , male 55.5%	Vaccinated 95%	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:** 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;[58] preprint; 2020	Patients with mild to critical COVID-19 infection. 10 assigned	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** No information

	to aprepitant 80 mg once a day for 3–5 days and 8 assigned to standard of care			symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Aprotinin

Uncertainty in potential benefits and harms. Further research 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					
Redondo-Calvo et al;[59] peer reviewed; 2021	Patients with severe COVID-19 infection. 28 assigned to aprotinin 500 KIU a day for 11 days and 32 assigned to SOC	Mean age 55, male 65%, hypertension 47.4%, diabetes 29.8%, COPD 10.8%, CHD 17%	Corticosteroids 96.5%, remdesivir 12%, tocilizumab 10.5%, Vaccinated 35.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: 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:** No information **Hospitalization:** No information

Arbidol

Uncertainty in potential benefits and harms. Further research 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					
Khodashahi et al;[60] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 50 assigned to arbidol 600 mg a day for 7 days and 50 assigned to SOC	Mean age 60.6 ± 19, male 55.6%, hypertension 13%, diabetes 12%	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.	**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

ArtemiC (artemisinin, curcumin, frankincense, and 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 (standard of care) and GRADE certainty of the evidence
RCT					
MGC-006 trial;[61] Hellou et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 33 assigned to ArtemiC (artemisinin, curcumin, frankincense and vitamin C) oral spray twice a day and 17 assigned to SOC	Mean age 52 ± , male 50%	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:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **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;[62] 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 or 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;[63] Ghati et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 221 assigned to aspirin 75 mg once a day for 10 days and 219 assigned to SOC	Mean age 53.1 ± 9.2, male 73.3%, hypertension 28.6%, diabetes 27.7%, CHD 1.1%, CKD 2.4%	Corticosteroids 27.3%, remdesivir 20.6%, hydroxychloroquine 9.9%, tocilizumab 0.6%, convalescent plasma 0.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably	**Mortality:** RR 0.95 (95%CI 0.89 to 1.02); RD -0.8% (95%CI -1.8% to 0.3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical**

				inappropriate.	**ventilation:** RR 0.94 (95%CI 0.84 to 1.05); RD -1% (95%CI -2.8% 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:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
RECOVERY - ASA trial;[64] 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;[53] Connors et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 144 assigned to aspirin 81 mg 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	
REMAP-CAP - ASA trial;[65] Bradbury et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 565 assigned to aspirin 75 to 100 mg a day for 14 days and 529 assigned to SOC	Median age 57, male 65%, hypertension %, diabetes 22.7%, CHD 4.2%, CKD 3.4%	Corticosteroids 98.1%, remdesivir 22%, tocilizumab 42.9%	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.	

Atazanavir/ritonavir

Uncertainty in potential benefits and harms. Further research 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					

Nekoukar et al;[66] peer reviewed; 2021	Patients with severe COVID-19 infection. 62 assigned to atazanavir/ritonavir 300/100 mg a day for 5 to 10 days and 62 assigned to lopinavir-ritonavir 200/50 mg a day for 5 to 10 days	Mean age 49.9 ± 12.6, male 55.6%, hypertension 16.9%, diabetes 27.4%, COPD 0.8%, asthma 1.6%,	Corticosteroids 42.7%, remdesivir 13.7%, tocilizumab 3.2%, azithromycin 50.8%,	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

Atovacuone

Uncertainty in potential benefits and harms. Further research 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					
STU-2020-0707 trial;[67] Jain et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 41 assigned to atovacuone 3000 mg a day for 10 days and 19 assigned to SOC	Mean age 50.9, male 63%, hypertension 63%, diabetes 63%, COPD 20%, asthma %, CHD 12%, CKD 33%, cancer 10%, obesity 38%	Corticosteroids 73.3%, remdesivir 60%, convalescent plasma 8.3%;	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

Auxora

Auxora may not increase severe adverse events. The effects of auxora on other importan outcomes 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 (standard of care) and GRADE certainty of the evidence
RCT					
CARDEA trial;[68] Bruen et al; Preprint; 2020	Patients with severe COVID-19 infection. 130 assigned to auxora initial dose 2.0 mg/kg (max 250 mg), followed by 1.6 mg/kg (max 200 mg) at 24 and 48 h and 131 assigned to SOC	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 adverse events	**Mortality:** RR 0.68 (95%CI 0.39 to 1.17); RD -5.1% (95%CI -9.8% to 2.7%); Low 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%); Very 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

Uncertainty in potential benefits and harms. Further research 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 ;[69] Carvelli et al ; preprint ; 2021	Patients with severe to critical COVID-19 infection. 103 assigned to avdoralimab 500 mg once followed by 200 mg every 48 hours and 104 assigned to SOC	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 adverse events	**Mortality:** RR 1.68 (95%CI 0.87 to 3.26); RD 10.9% (95%CI -2.1% to 36.2%); Very low 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%); Very 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[70] 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 150 pmol/kg/hr and 67 assigned to SOC	Mean age 61 ± NR, male 69%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information

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

Ayush-64

Uncertainty in potential benefits and harms. Further research 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					
Singh et al;[71] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 37 assigned to Ayush-64 1500 mg a day for 30 days and 37 assigned to SOC	Mean age 35.89, male 62.1%, comorbidities 0%	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.	

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;[72] Klussmann et al; preprint; 2021	Patients with mild COVID-19 infection. 56 assigned to azelastine (inhaled) 0.02 to 0.1% twice a	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No

	day for 11 days and 28 assigned to SOC				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[73] 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 0.92 (95%CI 0.77 to 1.1); RD -1.4% (95%CI -4% to 1.7%); Moderate certainty
Guvenmez et al;[74]	Patients with moderate	Mean age 58.7 ± 16,	NR	High for mortality and	

peer-reviewed; 2020	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	male 70.8%,		invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯ **Hospitalization:** RR 0.98 (95%CI 0.52 to 1.86); RD -0.1% (95%CI -2.3% to 4.1%); Low certainty ⊕⊕◯◯
COALITION II trial;[75] 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.	
RECOVERY trial[76] 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;[77] 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;[78] 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;[79] 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;[80] 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;[81] peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to lopinavir-ritonavir 200/50 mg twice a day	Mean age 58.1 ± 16.3, male 51.5%, hypertension 24.7%, diabetes 12.2%, asthma 4.5%, CHD 8.9%, CKD	Convalescent plasma 1.8%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events

	for 7 days and 110 assigned to azithromycin 500 mg once followed by 250 mg a day for 5 days	1.2%,		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
DAWn-AZITHRO trial;[82] Gyselinck et al; peer reviewed; 2021	Patients with sevre to critical COVID-19 infection. 119 assigned to AZT 500 mg a day for 5 days and 64 assigned to SOC	Mean age 62 ± 15, male 61.8%, hypertension 44.8%, diabetes 16.9%, COPD 8.2%, asthma 8.2%, CHD 9.8%, CKD 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.	

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;[83] 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;[84] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%	Antivirals 100%, interferon 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Bamlanivimab +/- etesevimab (monoclonal antibody)

Bamlanivimab may reduce hospitalizations and infections in exposed individuals. It is uncertain if it affects mortality or 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;[85] Chen et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700 mg, 2800 mg, or 7000 mg once and 143 assigned to standard of care	Mean age 45 ± 68, male 55%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.06); RD 1.2% (95%CI 3.6% to 5.4%); Moderate certainty ⊕⊕⊕○ **Symptomatic infection (prophylaxis studies):** RR 0.56 (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 ⊕⊕○○
ACTIV-3/TICO trial;[86] Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000 mg once and 151 assigned to SOC	Median age 71 ± 22, male 66%, hypertension 49%, diabetes 29%, COPD %, asthma 9%, CHD 4%, CKD 11%, obesity 52%	Corticosteroids 49%, remdesivir 95%,	Low for mortality and adverse events; high for symptom resolution. Notes: Significant loss to follow-up for symptom improvement/resolution outcome.	
Gottlieb et al;[87] 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;[88] Cohen et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 484 assigned to bamlanivimab 4200 mg once and 482	Median age 53	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	

	assigned to SOC				**Hospitalization:** RR 0.37 (95%CI 0.21 to 0.65); RD -3% (95%CI -3.8% to -1.7%); Moderate certainty ⨁⨁⨁◯
BLAZE-1 trial;[89] 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;[90] 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;[91] McCreary et al; peer reviewed; 2022	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;[92] Chew et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 159 assigned to bamlanivimab 700 to 7000 mg 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;[93] 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	
MANTICO trial;[94] Mazzaferri et al;	Patients with mild to moderate COVID-19	Mean age 65 ± 15, male 57.2%, diabetes 2.9%,	Vaccinated 28.6%	Low for mortality and mechanical ventilation;	

preprint; 2021	infection. 107 assigned to sotrovomab 500 mg once and 106 assigned to bamlanivimab + etesevimab 700/1400 mg once and 106 assigned to REGEN-COV2 600/600 mg once	COPD 16.7%, asthma %, CHD 37.9%, CKD 5.1%, immunosuppression19.6%, obesity 25.4%		high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
BLAZE-4 trial;[95] Dougan et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 225 assigned to bebtelovimab 175 mg once and 175 assigned to bebtelovimab 175 mg + bamlanivimab 700 mg + etesevimab 1400 mg mg once	Median age 35 ± , male 44.5%	Vaccinated 20.7%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

Baricitinib

Baricitinib reduces mortality and probably reduces mechanical ventilation requirements and improves time to symptom resolution, 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 (standard of care) and GRADE certainty of the evidence**
RCT					
ACTT-2 trial;[96] 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 0.73 (95%CI 0.57 to 0.92); RD -4.3% (95%CI -6.9% to -1.3%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 0.83 (95%CI 0.66 to 1.04); RD -2.9% (95%CI -5.9% to 0.7%); Moderate certainty ⊕⊕⊕◯
COV-BARRIER trial;[97] Marconi et al; peer reviewed;	Patients with moderate to severe COVID-19 infection. 764 assigned	Mean age 57.6 ± 14.1, male 63.1%, hypertension 47.9%,	Corticosteroids 79.3%, remdesivir 18.9%	Low for mortality and mechanical ventilation; low for symptom	

2021	to baricitinib 4 mg for 14 days and 761 assigned to SOC	diabetes 30%, COPD 4.6%, obesity 33%		resolution, infection, and adverse events	**Symptom resolution or improvement:** RR 1.27 (95%CI 1.13 to 1.42); RD 16.4% (95%CI 7.9% to 25.5%); Moderate 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
COV-BARRIER-IMV trial;[98] 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	
RECOVERY trial;[99] Horby et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 4148 assigned to baricitinib 4 mg a day for 10 days and 4008 assigned to SOC	Mean age 58.1± 15.5, male 66%, hypertension %, diabetes 23%, COPD 20.4%, asthma %, CHD 18.2%, CKD 2%,	Corticosteroids 95.2%, remdesivir 20.4%, tocilizumab 23%, Regeneron 11%; Vaccinated42%	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.	
ACTT-4 trial;[100] Wolfe et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 516 assigned to baricitinib 4 mg a day for 14 days and 494 assigned to dexamethasone 6 mg a day for 10 days	Mean age 58.3 ± 14, male 58%, hypertension 59.2%, diabetes 39.6%, COPD 9%, asthma 11%, CHD 9.6%, CKD 9.3%, immunosuppression 3.4%, cancer 5.6%, obesity 61.9%	Remdesivir 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Karampitsakos et al;[101] preprint; 2022	Patients with severe COVID-19 infection. 125 assigned to baricitinib 4 mg a day for 14 days and 126 assigned to TCZ 8 mg/kg once	Mean age 72.5, male 59.4%, hypertension 53.8%, cancer 9.2%, obesity 8%	Corticosteroids 100%, remdesivir 100%; Vaccinated 20.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PanCOVID19	Patients with severe	Median age 67, male	Corticosteroids 100%,	Low for mortality and	

trial;[102] Montejano et al; peer reviewed; 2022	COVID-19 infection. 145 assigned to baricitinib 2 to 4 mg a day for 14 days and 142 assigned to SOC	65.5%, hypertension 57.5%, diabetes 29.6%, obesity 18.8%	remdesivir 15.3%, Vaccinated 91%	mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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;[103] 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

Bebtelovimab

Uncertainty in potential benefits and harms. Further research 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-4 trial;[95] Dougan et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 252 assigned to bebtelovimab 175 +/- bamlanivimab/etesevimab mg once and 128 assigned to SOC	Median age 35 ± , male 44.5%	Vaccinated 20.7%	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:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯

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;[104] 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	Mean age 41.2	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No

	to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Pushkala et al;[105] 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.	

Bicarbonate (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					
Delic et al;[106] peer reviewed; 2022	Patients with critical COVID-19 infection. 42 assigned to bicarbonate (inhaled) twice a day and 52 assigned to SOC	Mean age 66, male 79.8%, hypertension 57.4%, diabetes 33%, CHD 5.3%, cerebrovascular disease 5.3%	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.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

					Hospitalization: No information

Bioven

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Rybakov et al;[107] 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

Boswellia extract

Uncertainty in potential benefits and harms. Further research 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					

Barzin Tond et al;[108] peer reviewed; 2021	Patients with severe COVID-19 infection. 24 assigned to Boswellia extract 300 ml a day and 23 assigned to SOC	Mean age 53.8, male 52%, hypertension 22%, diabetes 28%, COPD 2%, asthma 2%, CHD 2%, obesity 24%	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

Bromhexine hydrochloride

Bromhexine may reduce symptomatic infections in exposed individuals. Its effects on other clinical important outcomes 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 (standard of care) and GRADE certainty of the evidence
RCT					
Li T et al;[109] peer-reviewed; 2020	Patients with severe to critical COVID-19. 12 assigned to bromhexine hydrochloride 32 mf three times a day for 14 days and 6 assigned to standard of care	Median age 52 ± 15.5, male 77.8%, hypertension 33.3%, diabetes 11.1%	Corticosteroids 22.2%, interferon 77.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very

Ansarin et al;[110] 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.	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
Mikhaylov et al;[111] Peer reviewed; 2021	Individuals exposed to SARS-CoV-2 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;[112] 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;[113] preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 187 assigned to bromhexine 24 mg a day for 14 days and 185 assigned to SOC	Median age 40 , male 53.2%, hypertension 6.2%, diabetes 9.1%, COPD 0.5%, asthma 1.1%, CHD 8.3%, CKD 1.6%, immunocompromised 0.8%, cancer 0.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and 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;[114] 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

Camostat mesilate may 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 (standard of care) and GRADE certainty of the evidence

RCT					
CamoCO-19 trial;[115] 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:** RR 1.02 (95%CI 0.94 to 1.11); RD 1.2% (95%CI -3.6% to 6.6%); Low certainty ⊕⊕○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** Very low certainty ⊕○○○
Chupp et al;[116] 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	
CANDLE trial;[117] Kinoshita et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 78 assigned to camostat mesilate 2400 mg a day for 14 days and 77 assigned to SOC	Mean age 55.9 ± 18.4, male 50.3%, hypertension 28.4%, diabetes 17.4%, COPD 16.1%, asthma %, CHD 5.2%, CKD 5.8%, obesity 9.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Terada et al;[118] peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 56 assigned to camostat 600 mg + ciclesonide (inhaled) 1200 µg a day and 61 assigned to SOC	Mean age 58.3, male 64.9%, diabetes 24.8%, COPD 9.4%, CHD 2.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Tobback et al;[119] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 61 assigned to camostat mesilate 300 mg a day for 5 days and 29 assigned to SOC	Median age 40, male 45.6%, diabetes 1.1%, cancer 6.7%, obesity 6.7%	Vaccinated 7.8%	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;[120] Cariccchio et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 223 assigned to canakinumab 450–750 mg/kg once and 223 assigned to SOC	Median age 59, male 58.8%, hypertension 55.7%, diabetes 36.1%, COPD 7.3%, asthma 7.7%, CHD 20.3%, CKD 8.8%, cerebrovascular disease 5.9%	Corticosteroids 36.3%, remdesivir 20.7%, hydroxychloroquine 13.2%, azithromycin 37.4%, convalescent plasma 3.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Three C trial;[121] 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;[122] Crippa et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 49 assigned to cannabidiol 300 mg 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 ⊕○○○

CD24Fc (soluble CD24 appended to heavy chains 2 and 3 of human immunoglobulin G1)

Uncertainty in potential benefits and harms. Further research 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					
SAC-COVID trial;[123] Welker et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 116 assigned	Mean age 57.8 ± 14, male 74.8%, hypertension 54.7%,	Corticosteroids 83.3%, remdesivir 68.4%, hydroxychloroquine	Low for mortality and mechanical ventilation; low for symptom	**Mortality:** Very low certainty ⊕○○○

	to CD24Fc 480 mg once and 118 assigned to SOC	diabetes 21.4%, COPD 1.7%, asthma 9.4%, obesity 15.4%	1.3%, convalescent plasma 54.3%	resolution, infection and adverse events	**Invasive mechanical ventilation:** RR 0.57 (95%CI 0.34 to 0.96); RD -7.4% (95%CI -11.4% to -0.7%); Low certainty ⨁⨁◯◯ **Symptom resolution or improvement:** RR 1.18 (95%CI 1 to 1.39); RD 10.7% (95%CI -0.2% to 23.4%); 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;[124] preprint; 2021	Patients with mild to moderate COVID-19 infection. 31 assigned to CERC-002	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,	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical**

	16 mg/kg once and 31 assigned to SOC			and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	**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;[125] 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;[126] 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;[77] 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

Clazakizumab

Uncertainty in potential benefits and harms. Further research 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					
Lonze et al;[127] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 78 assigned to clazakizumab 12.5 to 25 mg a day and 74 assigned to SOC	Mean age 61.8 ± 12.2, male 70.4%, hypertension 63.2%, diabetes 42.4%, COPD 16.4%, asthma %, CHD 34.2%, immunosuppresive therapy 7.2%, cancer 8.6%, obesity 11.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** RR 0.66 (95%CI 0.43 to 1.01); RD -7.6% (95%CI -9.8% to 1.7%); Low certainty ⊕⊕○○ **Symptom resolution or improvement:** RR 1.23 (95%CI 0.87 to 1.76); RD 13.9% (95%CI -7.9% to 46%); Low certainty ⊕⊕○○ **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;[128] Song et al;	Patients with mild to moderate COVID-19	Mean age 59.9 ± 12.8, male 49.2%,	NR	High for mortality and mechanical ventilation;	**Mortality:** No information

preprint; 2021	infection. 41 assigned to clevudine 120 mg a day for 14 days and 20 assigned to SOC	hypertension 45.9%, diabetes 26.2%		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:** 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;[129] Altay et al; preprint; 2020	Patients with mild to moderate COVID-19. 71 assigned to cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 22 assigned to standard of care	Mean age 35.6 ± 47, male 60%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Outcome assessors not blinded. Possible reporting bias.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty
COVID-19-MCS	Patients with mild to	Mean age 36.3 , male	Hydroxychloroquine	High for mortality and	

trial;[130] Altay et al; peer reviewed; 2021	moderate COVID-19 infection. 229 assigned to cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 75 assigned to SOC	57.6%, hypertension 9.2%, diabetes 6.2%	81.9%	mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Hu et al;[131] 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 or improve time to symptom resolution. In mild ambulatory patients it may not have an important effect on 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;[132] 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 0.92 to 1.05); RD -0.2% (95%CI -1.3% to 0.8%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.89 to 1.02); RD -0.3% (95%CI -1.9% to 1.4%); Moderate certainty ⊕⊕⊕◯
Lopes et al;[133]	Patients with moderate	Median age 50.75 ±	Corticosteroids 40%,	High for mortality and	

preprint; 2020	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	26.2, male 40%, diabetes 31.4%, chronic lung disease 14.2%, coronary heart disease 40%	hydroxychloroquine 100%, azithromycin 100%, heparin 100%	invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptom resolution or improvement:** RR 1 (95%CI 0.98 to 1.02); RD 0% (95%CI -1.2% to 1.2%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.61 to 0.99); RD -2.2% (95%CI -4% to -0.1%); High certainty ⊕⊕⊕⊕ **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 ⊕⊕◯◯
Salehzadeh et al;[134] 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.	
Tardif et al;[135] 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;[136] 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;[137] 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;[138] Dorward et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 156 assigned to colchicine 500 μg a day for 14 days and 133 assigned to SOC	Mean age 61, male 50%, hypertension 19.5%, diabetes 10.9%, COPD or asthma 32.2%, CHD 8%, cerebrovascular disease, or other neurological diseases 5.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, hospitalization, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COLCOVID trial;[139] 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;[140] 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;[141] 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.	
Gorial et al;[142] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 80 assigned to colchicine 1 mg a day for 7 days followed by 0.5 mg a day for 14 days and 80 assigned to SOC	Median age 49, male 53.1%, hypertension 41.2%, diabetes 20.6%, COPD %, asthma 1.2%, cancer 2.5%, obesity 35%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mostafaie et al; NCT04392141, other; 2021	Patients with moderate to severe COVID-19 infection. 60 assigned to colchicine and 60 assigned to SOC	Mean age 53.5 ± 15.1, male 54.2%, hypertension 26.7%, diabetes 7.5%, cancer 5.8%,	NR	NA	
STRUCK trial;[143] Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to colchicine 1 mg a day for 4 weeks and 16 assigned to SOC	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD 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.	
Cecconi et al;[144] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 119 assigned to colchicine 1 mg once followed by 0.5 mg a day for 5 days	Mean age 65.1 ± 16, male 59%, hypertension 40%, diabetes 16%, COPD 4%, asthma 5%, CHD 7%	Corticosteroids 98%, remdesivir 15.5%, hydroxychloroquine 0%, lopinavir-ritonavir 0.8%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	and 120 assigned to SOC			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Rabbani et al;[145] peer reviewed; 2022	Patients with moderate to severe with cardiac injury COVID-19 infection. 48 assigned to colchicine 1.2 mg a day for 30 days and 45 assigned to SOC	Mean age 71, male 67.7%, hypertension 78.5%, diabetes 26.9%, COPD 10.8%, CKD 28%,	Corticosteroids 62.4%, remdesivir 69.9%, hydroxychloroquine 1.1%, convalescent plasma 14%	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;[146] 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 or mechanical ventilation requirements or improve time to symptom resolution. Convalescent plasma probably has no important effect on 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;[147] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 52 assigned to convalescent plasma 4 to 13 mL/kg of recipient body weight and 51 assigned to standard of care	Median age 70 ± 8, male 58.3%, hypertension 54.3%, diabetes 10.6%, coronary heart disease 25%, chronic kidney disease 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%	Corticosteroids 39.2%, antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 0.98 (95%CI 0.93 to 1.03); RD -0.3% (95%CI -1.1% to 0.5%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 1.02 (95% CI 0.94 to 1.11); RD 0.3% (95%CI -1% to 1.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 0.99 (95% CI 0.95 to 1.02); RD -0.6% (95%CI -3% to 1.2%); High certainty ⊕⊕⊕⊕
CONCOVID trial; Gharbharan et al;[148] 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;[149] 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.	**Symptomatic infection (prophylaxis studies):** Very low certainty ⊕○○○ **Adverse events:** RR 1.03 (95% CI 0.88 to 1.21); RD 0.3% (95%CI -1.2% to 2.1%); Low certainty ⊕⊕○○ **Hospitalization:** RR 0.77 (95% CI 0.57 to 1.03); RD -1.1% (95%CI -2.1% to 0.1%); Moderate certainty ⊕⊕⊕○
PLACID trial;[150] 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;[151] 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;[152] 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;[153] 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;[154] 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;[155] Ray et al; peer reviewed; 2020	Patients with severe COVID-19. 40 assigned to convalescent plasma 200 ml and 40 assigned to standard of care	Mean age 61 ± 11.5, male 71.2%, hypertension 43.7%, diabetes 58.7%, COPD 6.2%, CHD 10%, cerebrovascular disease 2.5%	Steroids 50%, remdesivir 31.2%, hydroxychloroquine 37.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RECOVERY-Plasma trial;[156] 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;[157] 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;[158] 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;[159] 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;[160] peer reviewed; 2021	Patients with severe COVID-19 infection. 30 assigned to CP 500 ml once or twice	Mean age 55.3 ± 13.6, male 55%, comorbidities 50%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection,	

	and 30 assigned to SOC			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
SBU-COVID19 - Convalescent Plasma trial;[161] 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;[162] peer reviewed; 2021	Patients with severe COVID-19 infection. 15 assigned to CP 250 ml once and 15 assigned to SOC	Median age 57 ± 10, male 70%, diabetes 30%, asthma 16.6%, cerebrovascular disease 43.3%	Corticosteroids 76.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
CAPSID trial;[163] 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;[164] 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;[165] 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;[166] 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;[167] 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;[168] Korley et al; peer reviewed; 2021	Patients with early mild to moderate COVID-19 infection with risk factors for	Median age 54 ± 21, male 46%, hypertension 42.3%, diabetes 27.8%, COPD 6.1%, CHD	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,

	severe disease. 257 assigned to CP 250 ml and 254 assigned to SOC	10%, CKD 5.3%, cancer 0.8%, obesity %		and adverse events
DAWn-Plasma trial;[169] 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;[170] Bar et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 40 assigned to CP two units and 39 assigned to SOC	Mean age 63 , male 45.6%, hypertension 67.1%, diabetes 40.5%, COPD 29.1%, CHD 29.1%, CKD 32.9%, immunosuppression 13.9%, cancer 26.6%, obesity 45.6%	Corticosteroids 83.5%, remdesivir 81%, hydroxychloroquine 2.5%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
TSUNAMI trial;[171] Manichetti et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 231 assigned to CP 200 ml 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;[172] 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	Median age 58 ± 11, male 66.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

	to SOC			
CSSC-004 trial;[173] Sullivan et al; peer reviewed; 2022	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%	Vaccinated 17.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
COP20 trial;[174] 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;[175] 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;[176] 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;[177] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 36 assigned	Mean age 59.8, male 62.6%, hypertension 56%, diabetes 38.3%	NR	Low for mortality and mechanical ventilation; high for symptom

	to CP 600 ml a day for 3 days and 71 assigned to SOC			resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
PROTECT-Patient trial;[178] van den Berg et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 52 assigned to CP 200-250 ml once and 51 assigned to SOC	Median age 56, male 40.8%, hypertension 54.4%, diabetes 38.8%, COPD 3.9%, CHD 2.9%, CKD 2.9%, cancer 1.9%, obesity 47.6%	Corticosteroids 94.2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events
LIFESAVER trial;[179] et al; other; 2021	Patients with severe to critical COVID-19 infection. 4 assigned to CP and 8 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review
RECOVER trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 43 assigned to CP and 47 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review
LACCPT trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 11 assigned to CP and 11 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review

CPC-SARS trial;[180] Fernández-Sánchez et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 29 assigned to CP 300 ml twice and 10 assigned to SOC	Mean age 55.9 ± 9.6, male 76.9%, hypertension 51.3%, diabetes 35.9%, COPD 2.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Herrick J et al;[179] other; 2021	Patients with severe to critical COVID-19 infection. 8 assigned to CP and 6 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Tatem G et al;[179] other; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to CP and 10 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Chowdhury FR et al;[179] other; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to CP and 10 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
PLACO-COVID trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 60 assigned to CP and 60 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from	

				systematic review	
ASCOT trial;[179] other; 2021	Patients with moderate to severe COVID-19 infection. 15 assigned to CP and 18 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Co-CLARITY trial;[179] other; 2021	Patients with moderate to severe COVID-19 infection. 13 assigned to CP and 12 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
Rego EM et al;[179] other; 2021	Patients with moderate to severe COVID-19 infection. 9 assigned to CP and 8 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
PERUCONPLASMA trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 12 assigned to CP and 13 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CP-COVID-19 trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 49 assigned	NR	NR	Low for mortality and mechanical ventilation; low for symptom	

	to CP and 51 assigned to SOC			resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CONFIDENT trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 150 assigned to CP and 151 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
PC/COVID-19 trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 38 assigned to CP and 36 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
COP-COVID-19 trial;[179] other; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to CP and 11 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from systematic review	
CCAP trial;[179] other; 2021	Patients with moderate to severe COVID-19 infection. 98 assigned to CP and 46 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment extracted from	

				systematic review	
COOPCOVID trial;[181] Song et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 87 assigned to CP 200 to 400 ml once and 42 assigned to SOC	Median age 61 ± , male 68%, one or more comorbidities 92%	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.	
COPLA-II trial;[182] Bajpai et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 200 assigned to CP 250 ml twice and 200 assigned to SOC	Mean age 55.5 ± 1.17, male 67.3%	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.	
CAPRI trial; NCT 04421404; other; 2021	Patients with moderate to severe COVID-19 infection. 16 assigned to CP 250 ml once and 18 assigned to SOC	Median age 57, male 44.1%	NR	NA	
CoVIP trial;[183] Bartelt et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 14 assigned to CP (high titer) 200 to 300 ml twice and 41 assigned to CP (normal titer) 200 to 300 ml twice	Median age 61, male 64%, hypertension 20%, diabetes 43.6%, COPD 16.3%, CHD 12.7%, immunosuppressive therapy 29.1%, cancer 5.5%, obesity 58.2%	Corticosteroids 90.9%, remdesivir 92.7%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Significant cross-over which affected blinding. No intention to treat analysis estimates provided.	

CSSC-001 trial;[184] Shoham et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 81 assigned to CP one unit once and 87 assigned to SOC	Median age 47, male 55%, diabetes 6.1%, asthma 5%, CHD 2.2%, immunosuppresive therapy 0.5%, cancer 1.1%	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Rojas et al;[185] peer reviewed; 2022	Patients with severe COVID-19 infection. 46 assigned to CP 250 ml twice and 45 assigned to SOC	Mean age 55, male 70.3%, hypertension 25.3%, diabetes 16.5%, COPD %, asthma 4.4%, CKD 5.5%	Corticosteroids 96.7%	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.	
Bargay-Lleonart et al;[186] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 37 assigned to CP 300 ml twice and 17 assigned to SOC	Mean age 58.2, male 61.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Self et al;[187] peer reviewed; 2022	Patients with moderate to critical COVID-19 infection. 487 assigned to CP 200 to 400 ml once and 473 assigned to SOC	Median age 60, male 57.3%, hypertension 60.5%, diabetes 34.1%, COPD 27%, CKD 17.7%, cancer 8.1%,	Corticosteroids 86.7%, remdesivir 70.8%, Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Balcells et al;[188] 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	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%,	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	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom**

	observed (43.3% received CP in this arm)	immunosuppression 12%, cancer 7%, obesity 12%		introduced bias to symptoms and adverse events outcomes results.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information
Non-RCT					
Joyner et al;[189] 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;[190] Leucker et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 22 assigned to	Mean age 56.6, male 54.5%, hypertension 70.4%, diabetes 43.1%, COPD 9.1%, asthma	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical**

	crizanlizumab 5 mg/kg once and 20 assigned to SOC	6.8%, CHD 11.3%, CKD 11.3%, cerebrovascular disease 2.2%,		and adverse events Notes:	**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

Curcumin + Piperine

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Askari et al;[191] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 23 assigned to curcumin + piperine 1000/10 mg a day for 14 days and 23 assigned to SOC	Mean age 47.6 ± 13.9, male 58.7%, hypertension 23.9%, diabetes 26.1%, CHD 15.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯

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

Curcumin + Quercetin + 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					
Khan et al;[192] peer reviewed; 2022	Patients with moderate COVID-19 infection. 25 assigned to curcumin + quercetin + Vit D 168 mg + 260 mg + 360 IU and 25 assigned to SOC	Mean age 43.9, male 50%, hypertension 28%, diabetes 34%	Vaccinated 52%	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

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;[193] 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;[194] 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

Degarelix

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

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

					certainty of the evidence
RCT					
[HITCH trial](#);[195] Nickols et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 62 assigned to degarelix 240 mg once and 34 assigned to SOC	Mean age 68.5 ± 8.4, male 100%, hypertension 78.1%, diabetes 51%, COPD 15.6%, asthma 12.5%, CHD 28.1%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** 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](#);[196] preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 116 assigned to DSMO three	Mean age 37.2 ± 8.7	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection,	**Mortality:** No information **Invasive mechanical

	applications a day for one month and 116 assigned to SOC			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information **Hospitalization:** No information

Dornase alfa (inhaled)

Doxycycline 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					
COVASE trial;[197] Porter et al; preprint; 2021	Patients with severe COVID-19 infection. 30 assigned to inhaled dornase alfa 5 mg a day for 7 days and 9 assigned to SOC	Mean age 56, male 76.9%, any commorbiditie 51.2%	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:** Very low certainty ⨁◯◯◯ **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Doxycycline

Doxycycline 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					
DOXYCOV trial;[198] 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):** Very low certainty ⨁◯◯◯ **Adverse events:** Very low certainty
PRINCIPLE trial;[199] 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;[200] Dhar et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 192 assigned	Mean age 58.6, male 63.8%, hypertension 53.2%, diabetes 35.7%,	Corticosteroids 81.4%, tocilizumab 1.3%,	Low for mortality and mechanical ventilation; high for symptom	

	to doxycycline 200 mg a day and 195 assigned to SOC	COPD 9%, asthma 7.5%, CHD 13.4%, cancer 1.3%,		resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	⊕○○○ **Hospitalization:** RR 1.16 (95%CI 0.76 to 1.76); RD 0.7% (95%CI -1.1% to 3.6%); Low certainty ⊕⊕○○
Stambouli et al;[201] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 56 assigned to doxycycline 100 mg a day for 6 weeks and 57 assigned to SOC	Mean age 38.4 ± 10.7, male 61%, hypertension 4.1%, diabetes 2.3%, COPD 0.6%, asthma 1.2%,	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Dupilumab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
SafeDrop trial;[202] Sasson et al; preprint; 2021	Patients with severe COVID-19 infection. 19 assigned to dupilumab 600 mg once followed by 300 mg on days 14 and 28 and 21 assigned to SOC	Mean age 61, male 57.5%, hypertension 45%, diabetes 37.5%, COPD 12.5%, asthma 20%, CHD 22.5%, CKD 25%, cancer 17.5%, obesity 72.5%	Corticosteroids 97.5%, remdesivir 85%, tocilizumab 0%; Vaccinated 65%	Some Concerns for mortality and mechanical ventilation; some Concerns 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

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;[203] 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;[204] 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.	

Edaravone

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Moslemi et al;[205] peer reviewed; 2022	Patients with severe COVID-19 infection. 19 assigned to edaravone 30 mg a day for 3 days and 19 assigned to SOC	Mean age 60.5, male 47.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[206] Delgado-Enciso et al;	Patients with mild to moderate COVID-19. 45 assigned to	Mean age 47 ± 14.6, male 53.5%, hypertension 18.9%,	Corticosteroids 3.65%, hydroxychloroquine 7.5%, ivermectin 9.4%,	High for mortality and invasive mechanical ventilation; high for	**Mortality:** Very low certainty ⊕◯◯◯

preprint; 2020	electrolyzed saline nebulizations 4 times a day for 10 days and 39 assigned to standard of care	diabetes 11.9%	ATB 30.6%	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):** Very low certainty ⊕○○○ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕○○○
ICU-VR trial; Gutiérrez-García et al;[207] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 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.	

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;[208] Matli et al; peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 17 assigned to nicorandil 20 mg a day, L-arginine 3 gr a day, folate 5 mg a day, nebivolol 2.5 to 5 mg 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;[209] 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

Ensitrelvir

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Mukae et al-2;[210] preprint; 2021	Patients with mild to moderate COVID-19 infection. 30 assigned to ensitrelvir 125 to 250 mg a day for 5 days and 17 assigned to SOC	Mean age 38.9, male 61.7%,	Vaccinated 80.8%	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:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information

Ensovibep

Ensovibep may not improve time to symptom resolution. The effectos of ensovibep on other importan outcomes 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					
ACTIV-3/TICO trial;[211] Barkauskas et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 247 assigned to ensovibep 600 mg once and 238 assigned to SOC	Median age 57 ± , male 56.7%, hypertension 39.4%, diabetes 23.5%, COPD 6.2%, asthma 9.3%, CHD %, CKD 9.5%, cerebrovascular disease %, immunosuppresive therapy 6.2%, cancer %, obesity 13.4%	Corticosteroids 72.9%, remdesivir 68.7%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated 31.6%	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:** RR 0.95 (95%CI 0.8 to 1.16); RD -2.8% (95%CI -13.1% to 9.7%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **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;[212] 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

Ethanol (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
Non-RCT					
Amoushahi et al;[213] preprint; 2022	Patients with moderate to severe COVID-19 infection. 44 assigned to ethanol (inhaled) 3 sprays, four times a day for 7 days and 55 assigned to SOC	Mean age 46.4 ± 12.8, male 43.7%,	Corticosteroids 100%, remdesivir 100%	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: Very low certainty ⊕○○○ **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;[214] 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:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No
Brennan et al;[215] peer reviewed; 2021	Patients with mild recent onset COVID-19 infection. 27 assigned to famotidine 60 mg a day for 14 days and 28 assigned to	Mean age 35 ± 20, male 36.4%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to	

	SOC			follow up.	information **Adverse events:** No information **Hospitalization:** No information
Pahwani et al;[216] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 89 assigned to famotidine 40 mg a day and 89 assigned to SOC	Mean age 51.5 ± 11.5, male 68.5%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Favipiravir

Favipiravir may increase mortality and mechanical ventilation requirements; it may not reduce hospitalizations 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;[217] 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days	Mean age not reported male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** RR 1.09 (95%CI 0.78 to 1.52); RD 1.4% (95%CI -3.6% to 8.3%); 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
Ivashchenko et al;[218] 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	Mean age not reported	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded	

	assigned to standard of care			study. Concealment of allocation is probably inappropriate.	⊕⊕⊕○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.87 (95%CI 0.48 to 1.58); RD -1.3% (95%CI -5.3% to 5.9%); Very low certainty ⊕○○○ **Hospitalization:** RR 1.33 (95%CI 0.64 to 1.78); RD 1.6% (95%CI -1.7% to 3.7%); Low certainty ⊕⊕○○
Lou et al;[84] 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.	
Doi et al;[219] 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;[220] preprint (now retracted); 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;[221] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection.	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%,	NR	High for mortality and invasive mechanical ventilation; high for	

	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	coronary heart disease 23.1%		symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Khamis et al;[222] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 44 assigned to favipiravir + inhaled interferon beta-1B 1600 mg once followed by 600 mg twice a day for 10 days + 8 million UI for 5 days and 45 assigned to standard of care	Mean age 55 ± 14, male 58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart disease 15%, chronic kidney disease 20%	Corticosteroids 67%, tocilizumab 35%, convalescent plasma 58%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Ruzhentsova et al;[223] 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;[224] 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;[225] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 100 assigned to favipiravir 3200 mf once followed by 1200 mg a day for 14 days and 100 assigned to SOC	Mean age 49.7 ± 13, male 50%, hypertension 28.5%, diabetes 9%, COPD 5%, asthma %, CHD 6%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Solaymani-Dodaran et al;[226] 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;[227] 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;[228] Bosaeed et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 125 assigned	Mean age 52 ± 13, male 59%, hypertension 40.9%, diabetes 42.1%,	Corticosteroids 88.6%, tocilizumab 9%	Low for mortality and mechanical ventilation; high for symptom	

	to favipiravir + HCQ 3600 mg + 800 mg once followed by 2400 mg + 400 mg a day for 5 days and 129 assigned to SOC	asthma 11.8%, CKD 2.4%		resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Shinkai et al;[229] peer reviewed; 2021	Patients with moderate COVID-19 infection. 107 assigned to favipiravir 3200 mg once followed by 1600 mg a day for 14 days and 49 assigned to SOC	Mean age 46.2, any comorbidities 75.6%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
FIGHT-COVID-19 trial;[230] 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 800 mg a day or darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day or favipiravir 6000 mg followed by 2400 mg + darunavir ritonavir 1200/200 mg a day + HCQ 400 mg 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;[231] Shenoy et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 175 assigned to	Mean age 51.9 ± 12.5, male 67.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	

	favipiravir 3600 mg on day 1 followed by 1600 mg a day for 10 days and 178 assigned to SOC			and adverse events	
Holubar et al;[232] 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;[233] 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;[234] Finberg et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 25 assigned to favipiravir 3600 mg once folowed by 2000 mg 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;[235] 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	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	

	days and 119 assigned to SOC				
Hassaniazad et al;[236] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg for 5 days and 31 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Mean age 53.7 ± 13.5, male 57.1%, hypertension 27%, diabetes 20.6%, COPD 1.6%, CHD 14.2%, obesity 7.9%	Interferon beta 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.	
FLARE trial;[237] Lowe et al; preprint; 2021	Patients with recent onset mild COVID-19 infection. 59 assigned to favipiravir 3600 mg once followed by 1600 mg a day for 7 days and 60 assigned to SOC	Mean age 40 ± 12, male 51.2%, obesity 16.7%, any comorbidity 15%	Vaccinated 51.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Tabarsi et al;[238] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 30 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Median age 57, male 58.1%, hypertension 12.9%, diabetes 21%, COPD %, asthma 3.2%, CHD 14.5%, CKD 3.2%, therapy %, cancer 4.8%, obesity 3.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
AlQahtani et al;[239] peer reviewed; 2021	Patients with moderate COVID-19 infection. 54 assigned to favipiravir 1600 mg once followed by 1200 mg a day for 10 days and 52 assigned to SOC	Mean age 44, male 47.1%, diabetes 26.1%, COPD 7.6%, asthma %, CHD 1.3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Rahman et al;[240] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 25 assigned to favipiravir 1200 mg a day for 5 days and 25 assigned to SOC	Mean age 37.8 ± 10.7, male 66%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
McMahon et al;[241] preprint; 2022	Patients with mild to moderate COVID-19 infection. 95 assigned to favipiravir 1800 mg once followed by 1600 mg a day for 14 days and 95 assigned to SOC	Mean age 36, male 54.8%	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;[242] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to HCQ	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No

					information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕○○○ **Hospitalization:** No information

Fenofibrate

Fenofibrate may not increase severe adverse events. The effects of fenofibrate on other importan outcomes 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					
FERMIN trial;[243] Chirinos et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 350 assigned to fenofibrate 145 mg a day for 10 days and 351 assigned to SOC	Mean age 49 ± 16, male 53%, hypertension 27%, diabetes 15%, COPD 12%, CHD 7%,	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:** RR 0.76 (95%CI 0.53 to 1.08); RD -2.5% (95%CI -4.8% to

					0.8%); Low certainty ⊕⊕◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯

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;[244] 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

Fluvoxamine

Fluvoxamine probably does not have an important effect on hospitalizations and may not increase 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;[245] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 80 assigned to fluvoxamine incremental dose to 100 mg three times a day for 15 days and 72 assigned to standard of care	Median age 45.5 ± 20.5, male 28.2%, hypertension 19.7%, diabetes 11%, asthma 17.1%, obesity 56.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.81 (95%CI 0.54 to 1.22); RD -1.9% (95%CI -4.7% to 2.2%); Low certainty ⊕⊕○○ **Hospitalization:** RR 0.79 (95%CI 0.6 to 1.03); RD -1% (95%CI -1.9% to 0.1%); Moderate certainty ⊕⊕⊕○
TOGETHER-Fluvoxamine trial;[246] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 741 assigned to fluvoxamine 100 mg a day for 10 days and 756 assigned to SOC	Median age 50 ± 18, male 42.5%, hypertension 13.2%, diabetes 16.5%, COPD 0.6%, asthma 1.9%, CHD 1.1%, CKD 0.3%, obesity 0.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events Notes:	
Seo et al;[247] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 26 assigned to fluvoxamine 200 mg a day for 10 days and 26 assigned to SOC	Mean age 53, male 59.6%, hypertension 26.9%, diabetes 7.7%, COPD 3.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-OUT trial;[248] Bramante et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 334 assigned to fluvoxamine 100	Median age 44.5, male 45.8%, hypertension 26.9%, diabetes 1.1%, obesity 47.2%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 56.4%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	

	mg a day for 14 days and 327 assigned to SOC			adverse events	

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;[249] 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

Gabapentin +/- 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					
Soltani et al;[250] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 127 assigned to gabapentin +/- montelukast 900 mg a day +/- 10 mg a day for 5 days and 53 assigned to dextromethorphan	Mean age 56.7, male 56.1%, hypertension 22.2%, diabetes 16.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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

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;[251] Gaughan et al; preprint; 2021	Patients with severe COVID-19 infection. 20 assigned to GB0139	Mean age 65, male 56%, hypertension 39%, diabetes 17%, asthma	NR	High for mortality and mechanical ventilation; high for symptom	**Mortality:** Very low certainty ⊕◯◯◯

	(inhaled) and 21 assigned to SOC	14.6%, CHD 24.4%, CKD 7.3%, cancer 9.7%,		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:** Very low certainty ⊕○○○ **Hospitalization:** No information

Gimsilumab (Anti-GM-CSF Monoclonal Antibody)

Gimsilumab may not reduce mortality nor 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					
BREATHE trial;[252] Criner et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 113 assigned to gimsilumab 400 mg on day 1 and 200 mg on day 8 and 112 assigned to SOC	Mean age 60 ± 14, male 68.4%, hypertension 46.2%, diabetes 20.9%, COPD 7.6%, asthma %, CHD 8%, CKD %, cerebrovascular disease %, immunosuppresive therapy %, cancer %, obesity 26.7%	Corticosteroids 87.5%, remdesivir 50.6%, hydroxychloroquine 4%, ltocilizumab 7.6%, azithromycin 32.4%, convalescent plasma 0.4%;	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.02 (95%CI 0.67 to 1.56); RD 0.3% (95%CI -5.3% to 6%); Low certainty ⊕⊕○○ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR

					0.98 (95%CI 0.82 to 1.16); RD -1.2% (95%CI -10.9% to 9.7%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Helium (inhaled)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Shogenova et al;[253] 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;[254] 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;[255] Jarczak et al; preprint; 2021	Patients with critical COVID-19 infection. 12 assigned to hemadsorption and 12 assigned to SOC	Mean age 64.5 , male 75%, hypertension 66.6%, diabetes 33.3%, CHD 4%, CKD 25%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Hydroxychloroquine and chloroquine

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 not have an important effect on the risk of infection; and in patients with mild, recent onset disease, it may not have an important effect on hospitalizations. 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;[256] 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 1.09 (95%CI 1 to 1.19); RD 1.4% (95%CI 0% to 3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.08 (95%CI 0.93 to 1.25); RD 1.4% (95%CI -1.2% to 4.3%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.93 to 1.1); RD 0.6% (95%CI -4.2% to 6.1%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 0.87 (95%CI 0.65 to 1.15); RD -2.2% (95%CI -6.1% to 2.7%); Low certainty ⊕⊕◯◯ **Severe Adverse events:** RR 0.90 (95%CI 0.66 to 1.22); RD -1% (95%CI -3.5% to 2.2%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR
Huang et al;[257] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to chloroquine 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RECOVERY - Hydroxychloroquine trial;[258] 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;[259] Mitja et al; preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 1116 assigned to	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, coronary heart	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for	

	hydroxychloroquine 800 mg once followed by 400 mg x once a day for 6 days and 1198 assigned to standard of care	disease 13.3%, Nervous system disease 4.1%		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.	0.82 (95%CI 0.61 to 1.1); RD -0.9% (95%CI -1.9% to 0.5%); Low certainty ⊕⊕○○
COVID-19 PEP trial;[260] Boulware et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 414 assigned to hydroxychloroquine 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	Median age 40 ± 6.5, male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma 7.6%, comorbidities 27.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Significant loss of information that might have affected the study's results.	
Cavalcanti et al trial;[261] 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;[262] 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	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	

	and 151 assigned to standard of care			inappropriate.	
COVID-19 PET trial;[263] 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;[264] Mitja et al; preprint; 2020	Patients with mild COVID-19 infection. 136 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 6 days and 157 assigned to standard of care	Mean age 41.6 ± 12.6, male 49%, comorbidities 53.2%	NR	High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Tang et al; peer-reviewed;[265] 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;[266] 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;[267] 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;[268] preprint; 2020	Patients with mild to severe COVID-19 infection. 21 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg twice a day for 6 days and 12 assigned to standard of care	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
HC-nCoV trial;[269] 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;[270] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to hydroxychloroquine 400 mg twice on day	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

	one followed by 200 mg tablets twice daily for 15 days and 97 assigned to standard of care			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
COVID-19 PREP trial;[271] Rajasingham et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 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;[272] 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;[273] Grau-Pujol et al; preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 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;[274] Abella et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 64 assigned	Median age 33 ± 46, male 31%, hypertension 21%, diabetes 3%,	NR	Low for mortality and invasive mechanical ventilation; low for

	to hydroxychloroquine 600 mg a day for 8 weeks and 61 assigned to standard of care	asthma 17%		symptom resolution, infection, and adverse events
WHO SOLIDARITY;[275] Pan et al; Preprint; 2020	Patients with moderate to critical COVID-19 infection. 948 assigned to HCQ 800 mg once followed by 200 mg twice a day for 10 days and 900 assigned to SOC	Age range 50 – 69 43.5% years old, male 59.8%, diabetes 21.9%, COPD 6.9%, asthma 4.9%, CHD 14.1%	Steroids 20.9%, convalescent plasma 1.4%, Anti IL6 2.1%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.
Davoodi et al;[242] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
COVID-19 PEP (University of Washington) trial; Barnabas et al;[276] Abstract; 2020	Individuals exposed to SARS-CoV-2 infection. 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;[277] Self et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 242	Median age 58.5 ± 24.5, male 56%, hypertension 52.8%, diabetes 34.6%,	Corticosteroids 18.4%, remdesivir 21.7%, azithromycin 19%	Low for mortality and mechanical ventilation; low for symptom

	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	COPD 8.1%, asthma %, coronary heart disease %, chronic kidney disease 8.8%,		resolution, infection, and adverse events	
HAHPS trial;[278] 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;[279] Dubee et al; peer reviewed; 2020	Patients with mild to moderate COVID-19. 124 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 8 days and 123 assigned to standard of care	Median age 77 ± 28, male 48.4%, hypertension 53.4%, diabetes 17.3%, COPD 11.2%, cerebrovascular disease 17.3%, obesity 27.7%	Corticosteroids 9.6%, lopinavir-ritonavir 1.2%, azithromycin 8.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
Q-PROTECT trial;[280] 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;[281] 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;[282] Hernandez-Cardenas et al; Preprint; 2020	Patients with severe to critical COVID-19. 106 assigned to hydroxychloroquine 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;[283] Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to hydroxychloroquine 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;[284] peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to hydroxychloroquine 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;[285] peer reviewed; 2020	Patients with moderate to severe COVID-19. 33 assigned to hydroxychloroquine 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;[286] Amaravadi et al; preprint; 2020	Patients with mild COVID-19 infection. 17 assigned to hydroxychloroquine 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;[287] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to ivermectin 42 mg and 115 assigned to hydroxychloroquine 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;[288] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 432 assigned to hydroxychloroquine 400 mg once followed by 200 mg a day for 42 days and 619 assigned to SOC (vitamin C)	Mean age 33, male 100%, hypertension 1%, diabetes 0.3%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOGETHER trial;[289] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 214 assigned to hydroxychloroquine 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;[290] Réa-Neto et al; peer reviewed;	Patients with severe to critical COVID-19 infection. 53 assigned	Median age 53 ±, male 66.7%, hypertension 38.1%, diabetes 25.7%,	Corticosteroids 72.4%, azithromycin 89.5%	High for mortality and mechanical ventilation; high for symptom	

2021	to hydroxychloroquine 800 mg once followed by 400 mg a day for 5 days and 52 assigned to SOC	COPD 8.6%, immunosuppressive therapy 5.7%		resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
CHEER trial;[291] Syed et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 154 assigned to hydroxychloroquine 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;[292] Sivapalan et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 61 assigned to hydroxychloroquine + 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;[293] Byakika-Kibwika et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 55 assigned to hydroxychloroquine 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;[294] Schwartz et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 111 assigned to hydroxychloroquine 800 mg once followed	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	

	by 400 mg for 5 days and 37 assigned to SOC				
HERO-HCQ trial ;[295] Naggie et al ; preprint ; 2021	Individuals exposed to SARS-CoV-2 infection. 683 assigned to hydroxychloroquine 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;[296] peer reviewed; 2021	Patients with mild COVID-19 infection. 42 assigned to hydroxychloroquine + 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;[297] preprint; 2021	Patients with mild to severe COVID-19 infection. 31 assigned to hydroxychloroquine + 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;[230] 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 hydroxychloroquine 800 mg a day or	Mean age 42 ± 15.7, male 47.8%, obesity 24.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	Darunavir ritonavir 1200/200 mg a day + hydroxychloroquine 400 mg a day or favipiravil 6000 mg followed by 2400 mg + darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day for 7 to 14 days.				
SEV-COVID trial;[298] 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 600 mg 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;[299] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to hydroxychloroquine 800 once followed by 400 mg a day for 5 days or chloroquine 500 mg a day for 7 days and 50 assigned to SOC	Mean age 37.6, male 95.3%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
WHIP COVID-19 trial;[300] McKinnon et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 398 assigned to hydroxychloroquine 400 mg a week or 400 mg once followed by	Mean age 44.9 ± 11.9, male 42%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	200 mg a day and 200 assigned to SOC				
PHYDRA trial;[301] Rojas-Serrano et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 62 assigned to hydroxychloroquine 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	
EPICOS trial;[302] Polo et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 231 assigned to hydroxychloroquine 200 mg a day and 223 assigned to SOC	Mean age 38, male 38.5%, hypertension 5%, diabetes 0.8%, COPD 0%, asthma 6.4%, CHD 0.7%, cancer 0.6%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	
COPE – Coalition V trial;[303] Avezum et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 689 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 7 days and 683 assigned to SOC	Median age 45 ± 20, male 46.9%, hypertension 53.4%, diabetes 16.2%, asthma 13%, CHD 3.4%, obesity 54.8%	Azithromycin 19%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
AlQahtani et al;[239] peer reviewed; 2021	Patients with moderate COVID-19 infection. 51 assigned to HCQ 800 mg once followed by 400 mg a day for 10 days and 52 assigned to SOC	Mean age 44, male 47.1%, diabetes 26.1%, COPD 7.6%, asthma %, CHD 1.3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Omehecatl trial;[304] Roy-García et al; preprint; 2021	Patients with moderate COVID-19 infection. 61 assigned to HCQ 400 mg +/- AZT 500 mg a day for	Mean age 37 ± , male 48.9%, commorbidities 27.2%	NR; Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	5 days and 31 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Tirupakuzhi et al;[305] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 213 assigned to HCQ 800 mg once followed by 400 mg a week for 12 weeks and 203 assigned to SOC	Mean age 32.1 ± 9.2, male 52.6%, hypertension 1.2%, diabetes 2.4%, COPD 0%, asthma %, CHD 0%	Vaccinated 76.3%	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.	
IRICT trial;[306] Elshafie et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 97 assigned to HCQ 400 mg once followed by 200 mg a day for 5 days and 102 assigned to SOC	Mean age 60, male 54.3%, hypertension 40.7%, diabetes 30.1%, CKD 10.6%, obesity 20.6%	Corticosteroids 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Choudhary et al;[307] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 99 assigned to HCQ 1400 mg once followed by 600 mg a day for 5 days and 99 assigned to SOC	Mean age 43, male 48%, hypertension 24%, diabetes 3.5%, asthma 7.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
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;[308] preprint; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to hyperbaric oxygen two sessions a day for 4 days and 9 assigned to SOC	Median age 65.4 ± 7.8, male 60%, hypertension 72%, diabetes 60%, COPD %, asthma 8%, CHD 24%, cancer 4%, obesity 8%	Corticosteroids 92%, tocilizumab 24%, convalescent plasma 80%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Blinding and concealment are probably inappropriate.	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom resolution or improvement:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information
Cannellotto et al;[309] peer reviewed; 2021	Patients with severe COVID-19 infection. 20 assigned to hyperbaric oxygen 5 sesions (90 minutes duration each) and 20 assigned to SOC	Mean age 55.2 ± 9.2, male 65%, hypertension 32.5%, diabetes 17.5%, COPD 5%, asthma 5%, CHD %, CKD 5%, cancer 5%, obesity 35%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. The study was stopped early for benefit.	
COVID-19-HBO trial;[310] Kjellberg et al; preprint; 2021	Patients with severe COVID-19 infection. 15 assigned to hyperbaric oxygen 60 minutes at 2.4 ATA for up tp 5 sesions and 15 assigned to SOC	Mean age 64, male 56.6%	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.	

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;[311] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to C-IVIG 0.15-0.3 g/kg once and 10 assigned to SOC	Mean age 56.5 ± 13.1, male 70%, hypertension 52%, diabetes 36%, COPD 10%, CHD 8%	Corticosteroids 100%, remdesivir 94%, tocilizumab 6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information
Parikh et al;[312] preprint; 2021	Patients with moderate to severe COVID-19 infection. 30 assigned to C-IVIG 30 ml 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;[313] 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	
COVID-Compromise trial;[314] Huygens et al; preprint; 2021	Immunocompromised patients with moderate to severe COVID-19 infection. 10 assigned to C-IVIG 15 gr once and 8 assigned to IVIG	Median age 58, male 55.5%, immunocompromised 100%	Corticosteroids 77.7%; Vaccinated 72.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Hypertonic saline (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					
Delic et al;[106] peer reviewed; 2022	Patients with critical COVID-19 infection. 42 assigned to hypertonic saline (inhaled) twice a day and 52 assigned to SOC	Mean age 65.7 , male 68%, hypertension 60.6%, diabetes 30.9%, CHD 7.4%, cerebrovascular disease 2.1%	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.	**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

hzVSF-v13

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Prasenohadi et al;[315] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 43 assigned to hzVSF-v13 200 to 400 mg once followed by two	Mean age 50.8 ± , male 61.3%, obesity 22.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information

	infusions of 100 to 200 mg and 19 assigned to SOC				**Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Ibrutinib

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
iNSPIRE trial;[316] Coutre et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 22 assigned to ibrutinib 420 mg a day for 14 to 28 days and 24 assigned to SOC	Median age 51.5, male 70%, hypertension 39%, diabetes 43%, COPD 2%, asthma 9%, CHD 2%, CKD 4%, obesity 24%	Corticosteroids 63%, remdesivir 72%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic**

					infection (prophylaxis studies): No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** 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;[317] 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;[318] 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;[319] peer-reviewed; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1 800 mg IV with a maximum of seven doses and 15 assigned to standard of care	Mean age 60 ± 9, male 73%, hypertension 30%, diabetes 27%, obesity 20%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information

Imatinib

Imatinib may not increase severe adverse events. The effects of imatinib on other importan outcomes 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					
COUNTER-COVID trial;[320] 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;[321] 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;[322] 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. Its effects on other important outcomes 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					
Lopardo et al;[323] 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;[324] 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 or 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;[325] 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 0.99 (95%CI 0.75 to 1.31); RD -0.2% (95%CI -4% to 5%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.01 (95%CI 0.87 to 1.18); RD 0.2% (95%CI -2.2% to 3.1%); 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):** Very low certainty ⊕◯◯◯ **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:** Very low certainty ⊕◯◯◯
WHO SOLIDARITY trial;[275] Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 2144 assigned to interferon beta-1a three doses over six days of 44µg and 2147 assigned to SOC	Age range 50-69 years old 46.3%, male 62.3%, diabetes 25.2%, COPD 5.4%, asthma 4.3%, CHD 22%	Steroids 58.7%, convalescent plasma 2.4%, Anti IL6 3.6%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.	
COVIFERON trial;[326] 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;[327] 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;[328] 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;[329] 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	
Castro-Rodriguez et al;[330] preprint; 2022	Individuals exposed to SARS-CoV-2 infection. 607 assigned to interferon beta-1a 125µg three time and 565 assigned to SOC	Mean age 34 ± , male 47.3%, diabetes 3.9%, COPD 0.1%, asthma 5.6%, CHD 5.1%, CKD 0.3%, cancer 1.2%	Corticosteroids %, Vaccinated 23.2%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. Significant loss to follow-up.	

Monk P et al;[331] 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;[332] 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 ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
COVIFERON trial;[326] 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.	
UW 20-535 trial;[333] Tam et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 51 assigned to interferon beta-1b 16 million IU a day for 5 days and 49 assigned to SOC	Mean age 65, male 52.8%, hypertension 42.3%, diabetes 22.6%, COPD %, asthma 3.8%, CHD 9.4%, CKD 4.2%, cerebrovascular disease 2.4%, cancer 8.5%, obesity 4.7%	Corticosteroids 29.2%, 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.	

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;[334] Peer reviewed; 2021	Patients with moderate COVID-19 infection. 18 assigned	Mean age 63 ± 12, male 44%	NR	High for mortality and mechanical ventilation; High for symptom	**Mortality:** No information

	to interferon gamma 500000 IU a day for 5 days and 18 assigned to SOC			resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[335] 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

Interleukin-2

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
STRUCK trial;[143] Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to IL-2 1.5 million IU per day for seven days and 16 assigned to SOC	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD 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.	**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

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;[336] Chahla et al; Preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 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;[337] Figueroa et al; preprint; 2021	Individuals exposed to SARS-CoV-2 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.	

Isothymol

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

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

					evidence
RCT					
Ojeda et al;[338] preprint; 2022	Patients with moderate to critical COVID-19 infection. 300 assigned to isothymol 6 mg until discharge and 300 assigned to SOC	Mean age 54, male 48.8%, hypertension 60.6%, diabetes 13.2%, asthma 24%, CHD 10.8%, CKD 5%, obesity 16.8%	Corticosteroids 12.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Unbalanced baseline risk (16% of included patients in intervention on mechanical ventilation vs. 9% in placebo).	**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

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;[339] 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯

				study. Concealment of allocation is probably inappropriate.	**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 reduce mortality or improve time to symptom resolution. In patients with recent onset disease, ivermectin probably does not have an important effect on hospitalizations and may not increase severe adverse events. It is uncertain if it reduces symptomatic infections when used as prophylaxis.

Study; publication status	Patients and 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;[340] Shouman et al; peer-reviewed; 2020	Individuals exposed to SARS-CoV-2 infection. 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 1 (95%CI 0.8 to 1.24); RD -0% (95%CI -3.2% to 3.8%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.82 (95%CI 0.58 to 1.17); RD -3.1% (95%CI -7.3% to 2.9%); Very Low certainty ⊕◯◯◯
Chowdhury et al;[341] preprint; 2020	Patients with mild to moderate COVID-19. 60 assigned to	Mean age 33.9 ± 14.1, male 72.4%	NR	High for mortality and invasive mechanical ventilation; high for	

	ivermectin plus doxycycline 200 µgm/kg single dose + 100 mg BID for 10days and 56 assigned to hydroxychloroquine plus azithromycin			symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptom resolution or improvement:** RR 1.04 (95%CI 0.98 to 1.1); RD 2.4% (95%CI -1.2% to 6%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** RR 1.01 (95%CI 0.54 to 1.89); RD 0.2% (95%CI -8% to 15.5%); Very low certainty ⊕◯◯◯ **Adverse events:** RR 1.05 (95%CI 0.69 to 1.62); RD 0.5% (95%CI -3.2% to 6.3%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 0.90 (95%CI 0.74 to 1.1); RD -0.5% (95%CI -1.2% to 0.5%); Moderate certainty ⊕⊕⊕◯
Podder et al;[342] 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.	
Hashim et al;[343] 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;[344] 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);[345] preprint (now retracted);	Patients with mild to moderate COVID-19. 100 assigned to	Mean age 55.2 ± 19.8, male 69.5%, hypertension 11.5%,	NR	High for mortality and mechanical ventilation; high for symptom	

2020	ivermectin 400 μgm/kg once for 4 days and 100 assigned to hydroxychloroquine	diabetes 14.5%, COPD %, asthma 5.5%, coronary heart disease 4%, chronic kidney disease %		resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
[Elgazzar et al](#) (severe);[345] 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);[345] preprint (now retracted); 2020	Individuals exposed to SARS-CoV-2 infection. 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](#);[346] 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](#);[347] preprint; 2020	Patients with mild to severe COVID-19. 120 assigned to ivermectin	Median age 67 ± 22, male 50%	NR	Some concerns for mortality and mechanical ventilation;	

	200-800 microg/kg and 60 assigned to standard of care			Some concerns for symptom resolution, infection, and adverse events Notes: Concealment of allocation possibly inappropriate.	
Ahmed et al;[348] 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;[349] 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;[350] 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;[351] 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;[352] 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;[336] Chahla et al; Preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 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;[353] 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;[354] 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;[355] 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;[356] 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;[357] 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;[358] 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;[285] peer reviewed; 2021	Patients with moderate to severe COVID-19. 36 assigned to ivermectin 12–18 mg once and 37	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%,	Corticosteroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events	

	assigned to SOC	cerebrovascular disease 5.3%		Notes: Concealment of allocation probably inappropriate.
Lopez-Medina et al;[359] 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;[287] peer-reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to ivermectin 42 mg and 115 assigned to HCQ or CQ	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer 3%, obesity 37.5%	Corticosteroids 98%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events
Pott-Junior et al;[360] peer-reviewed (now retracted); 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;[361] 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;[288] peer-	Individuals exposed to	Mean age 33, male	NR	Low for mortality and

reviewed; 2021	SARS-CoV-2 infection. 617 assigned to ivermectin 12 mg once and 619 assigned to SOC (vitamin C)	100%, hypertension 1%, diabetes 0.3%		mechanical ventilation; 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;[362] 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;[363] peer-reviewed; 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;[364] 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;[365] peer reviewed; 2021	Patients with mild COVID-19 infection.	Mean age 42.5 ± 15.5, male 52.7%,	NR	Low for mortality and mechanical ventilation;	

	250 assigned to ivermectin 24-36 mg and 251 assigned to SOC	hypertension 23.8%, diabetes 9.6%, COPD 2.8%, asthma 7.2%, CHD 1.8%, cancer 1.2%		low for symptom resolution, infection, and adverse events
COVER trial;[366] 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;[367] 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;[368] 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.
TOGHETER trial;[369] Reis et al; peer reviewed; 2021	Patients with recent onset mild COVID-19 infection. 679 assigned to ivermectin 400 μg/kg once a day for 3 days and 679 assigned to SOC	Median age 49, male 41.8%, hypertension 8.4%, diabetes 12.9%, COPD 3%, asthma 8.4%, CHD 1.8%, CKD 0.5%, obesity 49.7%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

SILVERBULLET trial;[370] De la Rocha et al; preprint; 2021	Patients with mild COVID-19 infection. 33 assigned to ivermectin and 33 assigned to soc	Mean age 38.5 ± 14.6, male 27.3%, hypertension 8.9%, diabetes 5.3%, CHD 7.1%, CKD 1.8%, obesity 19.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Cruz Arteaga et al; NCT04673214; other; 2021	Patients with mild COVID-19 infection. 65 assigned to ivermectin adjusted to body weight and 46 assigned to SOC	Age (18 – 65 years old) 96.4% , male 47.7%,	NR	NA	
ACTIV-6 trial;[371] Naggie et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 817 assigned to ivermectin 400 µg/kg for three days and 774 assigned to SOC	Median age 47, male 46.6%, diabetes 11.8%, COPD 3.65%, asthma 15.5%, CHD 4.5%, CKD 0.77%, cancer 3.02%, obesity 40.8%	Remdesivir 0.3%, Vaccinated 48.8%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Rezai_Mild trial;[372] Rezai et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 268 assigned to ivermectin 0.4 mg/kg a day for 3 days and 281 assigned to SOC	Mean age 35.4 ± 17.4, male 53.4%, hypertension 7.8%, diabetes 7.3%, asthma 2.4%, CHD 2.7%, cancer 0.6%, obesity 21.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Rezai_Severe trial;[372] Rezai et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 311 assigned to ivermectin 0.4 mg/kg a day for 3 days and 298 assigned to SOC	Mean age 53.8, male 47.8%, hypertension 28.4%, diabetes 31.7%, COPD %, asthma 3%, CHD 12.2%, obesity 73.3%	Corticosteroids 90.7%, remdesivir 98.2%, hydroxychloroquine 35%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	
Angkasekwinai treatement trial;[373] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 233 assigned to ivermectin 400–600 µg/kg/d and 214 assigned to SOC	Mean age 39.5 ± 12.1, male 43.2%, hypertension 11.2%, diabetes 6.9%, COPD 0.2%, CHD 1.8%, CKD 0.4%, cerebrovascular disease 0.2%, cancer	Vaccinated 74.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	

		0.2%,			
Angkasekwinai prevention trial;[373] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 259 assigned to ivermectin 400–600 µg/kg/d and 277 assigned to SOC	Mean age 37.6 ± 12, male 42.2%, hypertension 8.8%, diabetes 4.7%, COPD 0.2%, CHD 1.1%, cerebrovascular disease 0.4%, cancer 1.3%	Vaccinated 84.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Mirahmadizadeh et al;[374] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 261 assigned to ivermectin 12 to 24 mg once and 130 assigned to SOC	Mean age 39.3, male 53.9%, hypertension 6.1%, diabetes 3.8%, COPD 0.8%, CHD 0.8%, CKD 0.5%, cancer 0.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
George et al;[375] peer reviewed; 2022	Patients with hematological disorders and mild to moderate COVID-19 infection. 73 assigned to ivermectin 12 to 24 mg once and 39 assigned to SOC	Mean age 41.2 ± , male 70.5%, cancer 75.9%	Corticosteroids 62.5%, remdesivir 18.7%	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.	
PLATCOV - Iver trial;[376] Schilling et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 45 assigned to ivermectin 600µg/kg daily for seven days and 41 assigned to SOC	Mean age 28, male 45.5%	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.	
IRICT trial;[306] Elshafie et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 104 assigned to ivermectin 36 mg on days 1, 3 and 6 and	Mean age 59.4 ± , male 53.4%, hypertension 38.3%, diabetes 27.7%, CKD 9.2%, obesity 19.9%	Corticosteroids 100%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

	102 assigned to SOC				
Nimitvilai et al;[377] peer reviewed; 2022	Patients with mild COVID-19 infection. 57 assigned to ivermectin 0.6 mg/kg for 3 days and 56 assigned to HCQ 200 mg a day + darunavir/ritonavir 400/100 mg a day for 5 days	Mean age 40, male 45.1%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-OUT trial;[248] Bramante et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 410 assigned to Ivermectin 390 to 470 µg/kg a day for 3 days and 398 assigned to SOC	Median age 45.5, male 45.3%, hypertension 22.8%, diabetes 1.6%, obesity 47.4%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; vaccinated 55.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Ivermectin (inhaled)

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Aref et al;[378] 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;[379] 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
Gharebaghi et al;[380] 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.	**Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Tabarsi et al;[381] peer-reviewed; 2020	Patients with severe COVID-19. 52 assigned to IVIG 400 mg/kg daily for three doses and 32 assigned to standard of care	Mean age 53 ± 13, male 77.4%, hypertension 20.2%, diabetes 21.4%, COPD 1.2%, asthma %, coronary heart disease %, chronic kidney disease 4.7%, cancer 1.2%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Raman et al;[382] 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.	

Ixekizumab

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
STRUCK trial;[143] Pimenta Bonifácio et al; preprint; 2021	Patients with severe to critical COVID-19 infection. 16 assigned to ixekizumab 80 mg once and 16 assigned to SOC	Mean age 48.9 ± 12.2, male 61.7%, hypertension 45%, diabetes 21.7%, COPD 6.7%, CHD 5%	NR	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:** No information **Symptom**

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

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;[383] 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;[384] 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;[385] 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;[386] peer reviewed; 2021	Patients with mild to moderate COVID-19	Mean age 48.6, male 60.3%	NR	High for mortality and mechanical ventilation;	**Mortality:** No information

	infection. 36 assigned to lactoferrin 200 to 400 mg a day and 18 assigned to SOC			high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[387] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50 mg every 12 h (three doses) followed by 20 mg a day for 10 days and 5 assigned to standard of care	Mean age 52.5 ± 11.5, male 30%, hypertension 60%, chronic lung disease 10%	Umifenovir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

Wang et al;[388] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day followed by 20 mg a day for 8 days and 24 assigned to standard of care	Median age 55.7 ± 21.5, male 50%, hypertension 27.2%, diabetes 4.5%, chronic lung disease 4.5%, coronary heart disease 2.3%, cancer 2.3%	Corticosteroids 34.1%, hydroxychloroquine 56.8%, lopinavir-ritonavir 11.4%, umifenovir 75%, IVIG 20.4%, ATB 63.6%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Lenzilumab

Lenzilumab may reduce mechanical ventilation requirements and may not increase severe adverse events. The effects of lenzilumab on other importan outcomes 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					
LIVE-AIR trial;[389] 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%); Very 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;[390] Preprint; 2020	Patients with mild to moderate COVID-19. 25 assigned to levamisole 150 mg a day for 3 days and 25 assigned to SOC	Mean age 36.6 ± 13.7, male 60%,	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** **Mortality:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Asgardoon et al;[391] 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.	

					Hospitalization: Very low certainty ⊕○○○ **Hospitalization:** No information

Levilimab

Levilimab may improve time to symptom resolution; however, the certainty of the evidence was low. The effects of levilimab on other important outcomes 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					
CORONA trial;[392] Lomakin et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 103 assigned to levilimab 364 mg 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;[393] 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;[394] 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**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care**

	analyzed				and GRADE certainty of the evidence
RCT					
Guvenmez et al;[74] 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

Lithium

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Spuch et al;[395] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 15 assigned to lithium 400 mg a day and 15 assigned to	Mean age 58.6, male 56.7%, hypertension 30%, diabetes 3.3%, COPD %, CHD 6.7%, obesity 16.7%	Corticosteroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No

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

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;[396] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to lopinavir-ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Corticosteroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.11); RD 0.2% (95%CI -1.3% to 1.8%); Moderate certainty ⊕⊕⊕○ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕
ELACOI trial;[397] Li	Patients with	Mean age 49.4 ± 14.7,	Corticosteroids 12.5%,	Low for mortality and	

et al; peer-reviewed; 2020	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	male 41.7%	intravenous immunoglobulin 6.3%	invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**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 ⊕◯◯◯
RECOVERY - Lopinavir-ritonavir trial;[398] 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;[257] 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;[399] 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-	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	

	ritonavir 40 mg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-ritonavir			study. Concealment of allocation is probably inappropriate.	
Chen et al; preprint;[400] 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;[275] Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 1404 assigned to lopinavir-ritonavir 200/50MG twice a day for 14 days and 1368 assigned to SOC	Age range 50-69 years old 43.1%, male 59.6%, diabetes 24.2%, COPD 6.5%, asthma 4.9%, CHD 21%	Steroids 27.2%, convalescent plasma 1.4%, anti IL6 3%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.	
Sali et al;[401] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to sofosbuvir 400 mg a day and 32 assigned to lopinavir-ritonavir 400/100 mg every 12 hours	Mean age 56.5 ± 14, male 53.7%, diabetes 33%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Purwati et al;[402] Peer reviewed; 2020	Patients with mild to moderate COVID-19.	Median age 36.5 ± NR, male 95.3%	NR	High for mortality and mechanical ventilation;	

	128 assigned to lopinavir-ritonavir 500/100 a day, 123 assigned to HCQ 200 mg a day and 119 to SOC			High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
Kasgari et al;[403] 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;[404] 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;[289] Reis et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 244 assigned to lopinavir-ritonavir 1600 mg/400 mg once followed by 800 mg/200 mg a day for 9 days and 227 assigned to SOC	Mean age 53 ± 76, male 45%, hypertension 49.3%, diabetes 19.4%, COPD 2.5%, asthma 8.6%, CHD 3.9%, CKD 0.7%, cancer 1.2%, obesity 34.2%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
COPEP trial;[405] Labhardt et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 209 assigned	Median age 39 ± 22, male 50.6%, hypertension 8.2%,	NR	Low for mortality and mechanical ventilation; high for symptom	

	to lopinavir-ritonavir 400/10 mg a day for 5 days and 109 assigned to SOC	diabetes 3.1%, COPD 7.8%, CHD 2.5%, cancer 0.6%		resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Ghanei et al;[81] peer reviewed; 2021	Patients with severe COVID-19 infection. 110 assigned to lopinavir-ritonavir 200/50 mg twice a day for 7 days and 110 assigned to azithromycin 500 mg once followed by 250 mg 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;[230] 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 800 mg a day or darunavir ritonavir 1200/200 mg a day + HCQ 400 mg a day or favipiravil 6000 mg followed by 2400 mg + darunavir ritonavir 1200/200 mg a day + HCQ 400 mg 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;[298] Panda et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 24 assigned to	Mean age 49.1, male 75%, hypertension 32.7%, diabetes 27.7%, COPD 7.9%, asthma %,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and	

	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	CHD 11.9%, cancer 1%		adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Nekoukar et al;[66] peer reviewed; 2021	Patients with severe COVID-19 infection. 62 assigned to atazanavir/ritonavir 300/100 mg a day for 5 to 10 days and 62 assigned to lopinavir-ritonavir 200/50 mg a day for 5 to 10 days	Mean age 49.9 ± 12.6, male 55.6%, hypertension 16.9%, diabetes 27.4%, COPD 0.8%, asthma 1.6%	Corticosteroids 42.7%, remdesivir 13.7%, tocilizumab 3.2%, azithromycin 50.8%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Hassaniazad et al;[236] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg for 5 days and 31 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Mean age 53.7 ± 13.5, male 57.1%, hypertension 27%, diabetes 20.6%, COPD 1.6%, CHD 14.2%, obesity 7.9%	Interferon beta 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.
FLARE trial;[237] Lowe et al; preprint; 2021	Patients with mild recento onset COVID-19 infection. 60 assigned to lopinavir-ritonavir 800/200 mg a day for 7 days and 60 assigned to SOC	Mean age 40 ± 12, male 51.2%, obesity 16.7%, any comorbidity 15%	Vaccinated 51.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

Tabarsi et al;[238] peer reviewed; 2021	Patients with severe COVID-19 infection. 32 assigned to favipiravir 3200 mg once followed by 1200 mg a day for 7 days and 30 assigned to lopinavir-ritonavir 400/100 mg a day for 7 days	Median age 57, male 58.1%, hypertension 12.9%, diabetes 21%, COPD %, asthma 3.2%, CHD 14.5%, CKD 3.2%, therapy %, cancer 4.8%, obesity 3.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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;[406] 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 ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No
WINCOVID trial;[407] Ganesan et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 34 assigned to low-dose radiation therapy 0.5 Gy single session and 17 assigned to SOC	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 Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
IMpaCt-RT trial;[408] Singh et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 7 assigned to low-dose radiation therapy 0.7 Gy and 6 assigned to SOC	Median age 56 ± , male 53.8%	Corticosteroids 100%, remdesivir 46.1%, 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.	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](); [409] 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;[410] 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):** Very low certainty ⊕○○○ **Adverse events:** No information **Hospitalization:** No information
Davoodian et al;[411] 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;[412] 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;[413] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 48 assigned to melatonin 3 mg a day	Mean age 52.9, male 44.8%, hypertension 30.2%, diabetes 28.1%, COPD 3.1%, asthma 5.2%, CHD 15.6%,	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	

	for 10 days and 48 assigned to SOC	CKD 5.2%,		Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Hasan et al;[414] peer reviewed; 2021	Patients with severe COVID-19 infection. 82 assigned to melatonin 10 mg 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.
MeCOVID trial;[415] García-García et al; peer reviewed; 2021	Healthcare workers exposed to SARS-COV-2. 151 assigned to melatonin 2 mg a day for 12 weeks and 163 assigned to SOC	Median age 40, male 18.8%, hypertension 3.2%, CHD 0.3%, cancer 2.5%, obesity 0.3%	NR	Some Concerns for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Significant loss to follow up.
Alizadeh et al;[416] peer reviewed; 2021	Patients with critical COVID-19 infection. 33 assigned to melatonin 21 mg a day and 34 assigned to SOC	Mean age 63.5, male 64%	NR	Some Concerns for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.
Fogleman C et al trial;[417] ; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 32 assigned to melatonin 10 mg a day for 14 days and 34	Median age 52, male 44.9%, hypertension 26.5%, diabetes 16.3%	Vaccinated 2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

	assigned to SOC				

Mefenamic 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					
MEFECOVID-19 trial;[418] 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;[419] 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 0.6 (95%CI 0.41 to 0.86); RD -6.4% (95%CI -9.4% to -2.2%); 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
Shi et al;[420] 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;[421] preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell 100±20 ×106 UC-MSC twice and 12 assigned to standard of care	Mean age 58.7 ± 17.5, male 54.1%, hypertension 66.7%, diabetes 45.8%, coronary heart disease 12.5%, , cancer 4.2%, obesity 66.6%	Corticosteroids 90.4%, remdesivir 66.7%, hydroxychloroquine 12.5%, tocilizumab 20.8%, convalescent plasma 29.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Concealment of allocation probably inappropriate.	
Dilogo et al;[422] 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;[423] peer reviewed; 2021	Patients with severe COVID-19 infection.	Median age 65, male 37.9%, hypertension	Corticosteroids 67.2%	High for mortality and mechanical ventilation;	

	29 assigned to mesenchymal stem cell 1 × 106 cells per kilogram body weight, once and 29 assigned to SOC	25.8%, diabetes 13.8%, COPD 1.7%, CHD 10.3%, cerebrovascular disease 8.6%		high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Fathi-Kazerooni et al;[424] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 14 assigned to mesenchymal stem cell 5 ml a day for 5 days and 15 assigned to SOC	Mean age 50 ± , male 65.5%, hypertension 31%, diabetes 24.1%	Corticosteroids 100%, remdesivir 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Rebelatto et al;[425] peer reviewed; 2021	Patients with critical COVID-19 infection. 11 assigned to mesenchymal stem cell three doses of 5 × 105 cells/kg UC-MSCs and 6 assigned to SOC	Mean age 56, male 70.5%, hypertension 52.9%, diabetes 41.2%, COPD 5.9%, CKD 5.9%, obesity 52.9%		Some Concerns for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
DW-MSC trial;[426] Karyana et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 6 assigned to mesenchymal stem cell 5.0×10^7 cells to 1.0×10^8 cells and 3 assigned to SOC	Age range 31 to 47, male 66.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
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;[427] Reis et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 215 assigned to MTF 1500 mg 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 0.92 (95%CI 0.61 to 1.37); RD -0.4% (95%CI -1.9% to 1.8%); Low certainty ⊕⊕○○
DMMETCOV19-2 trial;[428] Ventura-López et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 10 assigned to metformin 1240 mg a day for 14 days and 10 assigned to SOC	Mean age 47.5, male 85%, hypertension 20%, diabetes 20%, COPD 10%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
COVID-OUT trial;[248] Bramante et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 663 assigned to metformin 1500 mg a day for 14 days and 398 assigned to SOC	Median age 45.5, male 44%, hypertension 26.7%, diabetes 2%, obesity 48.8%	Corticosteroids 1.5%, monoclonal antibodies 4.2%; Vaccinated 52.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Methylene blue

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hamidi-Alamdari et al;[429] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to methylene blue	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,	**Mortality:** No information **Invasive mechanical**

	1 mg/kg every 12 to 8 h for 14 days and 40 assigned to SOC			and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**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;[430] 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

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

Study; publication status	Patients and 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;[431] 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;[432] peer reviewed; 2021	Patients with moderate COVID-19 infection. 20 assigned to metronidazole 1 g 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 reduces hospitalizations in patients with recent onset mild to moderate disease and may improve symptom resolution. 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;[433] 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 0.35 (95%CI 0.06 to 2.19); RD -1.4% (95%CI - 15% to 19.4%); Very low certainty ⊕○○○ **Invasive mechanical ventilation:** RR 0.36 (95%CI 0.11 to 1.12); RD -11.1% (95%CI - 15.4% to -2.1%); Very low certainty ⊕○○○ **Symptom resolution or improvement:** RR 1.17 (95%CI 1.1 to 1.3); RD 10.3% (95%CI 3.6% to - 18.2%); Low certainty ⊕⊕○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.75 (95%CI 0.48 to 1.19); RD -2.6% (95%CI -5.3% to - 1.9%); Low certainty ⊕⊕○○ **Hospitalization:** RR 0.6 (95%CI 0.44 to 0.81); RD -1.9% (95%CI -2.7% to - 0.9%); High certainty ⊕⊕⊕⊕
AGILE trial;[434] Khoo et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 12 assigned to molnupiravir 600-1600 mg a day and 6 assigned to SOC	Median age 56 ± 58, male 27.8%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Fischer et al;[435] 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;[436] Bernal et al; 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	
CR216-21 trial;[437] Tippabhotla et al; preprint; 2021	Patients with mild COVID-19 infection. 610 assigned to	Mean age 36.5 ± 11, male 61.6%	NR	High for mortality and mechanical ventilation; high for symptom	

	molnupiravir 800 mg a day for 5 days and 610 assigned to SOC			resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Zou et al;[438] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 76 assigned to molnupiravir 1600 mg a day for 5 days and 31 assigned to SOC	Median age 39.8 ± , male 55.5%	Vaccinated 91.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
AGILE trial;[439] Khoo et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 90 assigned to molnupiravir 1600 mg a day for 5 days and 90 assigned to SOC	Mean age 42.5 ± , male 42.8%	Vaccinated 50%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
MOVe-IN trial;[440] Ariibas et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 226 assigned to molnupiravir 400 to 1600 mg a day for 5 days and 78 assigned to SOC	Mean age 57, male 66.6%	Corticosteroids 67.1%, remdesivir 23.7%; Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
MOVe-OUT - ph2 trial;[441] Caraco et al; peer reviewed; 2022	Patients with mild COVID-19 infection. 228 assigned to molnupiravir 400 to 1600 mg a day for 5 days and 74 assigned to SOC	Mean age 52.6, male 49.2%, diabetes 16.6%, COPD 3.6%, asthma %, CHD 8.3%, CKD 2.3%, immunosuppression 0%, cancer 1%, obesity 48.7%	Corticosteroids %, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated %	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events Notes:

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;[442] peer reviewed; 2021	Patients with moderate COVID-19 infection. 120 assigned to montelukast 10 to 20 mg a day and 60 assigned to SOC	Mean age 54.6 ± 15.3, male 42.2%, hypertension 30%, diabetes 19%, asthma 1.7%, CHD 1.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**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

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;[443] 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 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
GARGLES trial;[444] Mohamed et al; preprint; 2020	Patients with COVID-19. 10 assigned to mouthwash with povidone iodine or essential oils 3 times a day and 10 assigned to mouthwash with water or no mouthwash	Median age 28.9, male 80%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
KILLER trial;[445] 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;[446] 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;[447] 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;[448] Carrouel et al; preprint; 2021	Patients with mild COVID-19 infection. 76 assigned to mouthwash with ß-cyclodextrin-citrox three times a day and 78 assigned to SOC	Mean age 43.8 ± 15.5, male 45.7%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection, and adverse events	
Huang et al;[449] 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;[450] 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;[451] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 63 assigned to mouthwash with hydrogen peroxide 1%	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	

	three time a day and nasal wash with hydrogen peroxide 0.5% and 43 assigned to SOC			Notes: Significant number of patients excluded post-randomization resulting in potential inbalances in baseline risks
ACPREGCOV trial;[452] Damião Costa et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to mouthwash 15 mL of 0.12% chlorhexidine gluconate and 50 assigned to SOC	Mean age 39 ± 12, male 50%, hypertension 17%, diabetes 4%, obesity 25%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
BUCOSARS trial;[453] 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;[454] 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.
Alemany et al;[455] peer reviewed; 2022	Patients with mild COVID-19 infection. 60 assigned to mouthwash with 0.07% cetylpyridinium and 58 assigned to SOC	Mean age 46, male 41.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:

Barrueco et al;[456] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 35 assigned to mouthwash with povidone-iodine 2%, hydrogen peroxide 1%, cetylpyridinium chloride 0.07% or chlorhexidine 0.12% and 10 assigned to SOC	Mean age 62.4 ± , male 54.5%,	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Mupadolimab

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

Study; publication status	Patients and interventions 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;[457] 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;[458] 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;[459] peer-reviewed; 2020	Patients with severe COVID-19. 68	Mean age 58.5 ± 22.5, male 59.2%,	NR	Low for mortality and invasive mechanical	**Mortality:** Very low certainty ⊕◯◯◯

	assigned to NAC 21 g once and 67 assigned to standard of care	hypertension 46.6%, diabetes 37.7%, cancer 12.6%,		ventilation; low for symptom resolution, infection, and adverse events	**Invasive mechanical ventilation:** Very low certainty ⊕○○○ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information
Gaynitdinova et al;[460] 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;[461] 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.	

N-acetylcysteine (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					
Delic et al;[106] peer reviewed; 2022	Patients with critical COVID-19 infection. 39 assigned to N-acetylcysteine (inhaled) twice a day and 52 assigned to SOC	Mean age 68.3 ± , male 74.8%, hypertension 61.5%, diabetes 27.5%, COPD %, asthma %, CHD 7.7%, CKD %, cerebrovascular disease 4.4%	Corticosteroids 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:** No information **Symptom**

				allocation probably inappropriate.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

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;[462] 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%	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;[311] Fisher et al; preprint; 2021	Patients with moderate to critical COVID-19 infection. 55 assigned to namilumab and 54 assigned to SOC	Median age 62.8 ± 18, male 68.5%	Corticosteroids 90.7%, remdesivir 53.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information

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;[463] peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 20 assigned to nano-curcumin 160 mg 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;[464] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 14 assigned to nasal	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%,	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** No information

	hypertonic saline 250 cc twice daily, 14 assigned to nasal hypertonic saline plus surfactant and 17 assigned to standard of care	diabetes 6.6%, chronic lung disease 15.5%, coronary heart disease 4.4%,		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:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information
Yildiz et al;[465] 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;[466] peer reviewed; 2021	Patients with mild COVID-19 infection. 20 assigned to nasal hypertonic saline (Caclium rich hypertonic salts) and 20 assigned to SOC	Age range 22-45		Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Baxter et al;[467] 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	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care

	analyzed				and GRADE certainty of the evidence
RCT					
Nesari et al;[468] other; 2021	Individuals exposed to SARS-CoV-2 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;[469] 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	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	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** Very low certainty

	assigned to SOC			Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	⊕○○○ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** Very low certainty ⊕○○○
Cairns et al;[470] peer reviewed; 2021	Patients with mild COVID-19 infection. 33 assigned to niclosamide 2 g 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	

Nicotine patches

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Labro et al;[471] peer reviewed; 2022	Patients with critical COVID-19 infection. 106 assigned to nicotine patches 14 mg a day for a maximum of 30 days and 112 assigned to SOC	Mean age 61, male 69.7%, hypertension 58.7%, diabetes 41.4%, COPD 3.2%, cerebrovascular disease 8.3%, immunosuppresion 6%,	Corticosteroids 64.5%, tocilizumab 0.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.02 (95%CI 0.67 to 1.57); RD 0.3% (95%CI -5.2% to 5.7%); 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

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;[472] 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
Koshak et al;[473] 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.	

					Hospitalization: Very low certainty ⊕○○○

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;[474] 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;[475] 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):** Very low certainty ⊕◯◯◯ **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** Very low certainty ⊕◯◯◯
Fontanesi et al;[476] 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;[477] 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;[478] 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;[479] 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.
Medhat et al;[480] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 77 assigned to nitazoxanide 2000 mg a day for 14 days and 73 assigned to SOC	Mean age 45, male 45.3%, hypertension 21.3%, diabetes 19.3%	Corticosteroids 44%, hydroxychloroquine 7.3%	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.
COVER HCW trial;[481] Sokhela et al; peer reviewed; 2022	Patients with exposed to COVID-19 infection. 280 assigned to nitazoxanide 1000 mg a day for 1 week followed by 2000 mg a day for 24 weeks and 283 assigned to SOC	Median age 24, male 51.9%, hypertension 8.2%, diabetes 1.1%, COPD 2.2%	Vaccinated 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. Significant loss to follow-up.	

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;[482] preprint; 2021	Patients with severe COVID-19 infection. 14 assigned to inhaled nitric oxide (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:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information
Winchester et al;[483] 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.	
NO COV-ED trial;[484] Strickland et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 19 assigned to inhaled nitric oxide (iNO) 5 liters per minute and 15	Mean age 41, male 53.2%, hypertension 12.8%, diabetes 6.4%, COPD 14.9%, CHD 2.1%, immunosuppression	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	assigned to SOC	4.3%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Tandon et al;[485] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 64 assigned to nitric oxide nasal spray (NONS) 0.45 mL/dose six times a day for 8 days and 69 assigned to SOC	Mean age 37.8, male 64.4%, any commorbidities 12.1%	Vaccinated 46.1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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;[486] 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;[487] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 54 received NSAID and 1168 received alternative treatment schemes	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%, coronary heart disease 22.3%, chronic kidney disease 38.7%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function).	**Mortality:** OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕○○○
Jeong et al;[488] 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;[489] 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;[490] 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;[491] preprint; 2020	Individuals exposed to SARS-CoV-2 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;[492] peer-reviewed; 2020	Patients with moderate to critical	Mean age 61 ± 16.3, male 53.8%,	NR	High for mortality

	COVID-19 infection. 466 received NSAID and 839 received alternative treatment schemes	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%,		Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified).	
Esba et al;[493] 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).	

Norelgestromin and Ethinylestradiol

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cortés-Algara et al;[494] peer reviewed; 2021	Patients with moderate COVID-19 infection. 30 assigned to norelgestromin and ethinylestradiol 6 mg/ 0.6 mg and 14 assigned	Mean age 58.6 , male 38.6%, hypertension 29.5%, diabetes 34.1%, obesity 6.8%	Corticosteroids 65.9%, hydroxychloroquine 65.9%, azithromycin 93.2%, vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information

	to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Novaferon

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zheng et al;[399] 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;[495] 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;[496] 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;[497] 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;[498] Arnardottir et al; preprint; 2021	Patients with moderate to severe COVID-19 infection. 10 assigned to omega-3 10 g 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.	

OP-101

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PRANA trial;[499] Gusdon et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 17 assigned to OP-101 2 to 8 mg/kg once and 7 assigned to SOC	Median age 61, male 70.8%, hypertension 45.8%, diabetes 58.3%	Corticosteroids 100%, remdesivir 75%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** No information

Opaganib

Opaganib may not reduce mortality or mechanical ventilation; it may not increase severe adverse events but it may increase symptom resolution or improvement. Further research is needed.

Study; publication status	Patients and 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;[500] Winthrop et al;	Patients with moderate to severe	Median age 58 ± 29.8, male 64.3%	Corticosteroids 92.8%, remdesivir 45.2%	Low for mortality and mechanical ventilation;	**Mortality:** RR 0.94 (95%CI 0.66 to 1.34);

peer-reviewed; 2021	COVID-19 infection. 22 assigned to opaganib 1000 mg a day for 14 days and 18 assigned to SOC			low for symptom resolution, infection, and adverse events	RD -0.9% (95%CI -5.5% to -5.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.68 to 1.24); RD -1% (95%CI -5.5% to -4.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.1 (95%CI 0.95 to 1.27); RD 6% (95%CI -3% to -16.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.96 (95%CI 0.69 to 1.34); RD -0.4% (95%CI -3.2% to -3.5%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
Carvalho Neuenschwander et al;[501] preprint; 2022	Patients with severe COVID-19 infection. 230 assigned to opaganib 500 mg a day for 14 days and 233 assigned to SOC	Mean age 56.5, male 65.4%, diabetes 35%	Corticosteroids 94.2%, remdesivir 17.3%, convalescent plasma 1.7%; Vaccinated 0.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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

Ozone

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
PROBIOZOVID trial;[503] 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;[504] 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 or prophylactic dose anticoagulants may not reduce mortality, may not improve time to symptom resolution, and may 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					
ACTIV-4a trial;[505] Berger et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 293 assigned to P2Y12 inhibitors (ticagrelor 120 mg 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 1.02 (95%CI 0.64 to 1.62); RD 0.3% (95%CI -5.7% to 9.9%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **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
REMAP-CAP - P2Y12 trial;[65]	Patients with severe to critical COVID-19	Median age 57, male 67.2%, hypertension %,	Corticosteroids 97.4%, remdesivir 22%,	Low for mortality and mechanical ventilation;	

Bradbury et al; peer reviewed; 2021	infection. 455 assigned to P2Y12 inhibitors clopidogrel 75 mg a day or ticagrelor 120 mg a day or prsugrel 60 mg once followed by 5 to 10 mg a day for 14 days and 529 assigned to SOC	diabetes 39.3%, CHD 5.1%, CKD 3.9%	tocilizumab 43.7%	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 3.1 (95%CI 1.32 to 7.29); RD 21.4% (95%CI -3.3% to 64.2%); 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;[506] 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
Bushan et al;[507] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 119 assigned to Peg Interferon Alfa 1 µg/kg subcutaneous [SC] injection once	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	

	and 123 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Adverse events:** No information **Hospitalization:** No information

Peg-interferon (IFN) lamda

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ILIAD trial;[508] 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;[509] 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.	

Pembrolizumab

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COPERNICO trial;[510] Sanchez-Conde et al; preprint; 2021	Patients with severe COVID-19 infection. 7 assigned to pembrolizumab 200 mg on days 1 and 21 and 5 assigned to SOC	Mean age 68, male 75%	Corticosteroids 100%, remdesivir 33%	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

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;[511] 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;[512] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 40 assigned to pentoxifylline 1200 mg 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;[513] 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;[514] 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;[515] 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 ⊕○○○

Potassium canrenoate

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
SpiroCOVID19 trial;[516] Karolak et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 24 assigned to potassium canrenoate 400 mg a day for 7 days and 25 assigned to SOC	Mean age 62, male 53.1%, hypertension 63.2%, diabetes 28.6%, COPD %, asthma %, CHD 14.2%, cerebrovascular disease 2%	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:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Povidone iodine spray

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

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

Seet et al;[288] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 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 increase symptom resolution or improvement. 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;[517] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom**

				inappropriate.	**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;[518] 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;[519] Wischmeyer et al; peer reviewed; 2022	Individuals exposed to SARS-CoV-2 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;[520] 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	
Saviano et al;[521] peer reviewed; 2022	Patients with severe COVID-19 infection. 40 assigned to probiotics (*Bifidobacterium lactis* LA 304, *Lactobacillus salivarius* LA 302)and *Lactobacillus acidophilus* LA 201) twice a day for 10 days and 40 assigned to SOC	Mean age 59.6, male 55%, hypertension 38.7%, diabetes 17.5%, COPD 8.7%	Corticosteroids 100%; vaccinated 18.7%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Progesterone

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

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

	analyzed				**and GRADE certainty of the evidence**
RCT					
Ghandehari et al;[522] 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;[523] Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 g a day and 5 assigned to	Mean age 28.5 ± 3.85, male 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection,	**Mortality:** No information **Invasive mechanical**

	standard of care			and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**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;[524] 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;[525] 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

Prostacyclin (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					
ThIlo trial;[526] Haeberle et al; preprint; 2021	Patients with critical COVID-19 infection. 72 assigned to prostacyclin (inhaled) 3 times a day for 5 days and 72 assigned to SOC	Mean age 60, male 75%, hypertension 58.6%, diabetes 28.5%, COPD 7.6%, asthma 4.9%, CKD 6.9%, cancer 2.8%	Corticosteroids 51.4%, remdesivir 42.4%, tocilizumab 16%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.05 (95%CI 0.64 to 1.7); RD 0.8% (95%CI -5.7% to 11.2%); 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

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;[527] 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;[528] 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;[529] Cadegiani et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 423 assigned to proxalutide 300 mg 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%	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;[530] Cadegiani et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 75 assigned to proxalutamide 200 mg a day for 7 days and 102 assigned to SOC	Mean age 44.2 ± 12.1, male 0%, hypertension 31.1%, diabetes 8.5%, COPD 0.6%, obesity 18.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, 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;[531] 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;[532] 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;[533] 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;[534] 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;[535] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 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.	
Raloxifene **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Nicastri et al;[536] peer reviewed; 2021	Patients with moderate COVID-19 infection. 42 assigned to raloxifene 60 to 120 mg for 14 days and 19 assigned to SOC	Mean age 56.7 ± 10.1, male 54.1%, hypertension 26.2%, diabetes 0.66%, COPD %, asthma 1.6%	Corticosteroids 14.7%, remdesivir 1.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

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;[537] Amat-Santos et al; preprint; 2020	Individuals exposed to SARS-CoV-2 infection. 50 assigned	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%,	NR	Low for mortality and invasive mechanical ventilation; high for	**Mortality:** Very low certainty ⊕◯◯◯

	to ramipril 2.5 mg a day progressively increased to 10 mg a day and 52 assigned to standard of care	diabetes 20.65%, chronic lung disease 7.35%, coronary heart disease 22.45%, chronic kidney disease 34.15%, cerebrovascular disease 11.15%		symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** 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;[538] 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;[539] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 46 assigned to recombinant super-compound interferon 12 million IU twice daily (nebulization) and 48 assigned to interferon alfa	Median age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, chronic lung disease 1.1%, coronary heart disease 7.4%, cerebrovascular disease 5.3%, liver disease 6.4%	Corticosteroids 9.6%, ATB 22.3%, intravenous immunoglobulin 3.2%, lopinavir-ritonavir 44.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Regdanvimab (monoclonal antibody)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Streinu-Cercel et al;[540] Peer reviewed; 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%); Low certainty ⊕⊕○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** Very low certainty ⊕○○○
CT-P59 1.2 trial;[541] Kim et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 15 assigned to regdanvimab 20 to 80 mg 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:	

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;[542] 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 0.63 to 1.09); RD -2.7% (95%CI -5.9% to 1.4%); 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 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%);
RECOVERY - REGEN-COV trial;[543] Horby et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 4839 assigned to REGEN-COV (Regeneron) 8 g once and 4946 assigned to SOC	Mean age 61.9 ± 14.4, male 63%, diabetes 26.5%, COPD %, CHD 21%, CKD 5%	Corticosteroids 94%, azithromycin 3%, baricitinib 9%; vaccinated 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.	
O'Brien et al;[544] 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;[545] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 841 assigned to REGN-COV2	Median age 43 ± 25, male 45.9%, 6.8%, CKD 1.9%, immunosuppresive	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection,	

	(Regeneron) 1200 mg once and 842 assigned to SOC	therapy 1%, obesity 34.1%		and adverse events	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 0.24 (95%CI 0.08 to 0.76); RD -13.2% (95%CI -16% to -4.2%); High certainty ⊕⊕⊕⊕ **Adverse events:** RR 0.51 (95%CI 0.38 to 0.67); RD -5% (95%CI -6.3% to -3.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.28 (95%CI 0.19 to 0.42); RD -3.5% (95%CI -3.9% to -2.8%); Moderate certainty ⊕⊕⊕◯
OPTIMISE-C19 trial;[91] McCreary et al; peer reviewed; 2022	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;[546] peer-reviewed; 2021	Patients with moderate to severe COVID-19 infection. 804 assigned to REGN-COV2 (Regeneron) 2.4 to 8 gr once and 393 assigned to SOC	Median age 62 ± , male 54.1%	Corticosteroids 74.8%, remdesivir 54.9%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
R10933-10987-COV-20145 trial;[547] Portal Celhay et al; preprint; 2021	Patients with mild COVID-19 infection. 584 assigned to REGN-COV2 (Regeneron) 300 - 2400 mg once and 77 assigned to SOC	Mean age 34.6, male 44.3%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Isa et al;[548] 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;[549] 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;[550] 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	
MANTICO trial;[94] Mazzaferri et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 107 assigned to sotrovomab 500 mg once and 106 assigned to bamlanivimab + etesevimab 700/1400 mg once and 106 assigned to REGEN-COV2 600/600 mg once	Mean age 65 ± 15, male 57.2%, diabetes 2.9%, COPD 16.7%, asthma %, CHD 37.9%, CKD 5.1%, immunosuppression19.6%, obesity 25.4%	Vaccinated 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.	
PLATCOV - Regen trial;[376] Schilling et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 10 assigned to REGEN-COV 1200 mg once and 41 assigned to SOC	Mean age 27 , male 39%	Corticosteroids %, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %; Vaccinated %	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.	

Remdesivir

In hospitalized patients with moderate to critical disease, remdesivir probably reduces mortality and mechanical ventilation, and it may improve time to symptom resolution without increasing 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.

Study; publication status	**Patients and 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;[551] peer-	Patients with mild to critical COVID-19	Mean age 58.9 ± 15, male 64.3%,	NR	Low for mortality and invasive mechanical	**Mortality:** RR 0.93 (95%CI 0.89 to 1.03);

reviewed; 2020	infection. 541 assigned to remdesivir intravenously 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death and 522 assigned to standard of care	hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,		ventilation; low for symptom resolution, infection, and adverse events	RD -1.1% (95%CI -1.8% to 0.5%); Moderate certainty ⊕⊕⊕○ **Invasive mechanical ventilation:** RR 0.76 (95%CI 0.56 to 1.04); RD -4.2% (95%CI -7.6% to 0.7%); Moderate 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;[552] 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;[553] 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;[554] 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	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	

	care			study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.
WHO SOLIDARITY;[275] Pan et al; peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 4146 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 4129 assigned to SOC	Age range 50 – 69 years old 46.2%, male 63.4%, diabetes 27.2%, COPD 6.8%, asthma 5.9%, CHD 22.5%	Steroids 67.7%, convalescent plasma 3.3%, Anti IL6 4.5%	Low for mortality and mechanical ventilation; some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study wich might have introduced bias to symptoms and adverse events outomes results.
Mahajan et al;[555] 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;[556] peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 100 assigned to remdesivir 200 mg once followed by 100 mg 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;[557] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 52 assigned	Mean age 57, male 72%, hypertension 61.7%, diabetes 47.6%, COPD	Hydroxychloroquine 52.3%, tocilizumab 100%,	High for mortality and mechanical ventilation; high for symptom

	to remdesivir 200 mg once followed by 100 mg a day for 5 days plus tocilizumab and 56 assigned to HCQ 400 mg once followed by 200 mg a day for 5 days plus tocilizumab	2.8%, asthma 13.1%, CHD 21.5%, CKD 4.7%,		resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PINETREE trial;[558] 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;[559] 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.	

Remdesivir (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					
Gilead et al; NCT04539262; other; 2021	Patients with mild to moderate COVID-19 infection. 109 assigned to remdesivir (inh) 31 to 62 mg a day for 3 to	Age > 60 years old 12.9%, male 50%	NR	NA	**Mortality:** No information **Invasive mechanical ventilation:** No

	5 days and 45 assigned to SOC				information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** No information **Hospitalization:** Very low certainty ⊕○○○

Reparixin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
REPAVID-19 trial;[560] Landoni et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 36 assigned to reparixin 3600 mg a day for 7 days and 19 assigned to SOC	Mean age 61.7, male 76.4%, hypertension 43.6%, diabetes 23.6%, COPD %, CHD 12.7%, CKD 7.3%, obesity 20%	Corticosteroids 92.7%, remdesivir 23.6%	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 **Severe Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

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;[561] peer-reviewed; 2021	Patients with mild COVID-19 infection. 50 assigned to resveratrol 4 g 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 ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low
Reszinate trial;[562] 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	

					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;[563] 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;[564] 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

rhu-pGSN

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

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

BTI-202 trial;[565] DiNubile et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 31 assigned to rhu-pGSN 12 mg/kg three times and 30 assigned to SOC	Mean age 62.1 ± 11.6, male 57.4%, hypertension 41%, diabetes 32.8%	Corticosteroids 100%, remdesivir 98.4%	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:** No information **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;[400] 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	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	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or**

	32 assigned to ribavirin plus lopinavir-ritonavir			allocation is probably inappropriate.	**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;[566] 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 reduce mortality. 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;[567] 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:** RR 0.72 (95%CI 0.59 to 0.89); RD -4.5% (95%CI -6.5% to -1.7%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯
RUXCOVID trial;[568] Han et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection.	Mean age 56.5 ± 13.3, male 54%, diabetes 21.9%, obesity 47%	NR	Low for mortality and mechanical ventilation; low for symptom	

	287 assigned to ruxolitinib 10 mg a day for 14 to 28 days and 145 assigned to SOC			resolution, infection and adverse events	**Symptom resolution or improvement:** RR 1.05 (95%CI 0.89 to 1.24); RD 3% (95%CI -6.7% to 14.5%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
RUXCOVID-DEVENT trial; NCT04377620; other; 2021	Patients with critical COVID-19 infection. 164 assigned to ruxolitinib 10 to 30 mg a day and 47 assigned to SOC	Mean age 63.4 ± 12.7, male 64.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Sabizabulin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Barnette et al;[569] peer reviewed; 2022	Patients with severe COVID-19 infection. 98 assigned to sabizabulin 9 mg for up to 21 days and 52 assigned to SOC	Mean age 59.7 ± 14.7, male 68%, hypertension 60%, diabetes 37.3%, COPD %, CHD 4.7%, CKD 10%, cancer 5.3%, obesity 32.4%	Corticosteroids 82.7%, remdesivir 32.7%, tocilizumab 10%, baricitinib 12%; vaccinated 44.7%,	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:** 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;[570] 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%	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 0.97 (95%CI 0.81 to 1.16); RD -0.5% (95%CI -3% to 2.6%); Low certainty ⊕⊕○○ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.68 to 1.42); RD -0.3% (95%CI -5.5% to 7.3%); 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 ⊕⊕⊕○
Lescure et al;[571] 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	Patients with severe to critical COVID-19	Critical patient population: mean age 61	Corticosteroids 34.3%,	Low for mortality and mechanical ventilation;	

trial;[572] Sivapalasingam, et al; preprint; 2021 (two studies reported)	infection. 1148 assigned to sarilumab 200-400 mg once and 376 assigned to SOC	± 20, male 68.4%, hypertension 52.1%, diabetes 18.7%, obesity 46.5%		Low for symptom resolution, infection, and adverse events	**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%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
CORIMUNO-SARI trial;[573] Mariette, et al, peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 68 assigned to sarilumab 400 mg once and 76 assigned to SOC	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	
CORIMUNO-SARI ICU trial;[574] Hermine et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 48 assigned to sarilumab 400 mg 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;[575] García Vicuña et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to sarilumab 400 mg once and 10 assigned to SOC	Median age 61.5, male 67%, hypertension 43%, diabetes 17%, COPD 7%, CHD 10%, CKD 13%, obesity 10%	Steroids 83%, remdesivir 0%, hydroxychloroquine 20%, lopinavir-ritonavir 17%, tocilizumab %, azithromycin 60%, 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.	
SARICOR trial;[576] Merchante et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 76 assigned to sarilumab 200-400 mg 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;[577] Sancho-Lopez et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 99 assigned to sarilumab 200-400 mg 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.	
IRB 3305 trial;[578] Branch-Elliman et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 20 assigned to sarilumab 200 to 400 mg (subcutaneous) once and 30 assigned to SOC	Mean age 72.3 ± 12.7, male 92%, hypertension 86%, diabetes 50%, COPD 32%, asthma 16%, CHD 70%, CKD 18%, cancer 48%, obesity 62%	Corticosteroids 86%, remdesivir 80%, hydroxychloroquine 4%, tocilizumab 2%, convalescent plasma 2%;	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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;[579] 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	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom**

				symptoms and adverse events outcomes results.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Senicapoc

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
COVIPOC trial;[580] Granfeldt et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 20 assigned to senicapoc 50 mg twice and 26 assigned to SOC	Median age 66, male 65.2%, hypertension 34.8%, diabetes 28.3%, COPD 26%, CKD 4.5%, cancer 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.	**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

Sentinox

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Panatto et al;[581] peer reviewed; 2022	Patients with mild COVID-19 infection. 36 assigned to sentinox 0.005% 3 to 5 times a day and 18 assigned to SOC	Mean age 40.1 ± 13.7, male 81%, any commorbidities 4%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** Very low certainty ⨁◯◯◯ **Hospitalization:** Very low certainty ⨁◯◯◯

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;[582] 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;[583] Santamarina et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 20 assigned to sildenafil 75 mg a day for 7 days and 20 assigned to SOC	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 adverse events Notes: Blinding and 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 **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;[584] 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

Silymarin

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Aryan et al;[585] peer reviewed; 2022	Patients with severe COVID-19 infection. 25 assigned to silymarin 210 mg a day for 14 days and 25 assigned to SOC	Mean age 49 ± 11.1, male 48%	Corticosteroids 100%, remdesivir 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:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Severe adverse events: Very low certainty ⊕◯◯◯ **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;[586] 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 increase mortality and not reduce 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;[403] 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):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Sadeghi et al;[587] 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;[588] preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 10 days and 45 assigned to standard of care	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %, asthma 1%, coronary heart disease 8%	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	

Roozbeh et al;[589] 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;[387] 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;[590] Mobarak et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 541 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 10 days and 542 assigned to SOC	Median age 58, 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;[591] 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;[404] Preprint; 2021	Patients with mild to moderate COVID-19 infection. 58 assigned	Mean age 57.4 ± 15, male 44.6%, hypertension 25%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom	

	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	diabetes 21.4%, COPD 3.6%, CHD 15.2%, CKD 6.2%, immunosuppression 3.6%, cancer 10.7%		resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.
Khalili et al;[592] 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;[593] 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;[594] Sayad et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 40 assigned to sofosbuvir/velpatasvir 400/100 mg once a day for 10 days and 40 assigned to SOC	Mean age 54.1 ± 17.8, male 55%, hypertension 30%, diabetes 20%, COPD 10%, CHD 17.5%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
El-Bendari et al;[595] peer reviewed; 2021	Patients with moderate to severe	Mean age 53 ± 15, male 54.6%, hypertension	NR	High for mortality and mechanical ventilation;

	COVID-19 infection. 96 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 14 days and 78 assigned to SOC	21.3%, diabetes 37.3%, asthma 1.7%, CHD 10.9%		high for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.
Abbass et al;[596] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 80 assigned to sofosbuvir/daclatasvir 400/60 a day or sofosbuvir/ravidasvir 400/200 mg 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%).
Medhat et al;[597] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 70 assigned to sofosbuvir/ledipasvir 400/90 mg a day for 14 days and 73 assigned to SOC	Mean age 45, male 51%, hypertension 20.9%, diabetes 20.3%	Corticosteroids 49%, hydroxychloroquine 8.4%,	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.
Bozorgmehr et al;[598] peer reviewed; 2022	Patients with severe COVID-19 infection. 50 assigned to sofosbuvir 400 mg a day for 7 days and 50 assigned to SOC	Mean age 53.8 ± , male 44%, diabetes 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.
COVER HCW trial;[481] Sokhela et al;	Patients with exposed to COVID-19	Median age 24, male 51.9%, hypertension	Vaccinated 0%	Low for mortality and mechanical ventilation;

peer reviewed; 2022	infection. 265 assigned to sofosbuvir/daclatasvir 400/60 mg a day for 24 weeks and 283 assigned to SOC	8.2%, diabetes 1.1%, COPD 2.2%		high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	

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;[599] Gupta et al; peer reviewed; 2021	Patients with mild to moderate recent onset with risk factors COVID-19 infection. 528 assigned to sotrovimab 500 mg once and 529 assigned to SOC	Median age 53, male 45.9%, hypertension %, diabetes 21.6%, COPD 5.6%, asthma 16.8%, CHD 0.7%, CKD 1.2%, obesity 63.4%	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 0.34 (95%CI 0.16 to 0.68); RD -6.7% (95%CI -8.6% to -
OPTIMISE-C19 trial;[550] 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	
MANTICO trial;[94] Mazzaferri et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 107 assigned to sotrovomab 500 mg once and 106 assigned	Mean age 65 ± 15, male 57.2%, diabetes 2.9%, COPD 16.7%, asthma %, CHD 37.9%, CKD 5.1%,	Vaccinated 28.6%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	to bamlanivimab + etesevimab 700/1400 mg once and 106 assigned to REGEN-COV2 600/600 mg once	immunosuppression19.6%, obesity 25.4%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	3.3%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** RR 0.20 (95%CI 0.08 to 0.48); RD -3.8% (95%CI -4.6% to -2.5%); Moderate certainty ⊕⊕⊕◯

Spironolactone

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Asadipooya et al;[586] 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:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** No information **Hospitalization:** No
Bharti et al;[600] preprint; 2022	Patients with severe COVID-19 infection. 74 assigned to spironolactone 50 mg once followed by 25 mg a day for 21 days and 46 assigned to SOC	Mean age 48.8 ± 14.3, male 61.7%, hypertension 28.3%, diabetes 34.2%, COPD 1.7%, asthma 3.3%, CHD 5.8%, CKD 0.8%, cancer 0.8%	Corticosteroids 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss to follow up. Selective reporting: Patients with symptom progression were excluded.	

					information

Statins

Statins may reduce mortality; however, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
RESIST trial;[63] 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 0.92 (95%CI 0.73 to 1.15); RD -1.3% (95%CI -4.3% to 2.4%); 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
INSPIRATION/INSPIRATION-S trial;[601] 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	
Ghafouri et al;[602] peer reviewed; 2021	Patients with severe COVID-19 infection. 76 assigned to statin atorvastatin 20 mg for 7 to 14 days and 78 assigned to SOC	Mean age 51.8 ± 17.4, male 50.6%	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.	

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;[603] 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;[604] 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;[605] 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;[606] 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;[607] 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;[608] 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;[609] 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;[607] 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;[610] 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;[607] 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;[611] 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;[612] 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;[613] 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;[614] 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;[615] 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;[81] peer reviewed; 2021	Patients with severe COVID-19 infection. 116 assigned to predninoslone 25 mg 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.	

CORTIVID trial;[616] Les et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 34 assigned to methylprednisolone and 37 assigned to SOC	Mean age 58.4, male 69%, hypertension 32.4%, diabetes 18.3%, COPD 1.4%, asthma 2.8%, CKD 7%	Remdesivir 8.5%, tocilizumab 28.2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	
Ranjbar et al;[617] 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 0.97 (95%CI 0.78 to 1.21); RD -0.5% (95%CI -3.5% to 3.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 0.99 (95%CI 0.9 to 1.08); RD -0.6% (95%CI -5.5% to 4.8%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.82 (95%CI 0.6 to 1.11); RD -1.8% (95%CI -4.1% to 1.1%); Low certainty ⊕⊕◯◯ **Hospitalization:** No information
COVID STEROID 2 trial;[618] 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;[619] 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 6 mg 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;[620] peer reviewed; 2021	Patients with severe COVID-19 infection. 86 assigned to dexamethasone 16 to 24 mg a day and 47	Mean age 58, male 60.2%, hypertension 36%, diabetes 22.5%, COPD 6%, CHD 17.3%, CKD 1.5%,	Remdesivir 75.2%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	assigned to dexamethasone 8 mg a day for up to 10 days	cerebrovascular disease 6%, cancer 2.3%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
HIGHLOWDEXA trial;[621] 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;[622] 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 6 mg/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.
RCT-MP-COVID-19 trial;[623] Salvarani et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 151 assigned to three boluses of 1 g of methylprednisolone intravenously and 150 assigned to SOC	Median age 64 , male 72.1%, hypertension 52.2%, diabetes 14.9%, COPD 4.4%, obesity 22.9%	Corticosteroids 88.4%, remdesivir 15.3%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events
COVIDICUS trial;[624] Bouadma et al; peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 270 assigned to dexamethasone 14 mg a day for 5 days followed by dexamethasone 4 mg a day for 5 days and 276	Median age 67, male 75.8%, hypertension 55.4%, diabetes 37%, cancer 11.2%,	Corticosteroids %, remdesivir 17%, hydroxychloroquine 1.1%, lopinavir-ritonavir 2.2%, tocilizumab 1%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events

	assigned to dexamethasone 6 mg a day for 10 days				
Dastenae et al;[625] peer reviewed; 2022	Patients with severe to critical COVID-19 infection. 73 assigned to methylprednisolone 60 mg a day for 10 days and 71 assigned to dexamethasone 8 mg a day for 10 days	Mean age 63, male 55.9%, hypertension 47.6%, diabetes 25.9%, COPD 12.6%, asthma %, CHD 11.9%, CKD 6.3%,	Remdesivir 88.1%,	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 may improve time to symptom resolution but probably do not have an important effect on hospitalizations. Their effects on other important outcomes 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					
STOIC trial;[626] 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 1.09 (95%CI 0.99 to 1.2); RD 5.5% (95%CI -0.6% to 12.1%); Low certainty ⊕⊕○○ **Symptomatic infection**
PRINCIPLE trial;[627] Yu et al; peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 787 assigned to inhaled budesonide	Mean age 64.2 ± 7.6, male 48%, hypertension 44.3%, diabetes 21.4%, COPD 12.6%, CHD	NR	Some concerns for mortality and mechanical ventilation; Some concerns for	

	800µg twice daily for 14 days and 1069 assigned to SOC	15.8%, cerebrovascular disease 5.6%		symptom resolution, infection, and adverse events Notes: Non-blinded study. Significant loss to follow-up.	**(prophylaxis studies):** No information **Hospitalization:** RR 0.9 (95%CI 0.7 to 1.15); RD -0.5% (95%CI -1.4% to 0.7%); Moderate certainty ⊕⊕⊕◯ **Adverse events:** Very low certainty ⊕◯◯◯
Song et al;[628] 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;[629] 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;[630] 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;[140] 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.	
COVERAGE trial;[631] Duvignaud et al; peer reviewed; 2021	Patients with mild COVID-19 infection. 110 assigned to inhaled ciclesonide 640 µg of ciclesonide per day for 10 days and 107 assigned to SOC	Median age 63, male 48.9%, hypertension 41%, diabetes 15.2%, COPD 3.2%, CHD 5%, cerebrovascular disease 8.7%, cancer 5.9%, obesity 29.4%	Vaccinated13.8%	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.	
TACTIC-COVID trial;[632] Agusti et al; other; 2021	Patients with moderate to severe COVID-19 infection. 58 assigned to budesonide (inh) 400 µg/12 h and 62 assigned to SOC	Mean age 51.1 ± 13.7, male 47.1%,	Corticosteroids 17.8%, remdesivir 8.5%, hydroxychloroquine 8.5%, lopinavir-ritonavir 5.9%, tocilizumab 0.8%, azithromycin 9.3%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Terada et al;[118] peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 56 assigned to camostat 600 mg + ciclesonide (inhaled) 1200 µg a day and 61 assigned to SOC	Mean age 58.3, male 64.9%, diabetes 24.8%, COPD 9.4%, CHD 2.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

ACTIV-6 - Fluticazone trial;[633] Naggie et al; preprint; 2022	Patients with mild to moderate COVID-19 infection. 656 assigned to fluticazone 200 µg once a day for 14 days and 621 assigned to SOC	Median age 45, male 36.8%, hypertension 26.1%, diabetes 9.7%, COPD 1.4%, asthma 13%, CHD 4.7%, CKD 0.8%, cancer 3.4%,	Corticosteroids %, remdesivir 0.1%, monoclonar antibodies 2.7%, paxlovid 0.1%; Vaccinated 65.2%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Steroids (nasal corticosteroids)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Yildiz et al;[465] 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;[634] 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 ⨁◯◯◯

Tafenoquine

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

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

Dow et al;[635] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 45 assigned to tafenoquine 200 mg a day for 3 days followed by 200 mg once next week and 41 assigned to SOC	Mean age 43 ± 15, male 47.7%	Vaccinated 32.6%	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:** 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;[636] 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	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No information **Symptom**

				allocation is probably inappropriate.	**resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** No information

Tenofovir + emtricitabine

Tenofovir + emtricitabine may not reduce mortality but may reduce mechanical ventilation. However, certainty of the evidence was low. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
AR0-CORONA trial;[637] 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:** RR 0.97 (95%CI 0.49 to 1.92); RD -0.5% (95%CI -8.2% to 14.7%); Low certainty ⊕⊕○○ **Invasive mechanical ventilation:** RR 0.76 (95%CI 0.49 to 1.18); RD -4.2% (95%CI -8.8% to 3.1%); Low certainty ⊕⊕○○ **Symptom resolution or improvement:** Very low certainty
ARTAN-C19 trial;[638] Lima et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 81 assigned to tenofovir +/- emtricitabine 300/200 mg once a	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	

	day and 41 assigned to SOC			Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	⊕○○○ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕○○○ **Adverse events:** Very low certainty ⊕○○○ **Hospitalization:** Very low certainty ⊕○○○
EPICOS trial;[302] Polo et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 233 assigned to tenofovir +/- emtricitabine 245/200 mg a day and 223 assigned to SOC	Mean age 38.5, male 38%, hypertension 7.4%, diabetes 1.3%, COPD 0%, asthma 3.7%, CHD 0.4%, cancer 1.1%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Gaitan-Duarte et al;[146] 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.	
PanCOVID19 trial;[102] Montejano et al; peer reviewed; 2022	Patients with moderate COVID-19 infection. 177 assigned to tenofovir +/- emtricitabine 400/490 mg once followed by 200/245 mg once a day for 14 days and 178 assigned to SOC	Median age 67, male 64.5%, hypertension 61.1%, diabetes 27.3%, obesity 16.1%	Corticosteroids 100%, remdesivir 12.7%, baricitinib 50.5%; Vaccinated 91%	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.	

Thalidomide

Uncertainty in potential benefits and harms. Further research is needed

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

	analyzed				**and GRADE certainty of the evidence**
RCT					
Amra et al;[639] preprint; 2021	Patients with severe COVID-19 infection. 28 assigned to thalidomide 100 mg a day for 14 days and 23 assigned to SOC	Mean age 62 ± 10, male 54.9%, hypertension 33.3%, diabetes 37.2%, COPD 5.9%, CHD 9.8%	Corticosteroids 100%, hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information
Haghighi et al;[640] 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.	

Thymoquinone

Uncertainty in potential benefits and harms. Further research is needed

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Benchequoun et al;[641] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 23 assigned to thymoquinone	Age >55 29.1%, male 43.6%, hypertension 40%, diabetes 18.2%, obesity 38.2%	Vaccinated 16.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	**Mortality:** No information **Invasive mechanical**

	3000 mg a day and 19 assigned to SOC			adverse events Notes:	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

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;[642] Barret et al; peer reviewed; 2021	Patients with critical COVID-19 infection. 25 assigned to tPa 50 mg 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

Tixagevimab–cilgavimab

Tixagevimab-cilgavimab probably reduces mortality, hospitalizations, and SARS-COV-2 infections in exposed individuals, 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					
PROVENT trial;[643] Levin et al; peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 3441 assigned to tixagevimab-cilgavimab 300 mg once and 1731 assigned to SOC	Mean age 53.5 ± 15, male 53.9%, hypertension 35.9%, diabetes 14.1%, COPD 5.3%, asthma 11.1%, CHD 8.1%, CKD 5.2%, immunosuppresive therapy 3.3%, cancer 7.4%, obesity 41.7%	Vaccinated 0%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Most patients were not blinded which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.72 (95%CI 0.54 to 0.96); RD -4.5% (95%CI -7.4% to -0.6%); Moderate certainty ⊕⊕⊕○ **Invasive mechanical ventilation** No information **Symptom resolution or improvement:** RR 1.03 (95%CI 0.99 to 1.08); RD 2% (95%CI -0.6% to 4.7%); Moderate certainty ⊕⊕⊕○ **Symptomatic infection (prophylaxis studies):** RR 0.18 (95%CI 0.09 to 0.35);
TACKLE trial;[644] Montgomery et al; peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 452 assigned to tixagevimab-cilgavimab 600 mg once and 451 assigned to SOC	Mean age 46.1 ± 15.2, male 50%, hypertension 28%, diabetes 12%, immunosuppression therapy 5%, cancer 4%, obesity 43%	Corticosteroids 2.8%; vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
TICO trial;[645] Lane et al; peer reviewed; 2022	Patients with moderate COVID-19 infection. 710 assigned to tixagevimab-	Mean age 46.1 ± 15.2, male 50%, hypertension 28%, diabetes 12%, CHD 9%, CKD 2%,	Corticosteroids 73%, remdesivir 63.3%; vaccinated 26.5%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and	

	cilgavimab 600 mg once and 707 assigned to SOC	immunosuppression 5%, cancer 4%, obesity 43%		adverse events	RD -14.2% (95%CI -15.8% to -11.2%); Moderate certainty ⊕⊕⊕○ **Adverse events:** RR 0.95 (95%CI 0.69 to 1.31); RD -0.5% (95%CI -3.2% to 3.2%); Low certainty ⊕⊕○○ **Hospitalization:** RR 0.42 (95%CI 0.24 to 0.74); RD -2.8% (95%CI -3.6% to 1.3%); Moderate certainty ⊕⊕⊕○

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;[646] 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 0.86 (95%CI 0.79 to 93); RD -2.2% (95%CI -3.4% to -1.1%); High certainty ⊕⊕⊕⊕ **Invasive mechanical ventilation:** RR 0.84 (95%CI 0.79 to 0.91); RD -2.8% (95%CI -3.6% to -1.6%); High certainty ⊕⊕⊕⊕ **Symptom resolution or**
Wang et al;[647] 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.	**improvement:** RR 1.08 (95%CI 1.02 to 1.14); RD 4.8% (95%CI 1.2% to 8.5%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.95 (95%CI 0.87 to 1.04); RD -0.5% (95%CI -1.3% to 0.4%); Moderate certainty ⊕⊕⊕◯ **Hospitalization:** No information
Zhao et al;[227] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir plus tocilizumab	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
RCT-TCZ-COVID-19 trial;[648] 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;[649] 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;[650] 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	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	

	assigned to standard of care			introduced bias to symptoms and adverse events outcomes results.	
EMPACTA trial;[651] Salama et al; preprint; 2020	Patients with moderate to severe COVID-19. 249 assigned to tocilizumab 8 mg/kg once and 128 assigned to standard of care	Mean age 55.9 ± 14.4, male 59.2%, hypertension 48.3%, diabetes 40.6%, COPD 4.5%, asthma 11.4%, coronary heart disease 1.9%, cerebrovascular disease 3.4%, obesity 24.4%	Corticosteroids 59.4%, remdesivir 54.6%	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	
REMAP-CAP - tocilizumab trial;[570] 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%	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;[652] 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;[653] 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%, 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;[654] Rutgers et al; preprint; 2021	Patients with severe COVID-19 infection. 174 assigned to TCZ 8 mg/kg once or twice and 180 assigned to SOC	Median age 66.5 ± 16.5, male 67%, comorbidities 74.3%	Corticosteroids 88.4%, remdesivir 18.4%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.
Talaschian et al;[655] 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;[656] 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;[584] other; 2021	Patients with severe to critical COVID-19 infection. 10 assigned to TCZ 8 mg/kg once or twice and 11	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

	assigned to SOC			Notes: Risk of bias assessment extracted from a systematic review.	
CORIMUNO-TOCI ICU trial;[574] Hermine et al; Peer reviewed; 2021	Patients with critcal COVID-19 infection. 49 assigned to TCZ 8 mg/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 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.	
COV-AID trial; et al;[584] 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;[584] 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;[657] Broman et al; peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 57 assigned to TCZ 400 to 800 mg once and 29 assigned to SOC	Median age 58.5 ± 13.9, male 55.8%, hypertension 37.2%, diabetes 24.4%, COPD 3.5%, asthma 14%, CHD 5.81%, cancer 11.6%, obesity 63.5%	Steroids 77%, remdesivir 0%, convalescent plasma 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of	

				allocation probably inappropriate.
COVITOZ-01 trial; et al;[584] 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;[584] 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;[658] 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;[584] 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;[584] 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;[659] Soin et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 91 assigned to TCZ 6 mg/kg once or twice and 88 assigned to SOC	Median age 55 , male 85.5%, hypertension 39.4%, diabetes 41.1%, COPD 2.2%, CHD 15%, CKD 4.4%	Corticosteroids 91%, remdesivir 41.6%, convalescent plasma 0%	Low for mortality and mechanical ventilation; high for symptom resolution, infection, and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
TOCIDEX trial;[660] Hermine et al; peer reviewed; 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.	
Karampitsakos et al;[661] preprint; 2022	Patients with severe COVID-19 infection. 125 assigned to baricitinib 4 mg a day for 14 days and 126 assigned to TCZ 8 mg/kg once	Mean age 72.5, male 59.4%, hypertension 53.8%, cancer 9.2%, obesity 8%	Corticosteroids 100%, remdesivir 100%; vaccinated 20.3%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

MARIPOSA trial;[662] 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;[663] 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	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

	SOC				**Symptom resolution or improvement:** RR 1.1 (95%CI 0.98 to 1.23); RD 6.1% (95%CI 1.2% to 13.9%); Low certainty ⊕⊕○○ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 3.22 (95%CI 1.12 to 8.56); RD 22.6% (95%CI 1.2% to 77.1%); Low certainty ⊕⊕○○ **Hospitalization:** No information
Murugesan et al;[664] 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.	

Tranilast

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Saeedi-Boroujeni et al;[665] peer reviewed; 2021	Patients with severe COVID-19 infection. 30 assigned to tranilast 300 mg a day for 7 days and 30 assigned to SOC	Mean age 59.5, male 63.3%, hypertension 36.7%, diabetes 26.7%, COPD 16.6%, CKD 6.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	**Mortality:** Very low certainty ⊕○○○ **Invasive mechanical ventilation:** No information **Symptom resolution or**

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

Triazavirin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Wu et al;[666] 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

TXA-127

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
AAAT0535 trial;[667] Wagener et al; peer reviewed; 2022	Patients with severe COVID-19 infection. 11 assigned to TXA-127 0.5 mg/kg a day for 10 days and 9 assigned to SOC	Mean age 56, male 65%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** No information

Ultraviolet B phototherapy

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Lau et al;[668] peer reviewed; 2022	Patients with severe COVID-19 infection. 15 assigned to UVB escalating protocol for 8 days and 15 assigned to SOC	Mean age 66.9, male 60%, hypertension 50%, diabetes 16.7%	Corticosteroids 93.3%, remdesivir 76.7%, tocilizumab 30%, vaccinated 33.3%, Regeneron 3.3%	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

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;[217] preprint; 2020	Patients with moderate to critical COVID-19 infection.	Mean age NR ± NR, male 46.6%, hypertension 27.9%,	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** Very low certainty ⊕◯◯◯

	116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days	diabetes 11.4%		symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	**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;[397] 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;[669] 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;[670] 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;[671] 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;[672] 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;[673] preprint; 2021	Patients with mild to moderate COVID-19 infection. 60 assigned to umifenovir 800 mg twice a day for 14 days and 63 assigned to SOC	Mean age 46.7 ± 1.9, male 74.8%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection, and adverse events	

Verapamil

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

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

ReCOVery-SIRIO trial;[18] Navarese et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 72 assigned to verapamil 120 to 480 mg a day and 72 assigned to SOC	Median age 61.3 , male 62.3%, diabetes 23.7%, COPD 6.5%, cancer 7%	Remdesivir 1.9%, hydroxychloroquine 2.3%, azithromycin 6%, convalescent plasma 1.9%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Vitamin C

Vitamin C may increase symptom resolution or improvement. Vitamin C effects on other important outcomes 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					
Zhang et al;[674] 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	NR	High for mortality and invasive 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 ⊕◯◯◯ **Symptom**

		disease 20.4%		allocation is probably inappropriate.	**resolution or improvement:** RR 1.16 (95%CI 1.01 to 1.33); RD 9.7% (95%CI 0.6% to 20%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Kumari et al;[675] 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;[676] 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;[677] 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;[678] 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;[679] 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 2000 mg 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;[680] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 31 assigned to vitamin C 500 mg a day and 69 assigned to SOC	Mean age 62.4 ± , male 60%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
ALLIANCE trial;[681] Ried et al; peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 162 assigned to vitamin 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.	
Coppock et al;[682] peer reviewed; 2021	Patients with severe COVID-19 infection. 44 assigned to vitamin C 0.3 to 0.9 g/kg a day for 5 days and 22 assigned to SOC	Mean age 60, male 50%, hypertension 62.1%, diabetes 34.8%, COPD 19.7%	Corticosteroids 77.3%, remdesivir 92.4%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of	

				allocation probably inappropriate.	
Fogleman C et al trial;[417] peer reviewed; 2022	Patients with mild to moderate COVID-19 infection. 32 assigned to vitamin C 1000 mg a day for 14 days and 34 assigned to SOC	Median age 52, male 44.9%, hypertension 26.5%, diabetes 16.3%	Vaccinated 2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Vitamin D

Vitamin D probably does not reduce SARS-COV-2 infections in exposed individuals and may not reduce hospitalizations. Vitamin D effects on other important outcomes are uncertain.

Study; publication status	**Patients and 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;[683] 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%	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:** Very low certainty ⊕○○○ **Symptomatic infection (prophylaxis studies):** RR 1.25 (95%CI 0.93 to 1.67); RD 4.3% (95%CI -1.2% to 11.7%); Moderate certainty ⊕⊕⊕○
SHADE trial;[684] 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.	
Murai et al;[685] peer-reviewed; 2020	Patients with severe COVID-19. 117	Mean age 56.3 ± 14.6, male 56.3%,	NR	Low for mortality and mechanical ventilation;	

	assigned to vitamin D 200,000 IU once and 120 assigned to standard of care	hypertension 52.5%, diabetes 35%, COPD %, asthma 6.3%, coronary heart disease 13.3%, chronic kidney disease 1%,		Low for symptom resolution, infection, and adverse events	**Adverse events:** RR 1.03 (95%CI 0.84 to 1.26); RD 0.3% (95%CI -1.6% to 2.7%); Low certainty ⊕⊕◯◯ **Hospitalization:** RR 1.26 (95%CI 0.84 to 1.89); RD 1.2% (95%CI -0.8% to 4.3%); Low certainty ⊕⊕◯◯
Lakkireddy et al;[686] preprint; 2021	Patients with mild to moderate with low plasmatic vitamin D COVID-19 infection. 44 assigned to vitamin 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;[687] peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 36 assigned to vitamin D 5000 IU for 14 days and 33 assigned to vitamin 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;[688] peer reviewed; 2021	Patients with moderate to severe COVID-19 infection. 53 assigned to vitamin 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;[689] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 30 assigned to multivitamin vitamin D 600000 UI	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	

	once, vitamin A 25000 UI a day, vitamin E 300 UI a day, vitamin C 2000 mg a day in addition to others for 7 days, and 30 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
REsCue trial;[690] Bishop et al; preprint; 2021	Patients with mild to moderate COVID-19 infection. 65 assigned to vitamin 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	
Karonova et al;[691] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 45 assigned to cholecalciferol 50,000 IU/week for 2 weeks followed by 500 UI/day for 3 months and 46 assigned to cholecalciferol 5000 IU/day for 3 months	Mean age 35 ± 2, male 15.3%, obesity 16.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-VIT-D trial;[692] Cannata-Andía et al; peer reviewed; 2021	Patients with severe COVID-19 infection. 274 assigned to vitamin D Cholecalciferol 100.000UI once and 269 assigned to SOC	Median age 58, male 65%, hypertension 43.8%, diabetes 24.7%, COPD 4.2%, asthma 5.5%, CHD 21.2%	Corticosteroids 29.9%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
CORONAVIT trial;[693] Jolliffe et al; preprint; 2021	Individuals exposed to SARS-CoV-2 infection. 3030 assigned to vitamin D 800 to 3200 UI a day	Median age 60.2, male 67%, hypertension 3.7%, diabetes 4.2%, COPD 1.8%, asthma 15.3%, CHD 19.5%, obesity	NR; Vaccinated 1.3%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	and 2949 assigned to SOC	20.1%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Villasis-Keever et al;[694] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 150 assigned to vitamin D 4,000 IU cholecalciferol a day for 30 days and 152 assigned to SOC	Median age 37.5 ± 26, male 30%, hypertension 29.6%, diabetes 4.1%, obesity 25.6%	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.	
CARED-TRIAL trial;[695] Mariani et al; peer reviewed; 2021	Patients with moderate COVID-19 infection. 115 assigned to vitamin D 500 000 IU of vitamin D3 once and 103 assigned to SOC	Mean age 59.1 ± 10.6, male 52.8%, hypertension 43.1%, diabetes 26.6%, COPD 11.9%, CHD 4.6%, cancer 0.9%, obesity 39.9%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
COVIT-TRIAL trial;[696] Annweiler et al; peer reviewed; 2022	Patients with mild to severe COVID-19 infection. 127 assigned to vitamin D cholecalciferol 400.000 UI once and 127 assigned to vitamin D 50.000 UI	Median age 88 , male 46%, hypertension 70%, diabetes 21%, COPD 7%, CHD 43%, CKD 17%, cerebrovascular disease 19%, cancer 7%, obesity 22%	Corticosteroids 15%, hydroxychloroquine 0.4%,azithromycin 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Karonova et al;[697] peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 65 assigned to vitamin D cholecalciferol 100,000 IU and 64 assigned to SOC	Mean age 60.5, male 59.2%, hypertension 73.6%, diabetes 31.8%, COPD %, CHD 23.3%, obesity 38.8%	Vaccinated 0%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

Romero-Ibarguengoitia et al;[698] preprint; 2022	Individuals exposed to SARS-CoV-2 infection. 43 assigned to vitamin D 52,000 IU a month for 6 months and 42 assigned to SOC	Mean age 44.4 ± 11.1, male 58.8%, hypertension 10%, diabetes 7%, asthma 4.7%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Cervero et al;[699] peer reviewed; 2022	Patients with severe COVID-19 infection. 41 assigned to vitamin D cholecalciferol 10000 IU a day for 14 days and 44 assigned to Vit D 2000 IU a day for 14 days	Median age 65 ± , male 71%, hypertension 48%, diabetes 22%	Corticosteroids 87%, remdesivir 15%, tocilizumab 25%, azithromycin 44%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abroug et al;[700] preprint; 2022	Patients with mild with persistently positive PCR test at 14 days COVID-19 infection. 57 assigned to vitamin D cholecalciferol 200,000 IU once and 60 assigned to SOC	Mean age 42.7 ± 14, male 55.6%, hypertension 6.8%, diabetes 12%, asthma 6.8%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
D-COVID trial;[701] De Niet et al; peer reviewed; 2022	Patients with moderate to severe COVID-19 infection. 21 assigned to vitamin D cholecalciferol 25.000 UI a day for 4 days followed by 25.000 UI a week for 6 weeks and 22 assigned to SOC	Mean age 66, male 53.5%, hypertension 55.8%, diabetes 37.2%, COPD 32.6%, CKD 18.6%	Corticosteroids 100%, remdesivir 100%; Vaccinated 14%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
XAV-19 (swine glyco-humanized polyclonal antibodies) **Uncertainty in potential benefits and harms. Further research is needed.**					

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
POLYCOR trial;[702] 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

Zilucoplan

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
ZILU-COV trial;[703] Leeuw et al; peer-reviewed; 2021	Patients with severe COVID-19 infection. 54 assigned to	Median age 63, male 87%, hypertension 46%, diabetes 23%, asthma %,	Corticosteroids 86%, remdesivir 12%	High for mortality and mechanical ventilation; high for symptom	**Mortality:** Very low certainty ⨁◯◯◯

	zilucoplan 32.4 mg a day, subcutaneously, for 14 days and 24 assigned to SOC	CHD 24%, CKD 5%		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:** Very low certainty ⊕◯◯◯ **Hospitalization:** No information

Zinc

Zinc may not improve symptom resolution. However, the certainty of the evidence was low because of imprecision. Its effects on other clinical important outcomes 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					
Hassan et al;[704] 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:** RR 1.01 (95%CI 0.91 to
Abd-Elsalam et al;[705] peer-reviewed; 2020	Patients with mild to critical COVID-19. 96 assigned to zinc 220	Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; high for symptom	

	mg twice a day for 15 days and 95 assigned to standard of care			resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	1.12); RD 0.6% (95%CI -5.4% to 7.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⊕◯◯◯ **Adverse events:** No information **Hospitalization:** Very low certainty ⊕◯◯◯
Abdelmaksoud et al;[706] Peer reviewed; 2020	Patients with mild to critical COVID-19. 49 assigned to Zinc 220 mg twice a day and 56 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection, and adverse events Notes: Non-blinded study. Concealment of allocation is probably inappropriate.	
COVIDAtoZ -Zinc trial;[677] 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;[707] 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;[288] peer reviewed; 2021	Individuals exposed to SARS-CoV-2 infection. 634 assigned to zinc 80 mg and 500 mg a day for 42 days and 619 assigned	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	

	to SOC (vitamin C)			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Reszinate trial;[562] 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:	
Stambouli et al;[201] peer reviewed; 2022	Individuals exposed to SARS-CoV-2 infection. 59 assigned to zinc 15 mg a day for 6 weeks and 56 assigned to SOC	Mean age 38.4 ± 10.7, male 61%, hypertension 4.1%, diabetes 2.3%, COPD 0.6%, asthma 1.2%	Vaccinated 0%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	

α-lipoic acid

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

Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zhong et al;[708] 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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Standard of care	Steroids		
Mortality 28 days	Relative risk: 0.9 (CI 95% 0.8 - 1.01) Based on data from 8000 participants in 12 studies	**160** per 1000 Difference: **16 fewer per 1000** (CI 95% 32 fewer - 2 more)	**144** per 1000	**Moderate** Due to serious imprecision[1]	Steroids probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 5942 participants in 6 studies Follow up 28	**172** per 1000 Difference: **22 fewer per 1000** (CI 95% 48 fewer - 9 more)	**150** per 1000	**Moderate** Due to serious imprecision[2]	Steroids probably decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.27 (CI 95% 0.98 - 1.65) Based on data from 646 participants in 5 studies	**606** per 1000 Difference: **164 more per 1000** (CI 95% 12 fewer - 394 more)	**770** per 1000	**Moderate** Due to serious risk of bias[3]	Steroids probably increases symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.89 (CI 95% 0.68 - 1.17) Based on data from 833 participants in 6 studies	**102** per 1000 Difference: **11 fewer per 1000** (CI 95% 33 fewer - 17 more)	**91** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Steroids may have little or no difference on severe adverse events
Mortality (High vs standard dose) (Low risk of bias studies) 28 days	Relative risk: 0.97 (CI 95% 0.78 - 1.21) Based on data from 2060 participants in 5 studies	**160** per 1000 Difference: **5 fewer per 1000** (CI 95% 35 fewer – 34 more)	**155** per 1000	**Low** Due to very serious imprecision[5]	High dose steroids (i.e dexamethasone 12 mg a day) may not decreases mortality in comparison to standard dose steroids (i.e dexamethasone 6 mg a day)
Severe adverse events (High vs. standard dose) 28 days	Relative risk: 0.82 (CI 95% 0.6 – 1.11) Based on data from 1280 participants in 2 studies	**102** per 1000 Difference: **18 fewer per 1000** (CI 95% 41 fewer - 11 more)	**84** per 1000	**Low** Due to very serious imprecision[6]	High dose steroids (i.e dexamethasone 12 mg a day) may not increase severe adverse events in comparison to standard dose steroids (i.e dexamethasone 6 mg 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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Remdesivir		
Mechanical ventilation 28 days	Relative risk: 0.76 (CI 95% 0.56 - 1.04) Based on data from 9730 participants in 7 studies Follow up Median 28 days	**173** per 1000 Difference: **42 fewer per 1000** (CI 95% 76 fewer - 7 more)	**131** per 1000	**Moderate** Due to serious imprecision[1]	Remdesivir probably decrease mechanical ventilation requirements
Mortality 28 days	Relative risk: 0.93 (CI 95% 0.89 - 1.03) Based on data from 10855 participants in 8 studies Follow up Median 28 days	**160** per 1000 Difference: **11 fewer per 1000** (CI 95% 18 fewer - 5 more)	**149** per 1000	**Moderate** Due to serious imprecision[2]	Remdesivir probably reduces mortality
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 Difference: **61 more per 1000** (CI 95% 24 fewer - 170 more)	**667** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Remdesivir may improve symptom resolution or improvement
Severe adverse events	Relative risk: 0.77 (CI 95% 0.46 - 1.29) Based on data from 2430 participants in 4 studies	**102** per 1000 Difference: **23 fewer per 1000** (CI 95% 55 fewer - 30 more)	**79** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Remdesivir may have little or no difference on severe adverse events
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 Difference: **35 fewer per 1000** (CI 95% 43 fewer - 12 fewer)	**13** per 1000	**Low** Due to very serious imprecision[5]	Remdesivir may decrease hospitalizations (in patients with non-severe disease)

1. **Imprecision: serious.** Wide confidence intervals;
2. **Imprecision: serious.** Wide confidence intervals;
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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	HCQ		
Mortality 15 days	Relative risk: 1.09 (CI 95% 1 - 1.19) Based on data from 10904 participants in 16 studies	**160** per 1000	**171** per 1000	**Moderate** Due to serious risk of bias[1]	HCQ probably increases mortality
		Difference: **14 more per 1000** (CI 95% 0 fewer - 30 more)			
Mechanical ventilation 15 days	Relative risk: 1.08 (CI 95% 0.93 - 1.25) Based on data from 8667 participants in 10 studies	**173** per 1000	**187** per 1000	**Moderate** Due to serious risk of bias[2]	Hcq probably has little or no difference on mechanical ventilation
		Difference: **14 more per 1000** (CI 95% 12 fewer - 43 more)			
Symptom resolution or improvement 28 days	Relative risk: 1.01 (CI 95% 0.93 - 1.1) Based on data from 6601 participants in 10 studies Follow up 28 days	**606** per 1000	**612** per 1000	**Moderate** Due to serious inconsistency[3]	Hcq probably has little or no difference on symptom resolution or improvement
		Difference: **6 more per 1000** (CI 95% 42 fewer - 61 more)			
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 participants in 6 studies	**174** per 1000	**153** per 1000	**Low** Due to serious imprecision, Due to serious inconsistency[4]	Hcq may have little or no difference on covid-19 infections (in exposed individuals)
		Difference: **21 fewer per 1000** (CI 95% 49 fewer - 19 more)			
Hospitalizations (in patients with non-severe disease)	Relative risk: 0.82 (CI 95% 0.61 - 1.1) Based on data from 4255 participants in 9 studies	**48** per 1000	**39** per 1000	**Low** Due to very serious imprecision[5]	Hcq may have little or no difference on hospitalizations in patients with non-severe disease
		Difference: **9 fewer per 1000** (CI 95% 19 fewer - 5 more)			
Severe adverse events	Relative risk: 0.9 (CI 95% 0.66 - 1.22) Based on data from 10381 participants in 20 studies	**102** per 1000	**92** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Hcq may have little or no difference on severe adverse events
		Difference: **10 fewer per 1000** (CI 95% 35 fewer - 22 more)			

1. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
3. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: serious.** I2 82%; **Imprecision: no serious.** Secondary to inconsistency;
4. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies; **Imprecision: serious.** 95%CI includes no infection reduction;

5. **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. (Interactive online version)

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 8059 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: 1.22 (CI 95% 0.61 - 2.47)	**48** per 1000	**59** per 1000	**Very low**	We are uncertain whether LPV

	Based on data from 591 patients in 2 studies	Difference: **11 more per 1000** (CI 95% 18 fewer - 71 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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	CP		
Mechanical ventilation 28 days	Relative risk: 1.02 (CI 95% 0.94 - 1.11) Based on data from 14226 participants in 21 studies Follow up Median 28 days	**173** per 1000 Difference: **3 more per 1000** (CI 95% 10 fewer - 19 more)	**176** per 1000	**High**	Convalescent plasma has little or no difference on mechanical ventilation
Mortality 28 days	Relative risk: 0.98 (CI 95% 0.93 - 1.03) Based on data from 24156 participants in 50 studies Follow up Median 28 days	**160** per 1000 Difference: **3 fewer per 1000** (CI 95% 11 fewer - 5 more)	**157** per 1000	**High**[1]	Convalescent plasma has little or no difference on mortality
Symptom resolution or improvement 28 days	Relative risk: 0.99 (CI 95% 0.95 - 1.02) Based on data from 14487 participants in 13 studies Follow up 28 days	**606** per 1000 Difference: **6 fewer per 1000** (CI 95% 30 fewer - 12 more)	**600** per 1000	**High**	Cp has little or no difference on symptom resolution or improvement
Hospitalizations	Relative risk: 0.77 (CI 95% 0.57 - 1.03) Based on data from 2642 participants in 4 studies	**48** per 1000 Difference: **11 fewer per 1000** (CI 95% 21 fewer - 1 more)	**37** per 1000	**Moderate** Due to serious imprecision[2]	Coucalescent plasma probably has little or no difference on hospitalizations
Severe adverse events	Relative risk: 1.03 (CI 95% 0.88 - 1.21) Based on data from 7307 participants in 16 studies	**102** per 1000 Difference: **3 more per 1000** (CI 95% 12 fewer - 21 more)	**104** per 1000	**Low** Due to serious imprecision, Due to serious risk of bias[3]	Convalescent may have little or no difference on severe adverse events
Symptomatic infection	Relative risk: 0.92 (CI 95% 0.32 - 2.62) Based on data from 168 participants in 1 study	**174** per 1000 Difference: **14 fewer per 1000** (CI 95% 118 fewer - 282 more)	**160** per 1000	**Very low** Due to extremely serious imprecision[4]	We are uncertain whether cp increases or decreases symptomatic infection
Specific severe adverse events	Based on data from 20000 participants 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 lpv increases or decreases severe adverse events

1. **Inconsistency: no serious.** Point estimates vary widely;
2. **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals;
4. **Imprecision: ~extreme_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. (Interactive online version)

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: 0.86 (CI 95% 0.79 - 0.93) Based on data from 8541 participants in 21 studies Follow up Median 28 days	**160** per 1000	**136** per 1000	**High**	TCZ decreases mortality
		Difference: **22 fewer per 1000** (CI 95% 34 fewer - 11 fewer)			
Mechanical ventilation 28 days	Relative risk: 0.84 (CI 95% 0.79 - 0.91) Based on data from 7655 participants in 21 studies Follow up Median 28 days	**173** per 1000	**145** per 1000	**High**[1]	TCZ decreases mechanical ventilation
		Difference: **28 fewer per 1000** (CI 95% 36 fewer - 16 fewer)			
Symptom resolution or improvement 28 days	Relative risk: 1.08 (CI 95% 1.02 - 1.14) Based on data from 7077 participants in 11 studies Follow up 28 days	**606** per 1000	**648** per 1000	**Low** Due to serious imprecision, Due to serious risk of bias[2]	TCZ may increase symptom resolution or improvement
		Difference: **48 more per 1000** (CI 95% 12 more - 85 more)			
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	**Moderate** Due to serious risk of bias[3]	Tcz probably has little or no difference on severe adverse events
		Difference: **5 fewer per 1000** (CI 95% 14 fewer - 4 more)			

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

Summary of findings Table 7. (Interactive online version)

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 mg/kg twice a day); anticoagulants in prophylactic dose (i.e., enoxaparin 40 mg a day); no anticoagulants

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	ACO		
Mortality (full or intermediate dose vs. prophylactic dose in hospitalized patients) (excluding high risk of bias studies)	Relative risk: 0.99 (CI 95% 0.83 - 1.19) Based on data from 5874 participants in 10 studies	**160** per 1000 Difference: **2 fewer per 1000** (CI 95% 27 fewer - 30 more)	**158** per 1000	**Moderate** Due to serious imprecision[1]	Anticoagulantes in intermediate or full dose probably 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% 0.43 - 1.59) Based on data from 1115 participants in 4 studies	**70** per 1000 Difference: **13 fewer per 1000** (CI 95% 40 fewer - 41 more)	**57** per 1000	**Low** Due to very serious imprecision[2]	Anticoagulantes in intermediate dose may slightly reduce venous thromboembolic events
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 participants in 1 study	**9** per 1000 Difference: **14 more per 1000** (CI 95% 5 fewer - 106 more)	**23** per 1000	**Very low** Due to very serious imprecision[3]	It is uncertain if anticoagulants in prophylactic dose increase or decrease clinically important bleeding
Venous thromboembolic events (full dose vs. prophylactic dose in hospitalized patients)	Relative risk: 0.56 (CI 95% 0.44 - 0.71) Based on data from 5235 participants in 8 studies	**70** per 1000 Difference: **31 fewer per 1000** (CI 95% 39 fewer - 20 fewer)	**39** per 1000	**High**	Anticoagulantes 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: 1.56 (CI 95% 1.08 - 2.25) Based on data from 6343 participants in 11 studies	**19** per 1000 Difference: **11 more per 1000** (CI 95% 2 more - 24 more)	**30** per 1000	**Moderate** Due to serious imprecision[4]	Anticoagulantes in intermediate or full dose probably increases major bleeding
Hospitalization (prophylactic dose vs. no anticoagulants in mild ambulatory patients)	Relative risk: 0.94 (CI 95% 0.55 - 1.59) Based on data from 1549 participants in 4 studies	**48** per 1000 Difference: **3 fewer per 1000** (CI 95% 22 fewer - 28 more)	**45** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Anticoagulants may have little or no difference on hospitalization
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 participants in 1 study	**606** per 1000 Difference: **48 more per 1000** (CI 95% 48 fewer - 164 more)	**654** per 1000	**Low** Due to very serious imprecision[6]	Anticoagulants may have little or no difference on symptom resolution or improvement

Mortality: Intermediate dose (i.e enoxaparin 40 mg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40 mg a day)[7] 28 days	Relative risk: 0.29 (CI 95% 0.13 - 0.64) Based on data from 843 participants in 2 studies	**160** per 1000 **46** per 1000 Difference: **114 fewer per 1000** (CI 95% 139 fewer - 58 fewer)	**Very low** Due to very serious risk of bias[8]	We are uncertain whether ACO intermediate dose increases or decreases mortality in comparison to ACO prophylactic dose
Mortality: Therapeutic dose (i.e enoxaparin 1 mg/kg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40 mg a day)[9] 28 days	Relative risk: 2.02 (CI 95% 0.7 - 5.8) Based on data from 2409 participants in 5 studies	**160** per 1000 **323** per 1000 Difference: **163 more per 1000** (CI 95% 48 fewer - 768 more)	**Very low** Due to very serious risk of bias, Due to very serious imprecision[10]	We are uncertain whether ACO in therapeutic dose increases or decreases mortality in comparison to ACO in prophylactic dose

1. **Imprecision: serious.** Low number of patients;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Imprecision: very serious.** 95%CI includes harms and absence of harms;
4. **Imprecision: serious.** 95%CI includes harms and absence of harms;
5. **Risk of Bias: serious. Imprecision: serious.** 95%CI includes harms and absence of harms;
6. **Imprecision: very serious.** 95%CI includes harms and absence of harms;
7. Therapeutic dose (i.e enoxaparin 40 mg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40 mg a day)
8. **Risk of Bias: very serious.**
9. Therapeutic dose (i.e enoxaparin 1 mg/kg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40 mg a day)
10. **Risk of Bias: very serious. Imprecision: very serious.** 95%CI includes significant mortality reduction and increase.

Summary of findings Table 8. (Interactive online version)

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. (Interactive online version)

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: 0.99 (CI 95% 0.75 - 1.31) Based on data from 6869 patients in 6 studies Follow up Median 28 days	**160** per 1000 Difference: **2 fewer per 1000** (CI 95% 40 fewer - 50 more)	**171** per 1000	**Moderate** Due to serious imprecision[1]	IFN probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 1.01 (CI 95% 0.87 - 1.18) Based on data from 5052 patients in 4 studies Follow up 28 days	**173** per 1000 Difference: **2 more per 1000** (CI 95% 22 fewer - 31 more)	**168** per 1000	**Moderate** Due to serious imprecision[2]	IFN probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 0.96 (CI 95% 0.92 - 0.99) Based on data from 969 patients in 1 study Follow up 28 days	**606** per 1000 Difference: **24 fewer per 1000** (CI 95% 48 fewer - 6 fewer)	**582** per 1000	**Moderate** Due to serious imprecision[3]	IFN probably has little or no difference on symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.94 (CI 95% 0.65 - 1.37) Based on data from 877 patients in 1 study Follow up 28 days	**102** per 1000 Difference: **6 fewer per 1000** (CI 95% 36 fewer - 38 more)	**96** per 1000	**Low** Due to very serious imprecision[4]	IFN may have little or no difference on severe adverse events
Symptom resolution or improvement (inhaled)[5] 30 days	Hazard Ratio: 2.19 (CI 95% 1.03 - 4.69) Based on data from 81 patients in 1 study Follow up 28 days	**606** per 1000 Difference: **264 more per 1000** (CI 95% 11 more - 381 more)	**870** per 1000	**Low** Due to very serious imprecision[6]	IFN (inhaled) may increase symptom resolution or improvement

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

Summary of findings Table 10. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	**Absolute effect estimates** 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	**Very low** Due to serious imprecision, Due to very serious imprecision[1]	We are uncertain whether bamlanivimab increases or decreases mortality
		Difference: **51 fewer per 1000** (CI 95% 133 fewer - 288 more)			
Symptom resolution or improvement[2]	Relative risk: 1.02 (CI 95% 0.99 - 1.06) Based on data from 1750 patients in 3 studies	**606** per 1000	**618** per 1000	**Moderate** Due to serious imprecision[3]	Bamlanivimab probably has little or no difference on symptom resolution or improvement
		Difference: **12 more per 1000** (CI 95% 6 fewer - 36 more)			
Symptomatic infection	Relative risk: 0.56 (CI 95% 0.39 - 0.81) Based on data from 961 patients in 1 study Follow up 28 days	**174** per 1000	**97** per 1000	**Moderate** Due to serious imprecision[4]	Bamlanivimab probably decreases symptomatic infection
		Difference: **77 fewer per 1000** (CI 95% 106 fewer - 33 fewer)			
Severe adverse events[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	**Low** Due to very serious imprecision[6]	Bamlanivimab may not increase severe adverse events
		Difference: **12 more per 1000** (CI 95% 24 fewer - 62 more)			
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	**Moderate** Due to serious imprecision[8]	Bamlanivimab +/- etesevimab probably decreases hospitalization
		Difference: **30 fewer per 1000** (CI 95% 38 fewer - 17 fewer)			

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

Summary of findings Table 11. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Favipravir		
Mortality 28 days	Relative risk: 1.09 (CI 95% 0.78 - 1.52) Based on data from 2060 participants in 11 studies Follow up Median 28 days	**160** per 1000	**174** per 1000	**Low** Due to very serious imprecision[1]	Favipiravir may increase mortality
		Difference: **14 more per 1000** (CI 95% 35 fewer - 83 more)			
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	**Low** Due to very serious imprecision[2]	Favipravir may increase mechanical ventilation
		Difference: **47 more per 1000** (CI 95% 16 fewer - 131 more)			
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	**Moderate** Due to serious imprecision[3]	Favipiravir probably has little or no difference on symptom resolution or improvement
		Difference: **12 more per 1000** (CI 95% 36 fewer - 61 more)			
Hospitalization (in patients with non-severe disease)	Relative risk: 1.33 (CI 95% 0.64 – 1.78) Based on data from 824 participants in 5 studies Follow up 28 days	**48** per 1000	**64** per 1000	**Low** Due to very serious imprecision[4]	Favipiravir may not reduce hospitalizations
		Difference: **16 more per 1000** (CI 95% 17 fewer - 37 more)			
Severe adverse events 30 days	Relative risk: 0.87 (CI 95% 0.48 - 1.58) Based on data from 1370 participants in 8 studies Follow up 28 days	**606** per 1000	**527** per 1000	**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
		Difference: **79 fewer per 1000** (CI 95% 315 fewer - 351 more)			

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. **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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Ivermectin		
Mortality (Low risk of bias studies)	Relative risk: 1 (CI 95% 0.8 - 1.24) Based on data from 6522 participants in 13 studies	**160** per 1000 Difference: **0 fewer per 1000** (CI 95% 32 fewer - 38 more)	**158** per 1000	**Moderate** Due to serious imprecision[1]	Ivermectin probably has little or no difference on mortality
Mechanical ventilation (Low risk of bias studies)	Relative risk: 0.82 (CI 95% 0.58 - 1.17) Based on data from 3288 participants in 9 studies	**173** per 1000 Difference: **31 fewer per 1000** (CI 95% 73 fewer - 29 more)	**142** per 1000	**Very low** Due to very serious imprecision[2]	We are uncertain whether ivermectin increases or decreases mechanical ventilation (low risk of bias studies)
Symptom resolution or improvement (Low risk of bias studies)	Relative risk: 1.04 (CI 95% 0.98 - 1.1) Based on data from 3238 participants in 7 studies	**606** per 1000 Difference: **24 more per 1000** (CI 95% 12 fewer - 61 more)	**630** per 1000	**Moderate** Due to serious imprecision[3]	Ivermectin probably has little or no difference on symptom resolution or improvement
Symptomatic infection (Low risk of bias studies)[4]	Relative risk: 1.01 (CI 95% 0.54 - 1.89) Based on data from 536 participants in 1 study	**174** per 1000 Difference: **2 more per 1000** (CI 95% 80 fewer - 155 more)	**176** per 1000	**Very low** Due to very serious imprecision[5]	We are uncertain whether ivermectin increases or decreases symptomatic infection
Severe adverse events	Relative risk: 1.05 (CI 95% 0.69 - 1.62) Based on data from 2831 participants in 8 studies Follow up 28 days	**102** per 1000 Difference: **5 more per 1000** (CI 95% 32 fewer - 63 more)	**107** per 1000	**Very low** Due to very serious imprecision[6]	Ivermectin may have little or no difference on severe adverse events
Hospitalization (in non-severe patients)	Relative risk: 0.9 (CI 95% 0.74 - 1.1) Based on data from 6315 participants in 11 studies Follow up 28 days	**48** per 1000 Difference: **5 fewer per 1000** (CI 95% 12 fewer - 5 more)	**43** per 1000	**Moderate** Due to serious imprecision[7]	Ivermectin probably has little or no difference on hospitalization

1. **Imprecision: 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. **Imprecision: very serious.** Low number of patients;
6. **Imprecision: very serious.** 95%CI includes significant benefits and absence of benefits;
7. **Imprecision: serious.** Less than 200 events.

Summary of findings Table 13. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Baricitinib		
Mortality	Relative risk: 0.73 (CI 95% 0.57 - 0.92) Based on data from 11102 participants in 5 studies	**160** per 1000	**117** per 1000	**High**	Baricitinib decreases mortality
		Difference: **43 fewer per 1000** (CI 95% 69 fewer - 13 fewer)			
Invasive mechanical ventilation	Relative risk: 0.83 (CI 95% 0.66 - 1.04) Based on data from 9114 participants in 3 studies Follow up 30 days	**173** per 1000	**144** per 1000	**Moderate** Due to serious imprecision[1]	Baricitinib probably decreases invasive mechanical ventilation
		Difference: **29 fewer per 1000** (CI 95% 59 fewer - 7 more)			
Symptom resolution or improvement	Relative risk: 1.27 (CI 95% 1.13 - 1.42) Based on data from 2659 participants in 3 studies Follow up 30 days	**606** per 1000	**770** per 1000	**Moderate** Due to serious risk of bias[2]	Baricitinib probably improves symptom resolution or improvement
		Difference: **164 more per 1000** (CI 95% 79 more - 255 more)			
Severe adverse events	Relative risk: 0.78 (CI 95% 0.64 - 0.95) Based on data from 2659 participants in 3 studies Follow up 30 days	**102** per 1000	**80** per 1000	**Moderate** Due to serious risk of bias[3]	Baricitinib probably has little or no difference on severe adverse events
		Difference: **22 fewer per 1000** (CI 95% 37 fewer - 5 fewer)			

1. **Imprecision: serious.** Wide confidence intervals;
2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up;
3. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up.

Summary of findings Table 14. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Azythromicin		
Mortality	Relative risk: 1.01 (CI 95% 0.92 - 1.1) Based on data from 8967 participants in 6 studies	**160** per 1000	**162** per 1000	**Moderate** Due to serious imprecision[1]	Azythromicin probably has little or no difference on mortality
		Difference: **2 more per 1000** (CI 95% 13 fewer - 16 more)			
Invasive mechanical ventilation	Relative risk: 0.92 (CI 95% 0.77 - 1.1) Based on data from 8947 participants in 5 studies	**173** per 1000	**159** per 1000	**Moderate** Due to serious imprecision[2]	Azythromicin probably has little or no difference on invasive mechanical ventilation
		Difference: **14 fewer per 1000** (CI 95% 40 fewer - 17 more)			
Symptom resolution or improvement[3]	Relative risk: 1.02 (CI 95% 0.99 - 1.04) Based on data from 9690 participants in 6 studies	**606** per 1000	**618** per 1000	**High**	Azythromicin 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 participants 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 azythromicin 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 participants 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]	Azythromicin 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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Colchicine		
Mortality	Relative risk: 0.99 (CI 95% 0.92 - 1.05) Based on data from 18353 patients in 13 studies	**160** per 1000	**158** per 1000	**Moderate** Due to serious imprecision[1]	Colchicine probably has little or no difference on mortality
		Difference: **2 fewer per 1000** (CI 95% 13 fewer - 8 more)			
Invasive mechanical ventilation	Relative risk: 0.98 (CI 95% 0.89 - 1.07) Based on data from 17053 patients in 7 studies Follow up 30 days	**173** per 1000	**170** per 1000	**Moderate** Due to serious imprecision[2]	Colchicine probably has little or no difference on invasive mechanical ventilation
		Difference: **3 fewer per 1000** (CI 95% 19 fewer - 12 more)			
Symptom resolution or improvement	Relative risk: 1 (CI 95% 0.98 - 1.02) Based on data from 11784 patients in 5 studies Follow up 30 days	**173** per 1000	**175** per 1000	**High**	Colchicine has little or no difference on symptom resolution or improvement
		Difference: **0 more per 1000** (CI 95% 3 fewer - 3 more)			
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 0.99) Based on data from 4880 patients in 3 studies Follow up 30 days	**102** per 1000	**80** per 1000	**High**	Colchicine has little or no difference on severe adverse events
		Difference: **22 fewer per 1000** (CI 95% 40 fewer - 1 fewer)			
Pulmonary embolism	Relative risk: 5.55 (CI 95% 1.23 - 25.0) Based on data from 4399 patients in 1 study Follow up 30 days	**0.9** per 1000	**5.0** per 1000	**Low** Due to very serious imprecision[3]	Colchicine may have little or no difference on pulmonary embolism
		Difference: **4.1 more per 1000** (CI 95% 0.21 more - 21.6 more)			
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	**Moderate** Due to serious imprecision[4]	Colchicine probably has little or no difference on hospitalization (in patients with non-severe disease)
		Difference: **9 fewer per 1000** (CI 95% 18 fewer - 2 more)			

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. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir		
Invasive mechanical ventilation (Low RoB studies)	Relative risk: 1.02 (CI 95% 0.59 - 1.76) Based on data from 1163 participants in 2 studies Follow up 30 days	**173** per 1000 Difference: **3 more per 1000** (CI 95% 71 fewer - 131 more)	**176** per 1000	**Low** Due to very serious imprecision[1]	Sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir may have little or no difference on invasive mechanical ventilation
Mortality (Low RoB studies)	Relative risk: 1.14 (CI 95% 0.83 - 1.56) Based on data from 1163 participants in 2 studies	**160** per 1000 Difference: **22 more per 1000** (CI 95% 27 fewer - 90 more)	**182** per 1000	**Low** Due to very serious imprecision[2]	Sofosbuvir alone or in combination may have little or no difference on mortality
Severe adverse events	Relative risk: 0.35 (CI 95% 0.06 - 2.18) Based on data from 628 participants in 2 studies	**102** per 1000 Difference: **66 fewer per 1000** (CI 95% 96 fewer - 120 more)	**36** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir increases or decreases severe adverse events
Symptom resolution or improvement (Low RoB studies)	Relative risk: 1.01 (CI 95% 0.95 - 1.08) Based on data from 1163 participants in 2 studies Follow up 7 days	**606** per 1000 Difference: **6 more per 1000** (CI 95% 30 fewer - 48 more)	**612** per 1000	**Moderate** Due to serious imprecision[4]	Sofosbuvir alone or in combination probably has little or no difference on symptom resolution or improvement
Symptomatic infection	Relative risk: 0.52 (CI 95% 0.3 - 0.89) Based on data from 548 participants in 1 study	**174** per 1000 Difference: **84 fewer per 1000** (CI 95% 122 fewer - 19 fewer)	**90** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether sofosbuvir +/- daclatasvir, ledipasvir or velpatasvir increases or decreases symptomatic infection

1. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: very serious.** 95%CI includes significant benefits and harms;
3. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, 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. Imprecision: very serious.** Wide confidence intervals;
4. **Inconsistency: serious. Imprecision: serious.** Wide confidence intervals;
5. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, 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. Imprecision: very serious.** Wide confidence intervals.

Summary of findings Table 17. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	REGEN-COV (casirivimab and imdevimab)		
Mortality	Relative risk: 0.83 (CI 95% 0.63 - 1.09) Based on data from 16845 participants in 4 studies	**160** per 1000	**133** per 1000	**Low** Due to serious inconsistency, Due to serious imprecision[1]	Regen-cov (casirivimab and imdevimab) may decrease mortality
		Difference: **27 fewer per 1000** (CI 95% 59 fewer - 14 more)			
Mortality (seronegative)	Relative risk: 0.79 (CI 95% 0.71 - 0.89) Based on data from 3673 participants in 2 studies	**160** per 1000	**126** per 1000	**Moderate** Due to serious indirectness[2]	Regen-cov (casirivimab and imdevimab) probably decreases mortality in seronegative patients
		Difference: **34 fewer per 1000** (CI 95% 46 fewer - 18 fewer)			
Invasive mechanical ventilation	Relative risk: 0.79 (CI 95% 0.54 - 1.14) Based on data from 14575 participants in 3 studies Follow up 30 days	**173** per 1000	**137** per 1000	**Low** Due to very serious imprecision[3]	Regen-cov (casirivimab and imdevimab) may decrease invasive mechanical ventilation
		Difference: **36 fewer per 1000** (CI 95% 80 fewer - 24 more)			
Invasive mechanical ventilation (seronegative)	Relative risk: 0.82 (CI 95% 0.74 - 0.9) Based on data from 3603 participants in 2 studies	**173** per 1000	**142** per 1000	**Moderate** Due to serious indirectness, Due to serious imprecision[4]	Regen-cov (casirivimab and imdevimab) probably decreases invasive mechanical ventilation in seronegative patients
		Difference: **31 fewer per 1000** (CI 95% 45 fewer - 17 fewer)			
Symptom resolution or improvement	Relative risk: 1.06 (CI 95% 1.0 - 1.12) Based on data from 14746 participants in 3 studies	**606** per 1000	**642** per 1000	**Low** Due to serious imprecision, Due to serious inconsistency[5]	Regen-cov (casirivimab and imdevimab) may increase symptom resolution or improvement
		Difference: **36 more per 1000** (CI 95% 0 fewer - 73 more)			
Symptom resolution or improvement (seronegative)	Relative risk: 1.1 (CI 95% 1.06 - 1.14) Based on data from 6277 participants in 3 studies Follow up 30 days	**606** per 1000	**667** per 1000	**Moderate** Due to serious indirectness[6]	Regen-cov (casirivimab and imdevimab) probably increases symptom resolution or improvement in seronegative patients
		Difference: **61 more per 1000** (CI 95% 36 more - 85 more)			
Hospitalization (in patients with non-severe disease)	Relative risk: 0.28 (CI 95% 0.19 - 0.42)	**48** per 1000	**13** per 1000	**Moderate** Due to serious imprecision[7]	Regen-cov (casirivimab and imdevimab) probably reduces hospitalization in

	Based on data from 6732 participants in 4 studies Follow up 30 days	Difference: **35 fewer per 1000** (CI 95% 39 fewer - 28 fewer)		patients with recent onset non-severe disease
Symptomatic infection (in exposed individuals)	Relative risk: 0.24 (CI 95% 0.08 - 0.76) Based on data from 2856 participants in 3 studies Follow up 30 days	**174** per 1000 **42** per 1000 Difference: **132 fewer per 1000** (CI 95% 160 fewer - 42 fewer)	**High** 8	Regen-cov (casirivimab and imdevimab) decreases symptomatic infection in exposed individuals
Severe adverse events	Relative risk: 0.51 (CI 95% 0.38 - 0.67) Based on data from 12360 participants in 6 studies	**102** per 1000 **52** per 1000 Difference: **50 fewer per 1000** (CI 95% 63 fewer - 34 fewer)	**Moderate** Due to serious imprecision[9]	Regen-cov (casirivimab and imdevimab) probably has little or no difference on severe adverse events

1. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **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. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis; **Imprecision: very serious.**
3. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: very serious.** Wide confidence intervals;
4. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Indirectness: serious.** Subgroup analysis;
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. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up; **Imprecision: serious.** Low number of events;
8. **Risk of Bias: no serious.** Incomplete data and/or large loss to follow up;
9. **Imprecision: serious.** Wide confidence intervals.

Summary of findings Table 18. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Sotrovimab
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	Sotrovimab		
Mortality	Relative risk: 0.2 (CI 95% 0.01 - 4.16) Based on data from 1057 participants in 1 study	**160** per 1000	**32** per 1000	**Very low** Due to extremely serious imprecision[1]	We are uncertain whether sotrovimab increases or decreases mortality
		Difference: **128 fewer per 1000** (CI 95% 158 fewer - 506 more)			
Mechanical ventilation	Relative risk: 0.11 (CI 95% 0.01 - 2.06) Based on data from 1057 participants in 1 study	**174** per 1000	**19** per 1000	**Very low** Due to extremely serious imprecision[2]	We are uncertain whether sotrovimab increases or decreases mechanical ventilation
		Difference: **155 fewer per 1000** (CI 95% 172 fewer - 184 more)			
Hospitalization	Relative risk: 0.2 (CI 95% 0.08 - 0.48) Based on data from 1057 participants in 1 study	**48** per 1000	**10** per 1000	**Moderate** Due to serious imprecision[3]	Sotrovimab probably decreases hospitalization
		Difference: **38 fewer per 1000** (CI 95% 44 fewer - 25 fewer)			
Hospitalization (sotrovimab vs. REGEN-COV)	Relative risk: 1.07 (CI 95% 0.88 - 1.3) Based on data from 3558 participants in 1 study	**48** per 1000	**51** per 1000	**High**	Sotrovimab has little or no difference on hospitalization compared to REGEN-COV
		Difference: **3 more per 1000** (CI 95% 6 fewer - 14 more)			
Severe adverse events	Relative risk: 0.34 (CI 95% 0.18 - 0.68) Based on data from 1057 participants in 1 study	**102** per 1000	**35** per 1000	**Moderate** Due to serious imprecision[4]	Sotrovimab probably has little or no difference on severe adverse events
		Difference: **67 fewer per 1000** (CI 95% 84 fewer - 33 fewer)			

1. **Imprecision: ~extremely_serious.** Very low number of events;
2. **Imprecision: ~extremely_serious.** Very low number of events;
3. **Imprecision: serious;**
4. **Imprecision: serious.** Low number of patients.

Summary of findings Table 19. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Inhaled coticosteroids		
Symptom resolution or improvement[1]	Relative risk: 1.09 (CI 95% 0.99 - 1.2) Based on data from 3919 participants in 8 studies	**606** per 1000 Difference: **55 more per 1000** (CI 95% 6 fewer - 121 more)	**661** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Inhaled coticosteroids may increase symptom resolution or improvement
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.44 - 1.98) Based on data from 1560 participants in 1 study	**173** per 1000 Difference: **10 fewer per 1000** (CI 95% 97 fewer - 170 more)	**163** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether inhaled coticosteroids increases or decreases invasive mechanical ventilation
Mortality	Relative risk: 0.82 (CI 95% 0.44 - 1.53) Based on data from 2345 participants in 5 studies	**160** per 1000 Difference: **29 fewer per 1000** (CI 95% 90 fewer - 85 more)	**131** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[4]	We are uncertain whether inhaled coticosteroids increases or decreases mortality
Severe adverse events	Relative risk: 0.5 (CI 95% 0.23 - 1.12) Based on data from 2014 participants in 4 studies	**102** per 1000 Difference: **51 fewer per 1000** (CI 95% 79 fewer - 12 more)	**51** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision[5]	We are uncertain whether inhaled coticosteroids increases or decreases severe adverse events
Hospitalizations	Relative risk: 0.9 (CI 95% 0.7 - 1.15) Based on data from 3953 participants in 5 studies	**48** per 1000 Difference: **5 fewer per 1000** (CI 95% 14 fewer - 7 more)	**43** per 1000	**Moderate** Due to serious risk of bias[6]	Inhaled coticosteroids probably has little or no difference on hospitalizations

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

Summary of findings Table 20. (Interactive online version)

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	**Very low** Due to very serious imprecision[1]	There were too few who experienced the mortality, in order to determine whether fluvoxamine made a difference
		Difference: **50 fewer per 1000** (CI 95% 102 fewer - 43 more)			
Mechanical ventilation	Relative risk: 0.77 (CI 95% 0.45 - 1.3) Based on data from 1497 patients in 1 study	**173** per 1000	**133** per 1000	**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
		Difference: **40 fewer per 1000** (CI 95% 95 fewer - 52 more)			
Hospitalizations	Relative risk: 0.79 (CI 95% 0.6 - 1.03) Based on data from 2302 patients in 3 studies	**48** per 1000	**38** per 1000	**Moderate** Due to serious imprecision[3]	Fluvoxamine probably has little or no difference on hospitalizations
		Difference: **10 fewer per 1000** (CI 95% 19 fewer - 1 more)			
Severe adverse events[4]	Relative risk: 0.81 (CI 95% 0.54 - 1.22) Based on data from 1649 patients in 2 studies	**102** per 1000	**83** per 1000	**Low** Due to very serious imprecision[5]	Fluvoxamine may not increase severe adverse events
		Difference: **19 fewer per 1000** (CI 95% 47 fewer - 22 more)			

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 21. (Interactive online version)

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		
Symptom resolution	Relative risk: 1.17 (CI 95% 1.1 - 1.3) Based on data from 1513 participants in 2 studies Follow up 5	**606** per 1000	**1000** per 1000	**Low** Due to very serious risk of bias[1]	Molnupiravir may increase symptom resolution
		Difference: **394 more per 1000** (CI 95% 394 more - 394 more)			
Mortality	Relative risk: 0.35 (CI 95% 0.06 - 2.19) Based on data from 2202 participants in 4 studies	**160** per 1000	**56** per 1000	**Very low** Due to very serious imprecision[2]	We are uncertain whether molnupiravir increases or decreases mortality
		Difference: **104 fewer per 1000** (CI 95% 150 fewer - 190 more)			
Mechanical ventilation	Relative risk: 0.36 (CI 95% 0.11 - 1.12) Based on data from 1610 participants in 1 studies	**173** per 1000	**62** per 1000	**Very low** Due to very serious imprecision[3]	We are uncertain whether molnupiravir increases or decreases mortality
		Difference: **111 fewer per 1000** (CI 95% 154 fewer - 21 more)			
Hospitalization	Relative risk: 0.6 (CI 95% 0.44 - 0.81) Based on data from 4050 participants in 6 studies	**48** per 1000	**29** per 1000	**High**	Molnupiravir decreases hospitalization
		Difference: **19 fewer per 1000** (CI 95% 27 fewer - 9 fewer)			
Severe adverse events	Relative risk: 0.75 (CI 95% 0.48 - 1.19) Based on data from 2219 participants in 4 studies Follow up 29	**102** per 1000	**77** per 1000	**Low** Due to very serious imprecision[4]	Molnupiravir may have little or no difference on severe adverse events
		Difference: **25 fewer per 1000** (CI 95% 53 fewer - 19 more)			

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

Summary of findings Table 22. (Interactive online version)

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 study	**160** per 1000	**6** per 1000	**Very low** Due to very serious imprecision[1]	We are uncertain whether nirmatrelvir-ritonavir increases or decreases mortality
		Difference: **154 fewer per 1000** (CI 95% 160 fewer - 51 fewer)			
Hospitalization	Relative risk: 0.12 (CI 95% 0.06 - 0.25) Based on data from 2085 participants in 1 study	**48** per 1000	**6** per 1000	**Moderate** Due to serious imprecision[2]	Nirmatrelvir-ritonavir probably decreases hospitalizations
		Difference: **42 fewer per 1000** (CI 95% 45 fewer - 36 fewer)			
Severe adverse events	Relative risk: 0.49 (CI 95% 0.3 - 0.8) Based on data from 2224 participants in 1 study Follow up 29	**102** per 1000	**50** per 1000	**Moderate** Due to serious imprecision[3]	Nirmatrelvir-ritonavir probably has little or no difference on severe adverse events
		Difference: **52 fewer per 1000** (CI 95% 71 fewer - 20 fewer)			

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.

Summary of findings Table 23. (Interactive online version)

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

<table>
<tr><th rowspan="2">Outcome
Timeframe</th><th rowspan="2">Study results and measurements</th><th colspan="2">Absolute effect estimates</th><th rowspan="2">Certainty of the Evidence
(Quality of evidence)</th><th rowspan="2">Plain language summary</th></tr>
<tr><th>Standard of care</th><th>Molnupiravir</th></tr>
<tr><td rowspan="2">Mortality</td><td rowspan="2">Relative risk: 0.72
(CI 95% 0.59 - 0.89)
Based on data from 686 participants in 3 studies</td><td>160
per 1000</td><td>21
per 1000</td><td rowspan="2">Low
Due to serious imprecision and incositency[1]</td><td rowspan="2">Ruxolitinib may reduce mortality</td></tr>
<tr><td colspan="2">Difference: 45 fewer per 1000
(CI 95% 66 fewer - 18 fewer)</td></tr>
<tr><td rowspan="2">Mechanical ventilation</td><td rowspan="2">Relative risk: 0.99
(CI 95% 0.49 - 1.99)
Based on data from 474 patients in 2 study</td><td>173
per 1000</td><td>171
per 1000</td><td rowspan="2">Very low
Due to very serious imprecision[2]</td><td rowspan="2">It is uncertain if ruxolitinib increases or decreases mechanical ventilation</td></tr>
<tr><td colspan="2">Difference: 2 fewer per 1000
(CI 95% 32 fewer - 171 more)</td></tr>
<tr><td rowspan="2">Severe adverse events</td><td rowspan="2">Relative risk: 1.12
(CI 95% 0.69 - 1.82)
Based on data from 679 participants in 3 studies</td><td>102
per 1000</td><td>114
per 1000</td><td rowspan="2">Very low
Due to very serious imprecision[2]</td><td rowspan="2">It is uncertain if ruxolitinib increases or decreases mechanical ventilation</td></tr>
<tr><td colspan="2">Difference: 12 more per 1000
(CI 95% 79 fewer - 100 more)</td></tr>
<tr><td rowspan="2">Symptom resolution</td><td rowspan="2">Relative risk: 1.05
(CI 95% 0.89 – 1.24)
Based on data from 685 participants in 3 studies</td><td>606
per 1000</td><td>606
per 1000</td><td rowspan="2">Low
Due to very serious imprecision[2]</td><td rowspan="2">Ruxolitinb may no increase symptom resolution</td></tr>
<tr><td colspan="2">Difference: 30 more per 1000
(CI 95% 66 fewer - 145 more)</td></tr>
</table>

1. **Imprecision: serious.** Low number of patients; **Inconsistency: serious.** Significant not explained heterogeneity;
2. **Imprecision: very serious.** 95%CI including important benefits and harms.

Summary of findings Table 24. (Interactive online version)

Patients with COVID-19 infection
Intervention: CD24Fc
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	CD24Fc		
Mortality	Relative risk: 0.9 (CI 95% 0.49 - 1.69) Based on data from 234 participants in 1 study Follow up 29 days	**160** per 1000	**144** per 1000	**Very low** Due to extremely serious imprecision[1]	We are uncertain whether CD24Fc increases or decreases mortality
		Difference: **16 fewer per 1000** (CI 95% 82 fewer - 110 more)			
Invasive mechanical ventilation	Relative risk: 0.57 (CI 95% 0.34 - 0.96) Based on data from 234 participants in 1 study Follow up 29 days	**173** per 1000	**99** per 1000	**Low** Due to serious imprecision, Due to very serious imprecision[2]	CD24Fc may decrease invasive mechanical ventilation
		Difference: **74 fewer per 1000** (CI 95% 114 fewer - 7 fewer)			
Symptom resolution or improvement	Relative risk: 1.18 (CI 95% 1.0 - 1.39) Based on data from 234 participants in 1 study Follow up 29 days	**606** per 1000	**715** per 1000	**Low** Due to very serious imprecision[3]	CD24Fc may increase symptom resolution or improvement
		Difference: **109 more per 1000** (CI 95% 0 fewer - 236 more)			
Severe adverse events	Relative risk: 0.98 (CI 95% 0.61 - 1.57) Based on data from 234 participants in 1 study Follow up 29 days	**102** per 1000	**100** per 1000	**Very low** Due to extremely serious imprecision[4]	We are uncertain whether CD24Fc increases or decreases severe adverse events
		Difference: **2 fewer per 1000** (CI 95% 40 fewer - 58 more)			

1. **Imprecision: ~extreme_serious.** Low number of patients, Wide confidence intervals;
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients;
3. **Imprecision: very serious;**
4. **Imprecision: ~extreme_serious.** Wide confidence intervals, Low number of patients.

Summary of findings Table 25. (Interactive online version)

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	 Vitamin D	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Symptom resolution or improvement	Relative risk: 1.78 (CI 95% 1.1 - 2.94) Based on data from 43 participants in 1 study	**606** per 1000	**1079** per 1000	**Very low** Due to very serious imprecision, Due to serious risk of bias[1]	We are uncertain whether vitamin d increases or decreases invasive mechanical ventilation
		Difference: **473 more per 1000** (CI 95% 61 more - 1176 more)			
Mortality	Relative risk: 1.24 (CI 95% 0.8 - 1.91) Based on data from 1234 participants in 6 studies	**160** per 1000	**198** per 1000	**Very low** Due to very serious imprecision, Due to serious risk of bias[2]	We are uncertain whether vitamin D increases or decreases mortality
		Difference: **38 more per 1000** (CI 95% 32 fewer - 146 more)			
Invasive mechanical ventilation	Relative risk: 0.55 (CI 95% 0.31 - 1.0) Based on data from 561 participants in 3 studies	**173** per 1000	**95** per 1000	**Very low** Due to very serious imprecision, Due to serious risk of bias[3]	We are uncertain whether vitamin d increases or decreases invasive mechanical ventilation
		Difference: **78 fewer per 1000** (CI 95% 119 fewer - 0 fewer)			
Symptomatic infection (Excluding high RoB studies)	Relative risk: 1.25 (CI 95% 0.93 - 1.67) Based on data from 5979 participants in 1 studies Follow up 29 days	**174** per 1000	**218** per 1000	**Moderate** Due to serious risk of bias[4]	Vitamin D probably does not reduce symptomatic infections
		Difference: **44 more per 1000** (CI 95% 12 fewer - 117 more)			
Hospitalization	Relative risk: 1.26 (CI 95% 0.84 - 1.89) Based on data from 6281 participants in 2 studies	**48** per 1000	**60** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Vitamin D may not reduce hospitalizations
		Difference: **12 more per 1000** (CI 95% 8 fewer - 43 more)			
Severe adverse events	Relative risk: 1.03 (CI 95% 0.84 - 1.89) Based on data from 6197 participants in 2 studies Follow up 29 days	**102** per 1000	**105** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[6]	Vitamin D may not increase severe adverse events
		Difference: **3 more per 1000** (CI 95% 16 fewer - 91 more)			

1. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Wide confidence intervals, low number of patients;
2. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Low number of patients, wide confidence intervals;
3. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: very serious.** Wide confidence intervals, low number of patients;
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;

5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients;
6. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals, low number of patients.

Summary of findings Table 26. (Interactive online version)

Population: Patients with COVID-19 infection
Intervention: Tixagevimab–Cilgavimab
Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		SOC	Tixagevimab–Cilgavimab		
Symptom resolution or improvement	Relative risk: 1.03 (CI 95% 0.99 - 1.08) Based on data from 1417 participants in 1 study	**606** per 1000	**624** per 1000	**Moderate** Due to serious imprecision[1]	Tixagevimab– cilgavimab probably has little or no difference on symptom resolution or improvement
		Difference: **18 more per 1000** (CI 95% 6 fewer - 48 more)			
Mortality	Relative risk: 0.72 (CI 95% 0.54 - 0.96) Based on data from 7492 participants in 3 studies	**160** per 1000	**115** per 1000	**Moderate** Due to serious imprecision[2]	Tixagevimab– cilgavimab probably decreases mortality
		Difference: **45 fewer per 1000** (CI 95% 74 fewer - 6 fewer)			
Symptomatic infection	Relative risk: 0.18 (CI 95% 0.09 - 0.35) Based on data from 5172 participants in 1 study Follow up 29 days	**174** per 1000	**31** per 1000	**Moderate** Due to serious risk of bias[3]	Tixagevimab– cilgavimab probably decreases symptomatic infection
		Difference: **143 fewer per 1000** (CI 95% 158 fewer - 113 fewer)			
Severe adverse events	Relative risk: 0.95 (CI 95% 0.69 - 1.31) Based on data from 7492 participants in 3 studies	**102** per 1000	**97** per 1000	**Low** Due to very serious imprecision[4]	Tixagevimab– cilgavimab may have little or no difference on severe adverse events
		Difference: **5 fewer per 1000** (CI 95% 32 fewer - 32 more)			
Hospitalization	Relative risk: 0.42 (CI 95% 0.24 - 0.74) Based on data from 903 participants in 1 study	**102** per 1000	**43** per 1000	**Moderate** Due to serious imprecision[5]	Tixagevimab– cilgavimab probably decreases hospitalization
		Difference: **59 fewer per 1000** (CI 95% 78 fewer - 27 fewer)			

1. **Imprecision: serious.** Low number of patients;
2. **Imprecision: serious.** Low number of patients;
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. Imprecision: very serious.** Wide confidence intervals;
5. **Imprecision: serious.** Low number of patients.

References

1. World Health Organization. Commentaries: Off-label use of medicines for COVID-19 (Scientific brief, 31 March 2020) [Internet]. Geneva: World Health Organization; 2020 [cited 7 December 2020]. Available from: https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19
2. The L·OVE Platform. Methods for the special L·OVE of coronavirus infection [Internet] Santiago: Epistemonikos Foundation; 2020 [cited 7 December 2020]. Available from: https://app.iloveevidence.com/covid-19
3. World Health Organization. WHO R&D Blueprint novel Coronavirus: outline of trial designs for experimental therapeutics. WHO reference number WHO/HEO/R&D Blueprint (nCoV)/2020.4. Geneva: World Health Organization; 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1
4. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE Guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol 2019;111(July):105–14. Available from: https://doi.org/10.1016/j.jclinepi.2018.01.012.
5. Docherty AB, Mulholland RH, Lone NI, Cheyne CP, De Angelis D, Diaz-Ordaz K, et al. Changes in UK hospital mortality in the first wave of COVID-19: the ISARIC WHO Clinical Characterisation Protocol prospective multicentre observational cohort study. MedRxiv 2020. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.12.19.20248559
6. International Severe Acute Respiratory and emerging Infections Consortium, Hall M, Pritchard M, Dankwa EA, Baillie JK, Carson G, et al. ISARIC Clinical Data Report 20 November 2020 [Internet]. MedRxiv 2020. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.07.17.20155218
7. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet 2020;395:1973-1987. Available from: https://doi.org/10.1016/S0140-6736(20)31142-9.

8. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol 2017; 87: 4–13.
9. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. Journal of Clinical Epidemiology 2021; 137: 163–75.
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. Available from: https://doi.org/10.1136/bmj.l4898.
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–26.
12. Axfors C, Schmitt AM, Janiaud P, van 't Hooft J, Abd-Elsalam S, Abdo EF, et al.. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.09.16.20194571.
13. Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M. Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines. Swiss Med Wkly 2020;150:w20301. Available from: https://doi.org/10.4414/smw.2020.20301.
14. Pan-American Health Organization. Guidelines for critical care of seriously ill adult patients with coronavirus (COVID-19) in the Americas: short version v-1. Washington DC: PAHO;2020. Available from: https://iris.paho.org/handle/10665.2/52184
15. Yuan X, Yi W, Liu B, Tian S, Cao F, Wang R, et al. Pulmonary radiological change of COVID-19 patients with 99mTc-MDP treatment [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.04.07.20054767.
16. Fakharian A, Barati S, Mirenayat M, Rezaei M, Haseli S, Torkaman P, et al. Evaluation of adalimumab effects in managing severe cases of COVID-19: A randomized controlled trial. International Immunopharmacology. 2021 Oct;99:107961.
17. McElvaney OJ, McEvoy NL, Boland F, McElvaney OF, Hogan G, Donnelly K, et al. A randomized, double-blind, placebo-controlled trial of intravenous alpha-1 antitrypsin for acute respiratory distress syndrome secondary to COVID-19. Med. 2022 Mar;S2666634022001295.

18. Navarese EP, Podhajski P, Andreotti F, La Torre G, Gajda R, Radziwanowski A, et al. Ion channel inhibition with amiodarone or verapamil in symptomatic hospitalized nonintensive-care COVID-19 patients: The ReCOVery-SIRIO randomized trial. Cardiol J. 2022 Jul 29;VM/OJS/J/88627.
19. Siami Z, Aghajanian S, Mansouri S, Mokhames Z, Pakzad R, Kabir K, et al. Effect of Ammonium Chloride in addition to standard of care in outpatients and hospitalized COVID-19 patients: a randomized clinical trial. International Journal of Infectious Diseases. 2021 Apr;S1201971221003544.
20. Roshon M, Lemos-Filho L, Cherevka H, Goldberg L, Salottolo K, Bar-Or D. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of a Novel Inhaled Biologic Therapeutic in Adults with Respiratory Distress Secondary to COVID-19 Infection. Infect Dis Ther [Internet]. 2021 Nov 14 [cited 2021 Dec 6]; Available from: https://link.springer.com/10.1007/s40121-021-00562-z
21. Bureau S, Dougados M, Tibi A, Azoulay E, Cadranel J, Emmerich J, et al. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. The Lancet Respiratory Medicine. 2021 Jan;S2213260020305567.
22. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early Anakinra Treatment for COVID-19 Guided by Urokinase Plasminogen Receptor [Internet]. Infectious Diseases (except HIV/AIDS); 2021 May [cited 2021 May 24]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.16.21257283
23. Declercq J, Van Damme KFA, De Leeuw E, Maes B, Bosteels C, Tavernier SJ, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. The Lancet Respiratory Medicine. 2021 Oct;S2213260021003775.
24. Kharazmi AB, Moradi O, Haghighi M, Kouchek M, Manafi-Rasi A, Raoufi M, et al. A randomized controlled clinical trial on efficacy and safety of anakinra in patients with severe COVID-19. Immun Inflamm Dis. 2021 Nov 11;iid3.563.
25. Elmekaty EZI, Maklad A, Abouelhassan R, Munir W, Mohamed Ibrahim MI, Nair A, et al. Efficacy of Anakinra in the Management of Patients with COVID-19 Infection: A Randomized Clinical Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jul

[cited 2022 Jul 18]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.07.04.22277207

26. Audemard-Verger A, Le Gouge A, Pestre V, Courjon J, Langlois V, Vareil MO, et al. Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial. Plavec D, editor. PLoS ONE. 2022 Aug 4;17(8):e0269065.
27. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet Respir Med. 2021 Jan 7.
28. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, dos Santos TM, Mazza L, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial. JAMA. 2021 Jan 19;325(3):254.
29. Bauer A, Schreinlechner M, Sappler N, Dolejsi T, Tilg H, Aulinger BA, et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. The Lancet Respiratory Medicine. 2021 Jun;S2213260021002149.
30. Tornling G, Batta R, Porter JC, Williams B, Bengtsson T, Parmar K, et al. Seven days treatment with the angiotensin II type 2 receptor agonist C21 in hospitalized COVID-19 patients; a placebo-controlled randomised multi-centre double-blind phase 2 trial. EClinicalMedicine. 2021 Nov;41:101152.
31. Comparison of Losartan and Amlodipine Effects on the Outcomes of Patient with COVID-19 and Primary Hypertension: A Randomized Clinical Trial. International Journal of Clinical Practice [Internet]. 2021 Mar [cited 2021 Mar 4]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/ijcp.14124
32. Puskarich M, Cummins NW, Ingraham N, Wacker DA, Reilkoff R, Driver BE, et al. Effect of Losartan on Symptomatic Outpatients with COVID-19: A Randomized Clinical Trial. SSRN Journal [Internet]. 2021 [cited 2021 Mar 24]; Available from: https://www.ssrn.com/abstract=378746

33. Geriak M, Haddad F, Kullar R, Greenwood KL, Habib M, Habib C, et al. Randomized Prospective Open Label Study Shows No Impact on Clinical Outcome of Adding Losartan to Hospitalized COVID-19 Patients with Mild Hypoxemia. Infect Dis Ther [Internet]. 2021 May 11 [cited 2021 May 18]; Available from: https://link.springer.com/10.1007/s40121-021-00453-3
34. Duarte M, Pelorosso F, Nicolosi LN, Victoria Salgado M, Vetulli H, Aquieri A, et al. Telmisartan for treatment of Covid-19 patients: An open multicenter randomized clinical trial. EClinicalMedicine. 2021 Jul;37:100962.
35. Najmeddin F, Solhjoo M, Ashraf H, Salehi M, Rasooli F, Ghoghaei M, et al. Effects of Renin-Angiotensin-Aldosterone Inhibitors on Early Outcomes of Hypertensive COVID-19 Patients: A Randomized Triple-Blind Clinical Trial. American Journal of Hypertension. 2021 Jul 15;hpab111.
36. Puskarich MA, Ingraham NE, Merck LH, Driver BE, Wacker DA, Black LP, et al. Effect of losartan on hospitalized patients with COVID-19-induced lung injury: A randomized clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Aug [cited 2021 Nov 24]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.08.25.21262623
37. Freilich D, Victory J, Jenkins P, Gadomski A. COVIDMED – An early pandemic randomized clinical trial of losartan treatment for hospitalized COVID-19 patients. Contemporary Clinical Trials Communications. 2022 Oct;29:100968.
38. Sharma A, Elharram M, Afilalo J, Flannery A, Afilalo M, Tselios C, et al. A Randomized Controlled Trial of Renin-Angiotensin-Aldosterone System Inhibitor Management in Patients Admitted in Hospital with COVID-19. American Heart Journal. 2022 Feb;S0002870322000242.
39. Bertoldi Lemos AC, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, Miranda CH. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID). Thromb Res 2020;196:359-366. Available from: https://doi.org/10.1016/j.thromres.2020.09.026.
40. The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 4;NEJMoa2103417.
41. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic

Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA [Internet]. 2021 Mar 18 [cited 2021 Mar 22]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2777829

42. Perepu U, Chambers I, Wahab A, Ten Eyck P, Wu C, Dayal S, et al. Standard Prophylactic Versus Intermediate Dose Enoxaparin in Adults with Severe COVID-19: A Multi-Center, Open-Label, Randomised Controlled Trial. SSRN Journal [Internet]. 2021 [cited 2021 May 18]; Available from: https://www.ssrn.com/abstract=3840099
43. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, et al. Therapeutic Anticoagulation in Non-Critically Ill Patients with Covid-19 [Internet]. Intensive Care and Critical Care Medicine; 2021 May [cited 2021 May 27]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.13.21256846
44. Lopes RD, de Barros e Silva PGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. The Lancet. 2021 Jun;S0140673621012034.
45. Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ. 2021 Oct 14;n2400.
46. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med [Internet]. 2021 Oct 7 [cited 2021 Oct 15]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2785004
47. Marcos M, Carmona-Torre F, Vidal Laso R, Ruiz-Artacho P, Filella D, Carbonell C, et al. Therapeutic vs. prophylactic bemiparin in hospitalized patients with non-severe COVID-19 (BEMICOP): an open-label, multicenter, randomized trial. Thromb Haemost. 2021 Oct 12;a-1667-7534.

48. Oliynyk O, Barg W, Slifirczyk A, Oliynyk Y, Dubrov S, Gurianov V, et al. Comparison of the Effect of Unfractionated Heparin and Enoxaparin Sodium at Different Doses on the Course of COVID-19-Associated Coagulopathy. Life. 2021 Sep 30;11(10):1032.
49. Morici N, Podda G, Birocchi S, Bonacchini L, Merli M, Trezzi M, et al. Enoxaparin for thromboprophylaxis in hospitalized COVID-19 patients: The X-COVID-19 Randomized Trial. Eur J Clin Investigation [Internet]. 2021 Dec 26 [cited 2022 Jan 7]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/eci.13735
50. Muñoz-Rivas N, Aibar J, Gabara-Xancó C, Trueba-Vicente Á, Urbelz-Pérez A, Gómez-Del Olmo V, et al. Optimal thromboprophylaxis strategies in non-critically ill patients with COVID-19 pneumonia. The PROTHROMCOVID Randomized Controlled Trial [Internet]. Cardiovascular Medicine; 2022 May [cited 2022 Jun 2]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.05.03.22274594
51. Blondon M, Cereghetti S, Pugin J, Marti C, Darbellay Farhoumand P, Reny J, et al. Therapeutic anticoagulation to prevent thrombosis, coagulopathy, and mortality in severe COVID-19: The Swiss COVID-HEP randomized clinical trial. Res Pract Thromb Haemost [Internet]. 2022 May [cited 2022 Jun 2];6(4). Available from: https://onlinelibrary.wiley.com/doi/10.1002/rth2.12712
52. Kumar D, Kaimaparambil V, Chandralekha S, Lalchandani J. Oral Rivaroxaban in the Prophylaxis of COVID-19 Induced Coagulopathy. J Assoc Physicians India. 2022 Feb;70(2):11–2.
53. Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, et al. Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: The ACTIV-4B Randomized Clinical Trial. JAMA. 2021 Oct 11;
54. Ananworanich J, Mogg R, Dunne MW, Bassyouni M, David CV, Gonzalez E, et al. Randomized study of rivaroxaban vs. placebo on disease progression and symptoms resolution in high-risk adults with mild COVID-19. Clinical Infectious Diseases. 2021 Sep 15;ciab813.
55. Barco S, Voci D, Held U, Sebastian T, Bingisser R, Colucci G, et al. Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (OVID): a randomised, open-label, parallel-group, multicentre, phase 3 trial. The Lancet Haematology. 2022 Jun;S2352302622001752.

56. Cools F, Virdone S, Sawhney J, Lopes RD, Jacobson B, Arcelus JI, et al. Thromboprophylactic low-molecular-weight heparin versus standard of care in unvaccinated, at-risk outpatients with COVID-19 (ETHIC): an open-label, multicentre, randomised, controlled, phase 3b trial. The Lancet Haematology. 2022 Aug;9(8):e594–604.
57. Kumar DrGS, Vadgaonkar DrA, Purunaik DrS, Shelatkar R, Vaidya VG, Ganu DrG, et al. Efficacy and Safety of Aspirin, Promethazine, and Micronutrients for Rapid Clinical Recovery in Mild to Moderate COVID-19 Patients: A Randomized Controlled Clinical Trial. Cureus [Internet]. 2022 May 30 [cited 2022 Jul 18]; Available from: https://www.cureus.com/articles/96829-efficacy-and-safety-of-aspirin-promethazine-and-micronutrients-for-rapid-clinical-recovery-in-mild-to-moderate-covid-19-patients-a-randomized-controlled-clinical-trial
58. Mehboob R, Ahmad F, Qayyum A, Rana MA, Tariq MA, Akram J. Aprepitant as a combinant with dexamethasone reduces the inflammation via neurokinin 1 receptor antagonism in severe to critical COVID-19 patients and potentiates respiratory recovery: a novel therapeutic approach [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.08.01.20166678.
59. Redondo-Calvo FJ, Padín JF, Muñoz-Rodríguez JR, Serrano-Oviedo L, López-Juárez P, Porras Leal ML, et al. Aprotinin treatment against SARS-CoV-2: A randomized phase III study to evaluate the safety and efficacy of a pan-protease inhibitor for moderate COVID-19. Eur J Clin Investigation [Internet]. 2022 Apr 5 [cited 2022 Apr 27]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/eci.13776
60. Khodashahi R, Naderi H, Bojdy A, Heydari AA, Sani AT, Ghabouli MJ, et al. Comparison the Effect of Arbidol Plus Hydroxychloroquine vs Hydroxychloroquine Alone in Treatment of COVID-19 Disease: A Randomized Clinical Trial. CRMR. 2021 Mar 1;16(4):252–62.
61. Hellou E, Mohsin J, Elemy A, Hakim F, Mustafa-Hellou M, Hamoud S. Effect of ArtemiC in patients with COVID-19: A Phase II prospective study. J Cellular Molecular Medi. 2022 May 19;jcmm.17337.
62. Trieu V, Saund S, Rahate PV, Barge VB, Nalk KS, Windlass H, et al. Targeting TGF-β pathway with COVID-19 Drug Candidate ARTIVeda/PulmoHeal Accelerates Recovery from Mild-Moderate COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS);

2021 Feb [cited 2021 Feb 16]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.01.24.21250418

63. Ghati N, Bhatnagar S, Mahendran M, Thakur A, Prasad K, Kumar D, et al. Statin and aspirin as adjuvant therapy in hospitalised patients with SARS-CoV-2 infection: a randomised clinical trial (RESIST trial). BMC Infect Dis. 2022 Dec;22(1):606.
64. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2021 Nov;S0140673621018250.
65. REMAP-CAP Writing Committee for the REMAP-CAP Investigators, Florescu S, Stanciu D, Zaharia M, Kosa A, Codreanu D, et al. Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2022 Mar 22 [cited 2022 Apr 4]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2790488
66. Nekoukar Z, Ala S, Moradi S, Hill A, Davoudi Badabi AR, Alikhani A, et al. Comparison of the Efficacy and Safety of Atazanavir/Ritonavir Plus Hydroxychloroquine with Lopinavir/Ritonavir Plus Hydroxychloroquine in Patients with Moderate COVID-19, A Randomized, Double-blind Clinical Trial. Iran J Pharm Res. 2021;20(4):278–88.
67. Jain MK, Lemos JA de, McGuire DK, Ayers C, Eiston JL, Sanchez CL, et al. Atovaquone for Treatment of COVID-19: A Prospective Randomized, Double-Blind, Placebo-Controlled Clinical Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 May [cited 2022 Jun 2]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.05.24.22275411
68. Bruen C, Al-Saadi M, Michelson E, Tanios M, Mendoza-Ayala R, Miller J, et al. Auxora Improves Outcomes in Patients With Severe COVID-19 Pneumonia: A Randomized Clinical Trial. SSRN Journal [Internet]. 2021 [cited 2021 Dec 20]; Available from: https://www.ssrn.com/abstract=3976177
69. Carvelli J, Meziani F, Dellamonica J, Cordier P-Y, Allardet-Servent J, Fraisse M, et al. Avdoralimab (anti-C5aR1 mAb) Versus Placebo in Patients With Severe COVID-19: Results From a Randomized Controlled Trial (FORCE). SSRN Journal [Internet]. 2022 [cited 2022 Feb 21]; Available from: https://www.ssrn.com/abstract=4028533
70. Youssef JG, Lee R, Javitt J, Lavin P, Jayaweera D. Effectiveness of ZYESAMITM (Aviptadil) in Accelerating Recovery and Shortening Hospitalization in Critically-Ill

Patients with COVID-19 Respiratory Failure: Interim Report from a Phase 2B/3 Multicenter Trial. SSRN Journal [Internet]. 2021 [cited 2021 Apr 8]; Available from: https://www.ssrn.com/abstract=3794262

71. Singh H, Srivastava S, Yadav B, Rai AK, Jameela S, Muralidharan S, et al. AYUSH-64 as an adjunct to standard care in mild to moderate COVID-19: An open-label randomized controlled trial in Chandigarh, India. Complementary Therapies in Medicine. 2022 Jun;66:102814.
72. Klussmann JP, Lehmann C, Grosheva M, Sahin K, Nagy E, Szijártó V, et al. COVID-19: Azelastine nasal spray Reduces Virus-load In Nasal swabs (CARVIN). Early intervention with azelastine nasal sprays reduces viral load in SARS-CoV-2 infected patients. First report on a double-blind placebo-controlled phase II clinical trial. [Internet]. In Review; 2021 Sep [cited 2021 Sep 21]. Available from: https://www.researchsquare.com/article/rs-864566/v1
73. Sekhavati E, Jafari F, SeyedAlinaghi S, Jamali Moghadam Siahkali S, Sadr S, Tabarestani M, et al. Safety and effectiveness of azithromycin in patients with COVID-19: an open-label randomized trial. Int Journal Antimicrob Ag 2020;56(4):106143. Available from: https://doi.org/10.1016/j.ijantimicag.2020.106143.
74. Guvenmez O, Keskin H, Ay B, Birinci S, Kanca MF. The comparison of the effectiveness of lincocin® and azitro® in the treatment of COVID-19-associated pneumonia: a prospective study. J Popul Ther Clin Pharmacol 2020;27(S Pt1):e5–10. Available from : https://doi.org/10.15586/jptcp.v27iSP1.684.
75. Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 2020;396:959-67. Available from: https://doi.org/10.1016/S0140-6736(20)31862-6.
76. Horby PW, Roddick A, Spata E, Staplin N, Emberson JR, Pessoa-Amorim G, Peto L, et al. 2020. Azithromycin in Hospitalised Patients with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial. Preprint. Infectious Diseases (except HIV/AIDS). https://doi.org/10.1101/2020.12.10.20245944.

77. Rashad A, Nafady A, Hassan M, Mansour H, Taya U, Bazeed S, et al. Therapeutic efficacy of macrolides in management of patients with mild COVID-19. ResearchSquare [Internet]. 2021
78. Butler CC, Dorward J, Yu L-M, Gbinigie O, Hayward G, Saville BR, et al. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet. 2021 Mar;S014067362100461X.
79. Hinks TS, Cureton L, Knight R, Wang A, Cane JL, Barber VS, et al. A randomised clinical trial of azithromycin versus standard care in ambulatory COVID-19 – the ATOMIC2 trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 May 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.21.21255807
80. Oldenburg CE, Pinsky BA, Brogdon J, Chen C, Ruder K, Zhong L, et al. Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA [Internet]. 2021 Jul 16 [cited 2021 Aug 2]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2782166
81. Ghanei M, Solaymani-Dodaran M, Qazvini A, Ghazale AH, Setarehdan SA, Saadat SH, et al. The efficacy of corticosteroids therapy in patients with moderate to severe SARS-CoV-2 infection: a multicenter, randomized, open-label trial. Respir Res. 2021 Dec;22(1):245.
82. Gyselinck I, Liesenborghs L, Belmans A, Engelen MM, Betrains A, Van Thillo Q, et al. Azithromycin for treatment of hospitalised COVID-19 patients: a randomised, multicentre, open-label clinical trial (DAWn-AZITHRO). ERJ Open Res. 2022 Jan;8(1):00610–2021.
83. Ren Z, Luo H, Yu Z, Song J, Liang L, Wang L, et al. A randomized, open-label, controlled clinical trial of azvudine tablets in the treatment of mild and common COVID-19, a pilot study. Adv Sci 2020;7:2001435. Available from: https://doi.org/10.1002/advs.202001435.
84. Lou Y, Liu L, Qiu Y. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.04.29.20085761.

85. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. N Engl J Med 2020; NEJMoa2029849. Available from: https://doi.org/10.1056/NEJMoa2029849.
86. ACTIV-3/TICO LY-CoV555 Study Group. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med. 2020 Dec 22;NEJMoa2033130.
87. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2021
88. Cohen MS, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA [Internet]. 2021 Jun 3 [cited 2021 Jun 15]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2780870
89. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021 Jul 14;NEJMoa2102685.
90. Chen P, Datta G, Li YG, Chien J, Price K, Chigutsa E, et al. First in Human Study of Bamlanivimab in a Randomized Trial of Hospitalized Patients with COVID-19. Clinical Pharmacology & Therapeutics. 2021 Aug 28;cpt.2405.
91. Huang DT, McCreary EK, Bariola JR, Minnier TE, Wadas RJ, Shovel JA, et al. Effectiveness of Casirivimab-Imdevimab and Sotrovimab During a SARS-CoV-2 Delta Variant Surge: A Cohort Study and Randomized Comparative Effectiveness Trial. JAMA Netw Open. 2022 Jul 14;5(7):e2220957.
92. nasopharyngeal SARS-CoV-2 RNA levels but not symptom duration in non-hospitalized adults with COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Dec [cited 2021 Dec 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.17.21268009
93. Huang DT, McCreary EK, Bariola JR, Minnier TE, Wadas RJ, Shovel JA, et al. Effectiveness of casirivimab and imdevimab, and sotrovimab during Delta variant surge: a prospective cohort study and comparative effectiveness randomized trial [Internet].

Infectious Diseases (except HIV/AIDS); 2021 Dec [cited 2022 Jan 10]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.23.21268244

94. Mazzaferri F, Mirandola M, Savoldi A, De Nardo P, Morra M, Tebon M, et al. Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron Variant of Concern [Internet]. Infectious Diseases (except HIV/AIDS); 2022 May [cited 2022 Jun 2]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.05.06.22274613
95. Dougan M, Azizad M, Chen P, Feldman B, Frieman M, Igbinadolor A, et al. Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Mar [cited 2022 Jul 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.03.10.22272100
96. Kalil AC., Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, et al. 2020. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. New England Journal of Medicine, December, NEJMoa2031994. https://doi.org/10.1056/NEJMoa2031994.
97. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine. 2021 Sep;S2213260021003313.
98. Ely EW, Ramanan AV, Kartman CE, de Bono S, Liao R, Piruzeli MLB, et al. Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomised, Placebo-Controlled Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Oct [cited 2021 Oct 18]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.10.11.21263897
99. Abani O, Abbas A, Abbas F, Abbas J, Abbas K, Abbas M, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. The Lancet. 2022 Jul;400(10349):359–68.
100. Wolfe CR, Tomashek KM, Patterson TF, Gomez CA, Marconi VC, Jain MK, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a

randomised, double-blind, double placebo-controlled trial. The Lancet Respiratory Medicine. 2022 May;S2213260022000881.

101. Karampitsakos T, Papaioannou O, Tsiri P, Katsaras M, Katsimpris A, Kalogeropoulos AP, et al. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jun [cited 2022 Jul 6]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.06.13.22276211

102. Montejano R, de la Calle-Prieto F, Velasco M, Guijarro C, Queiruga-Parada J, Jiménez-González M, et al. Tenofovir Disoproxil Fumarate/Emtricitabine and Baricitinib for Patients at High Risk of Severe COVID-19: The PANCOVID Randomized Clinical Trial. Clinical Infectious Diseases. 2022 Jul 30;ciac628.

103. Padmanabhan U, Mukherjee S, Borse R, Joshi S, Deshmukh R. Phase II clinical trial for evaluation of BCG as potential therapy for COVID-19 [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.10.28.20221630.

104. Raghavan K, Dedeepiya VD, Suryaprakash V, Rao K-S, Ikewaki N, Sonoda T, et al. Beneficial effects of novel aureobasidium pullulans strains produced beta-1,3-1,6 glucans on interleukin-6 and D-dimer levels in COVID-19 patients; results of a randomized multiple-arm pilot clinical study. Biomedicine & Pharmacotherapy. 2021 Sep;112243.

105. Pushkala S, Seshayyan S, Theranirajan E, Sudhakar D, Raghavan K, Dedeepiya VD, et al. Efficient control of IL-6, CRP and Ferritin in Covid-19 patients with two variants of Beta-1,3-1,6 glucans in combination, within 15 days in an open-label prospective clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Dec [cited 2021 Dec 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.14.21267778

106. Delić N, Matetic A, Domjanović J, Kljaković-Gašpić T, Šarić L, Ilić D, et al. Effects of Different Inhalation Therapy on Ventilator-Associated Pneumonia in Ventilated COVID-19 Patients: A Randomized Controlled Trial. Microorganisms. 2022 May 28;10(6):1118.

107. Rybakov A.R., Zhebelenko Y.G., Dubrov S.O., Vdovenko D.V., Kavardakova N.V., Matsibokh S.V., et al. The Results of the Clinical Study: An Open-label Multicenter Randomized Trial to Evaluate the Efficacy of Bioven, Manufactured by

Biopharma Plasma, LLC, in Complex Therapy of Patients with Pneumonia Induced by COVID-19/SARS-COV-2 / РЕЗУЛЬТАТИ КЛІНІЧНОГО ДОСЛІДЖЕННЯ «ВІДКРИТЕ БАГАТОЦЕНТРОВЕ РАНДОМІЗОВАНЕ ДОСЛІДЖЕННЯ З ОЦІНКИ ЕФЕКТИВНОСТІ ПРЕПАРАТУ БІОВЕН, ВИРОБНИЦТВА ТОВ «БІОФАРМА ПЛАЗМА», В КОМПЛЕКСНІЙ ТЕРАПІЇ ПАЦІЄНТІВ З ПНЕВМОНІЄЮ, ЩО ВИКЛИКАНА КОРОНАВІРУСНОЮ ІНФЕКЦІЄЮ COVID-19. Pain, Anaesthesia and Intensive Care. 2020;4(93):9–21.

108. Barzin Tond S, Balenci L, Khajavirad N, Salehi M, Tafakhori A, Shahmohammadi MR, et al. Inflawell® improves neutrophil-to-lymphocyte ratio and shortens hospitalization in patients with moderate COVID-19, in a randomized double-blind placebo-controlled clinical trial. Inflammopharmacol [Internet]. 2022 Feb 24 [cited 2022 Mar 11]; Available from: https://link.springer.com/10.1007/s10787-022-00928-w

109. Li T, Sun L, Zhang W, Zheng C, Jiang C, Chen M, et al. Bromhexine hydrochloride tablets for the treatment of moderate COVID-19: an open-label randomized controlled pilot study. Clin Transl Sci 2020;13(6):1096-1102. Available from: https://doi.org/10.1111/cts.12881.

110. Ansarin K, Tolouian R, Ardalan M, Taghizadieh A, Varshochi M, Teimouri S, et al. 2020. Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: a randomized clinical trial. Bioimpacts 2020;10(4):209–15. Available from: https://doi.org/10.34172/bi.2020.27.

111. Mikhaylov EN, Lyubimtseva TA, Vakhrushev AD, Stepanov D, Lebedev DS, Vasilieva EYu, et al. Bromhexine Hydrochloride Prophylaxis of COVID-19 for Medical Personnel: A Randomized Open-Label Study. Tharmalingam J, editor. Interdisciplinary Perspectives on Infectious Diseases. 2022 Jan 29;2022:1–7.

112. Tolouian R, Mulla ZD, Jamaati H, Babamahmoodi A, Marjani M, Eskandari R, et al. Effect of bromhexine in hospitalized patients with COVID-19. J Investig Med. 2021 Mar 15;jim-2020-001747.

113. Tolouian R, Moradi O, Mulla ZD, Ziaie S, Haghighi M, Esmaily H, et al. Bromhexine, for Post Exposure COVID-19 Prophylaxis: A Randomized, Double-Blind, Placebo Control Trial. SSRN Journal [Internet]. 2021 [cited 2022 Jan 11]; Available from: https://www.ssrn.com/abstract=3989849

114. Elamir YM, Amir H, Lim S, Rana YP, Lopez CG, Feliciano NV, et al. A randomized pilot study using calcitriol in hospitalized COVID-19 patients. Bone. 2022 Jan;154:116175.

115. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, et al. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. EClinicalMedicine. 2021 Apr;100849.

116. Chupp G, Spichler-Moffarah A, Søgaard OS, Esserman D, Dziura J, Danzig L, et al. A Phase 2 Randomized, Double-Blind, Placebo-controlled Trial of Oral Camostat Mesylate for Early Treatment of COVID-19 Outpatients Showed Shorter Illness Course and Attenuation of Loss of Smell and Taste [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jan [cited 2022 Feb 16]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.01.28.22270035

117. Kinoshita T., Masahiro Shinoda, Yasuhiro Nisizaki, Katsuya Shiraki, Yuji Hirai, Yoshiko Kichikawa, et al. Phase 3, multicentre, double-blind, randomised, parallel-group, placebo-controlled study of camostat mesilate (FOY-305) for the treatment of COVID-19 (CANDLE study). medRxiv [Internet]. 2022; Available from: http://www.epistemonikos.org/documents/17575b0440c65ac971614982e92008e43db4297f

118. Terada J, Fujita R, Kawahara T, Hirasawa Y, Kinoshita T, Takeshita Y, et al. Favipiravir, camostat, and ciclesonide combination therapy in patients with moderate COVID-19 pneumonia with/without oxygen therapy: An open-label, single-center phase 3 randomized clinical trial. eClinicalMedicine. 2022 Jul;49:101484.

119. Tobback E, Degroote S, Buysse S, Delesie L, Van Dooren L, Vanherrewege S, et al. Efficacy and safety of camostat mesylate in early Covid-19 disease in an ambulatory setting: A randomized placebo-controlled phase II trial. International Journal of Infectious Diseases. 2022 Jul;S1201971222003885.

120. Caricchio R, Abbate A, Gordeev I, Meng J, Hsue PY, Neogi T, et al. Effect of Canakinumab vs Placebo on Survival Without Invasive Mechanical Ventilation in Patients Hospitalized With Severe COVID-19: A Randomized Clinical Trial. JAMA. 2021 Jul 20;326(3):230–9.

121. Cremer PC, Sheng CC, Sahoo D, Dugar S, Prada RA, Wang TKM, et al. Double-Blind Randomised Proof-of-Concept Trial of C anakinumab in Patients with C OVID-19 Associated C ardiac Injury and Heightened Inflammation. European Heart Journal Open. 2021 Jul 29;oeab002.

122. Crippa JAS, Pacheco JC, Zuardi AW, Guimarães FS, Campos AC, Osório F de L, et al. Cannabidiol for COVID-19 Patients with Mild to Moderate Symptoms (CANDIDATE Study): A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Cannabis and Cannabinoid Research. 2021 Oct 7;can.2021.0093.

123. Welker J, Pulido JD, Catanzaro AT, Malvestutto CD, Li Z, Cohen JB, et al. Efficacy and safety of CD24Fc in hospitalised patients with COVID-19: a randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Infectious Diseases. 2022 Mar;S1473309922000585.

124. Perlin DS, Neil GA, Anderson C, Zafir-Lavie I, Roadcap L, Raines S, et al. CERC-002, a human anti-LIGHT mAb reduces respiratory failure and death in hospitalized COVID-19 ARDS patients [Internet]. Pharmacology and Therapeutics; 2021 Apr [cited 2021 Apr 12]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.03.21254748

125. Thakar A, Panda S, Sakthivel P, Brijwal M, Dhakad S, Choudekar A, et al. Chloroquine nasal drops in asymptomatic & mild COVID-19: An exploratory randomized clinical trial. Indian J Med Res. 2021;0(0):0.

126. Cruz LR, Baladron I, Rittoles A, Diaz PA, Valenzuela C, Santana R, et al. Treatment with an anti-CK2 synthetic peptide improves clinical response in COVID-19 patients with pneumonia: a randomized and controlled clinical trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.09.03.20187112.

127. Lonze BE, Spiegler P, Wesson RN, Alachkar N, Petkova E, Weldon EP, et al. A Randomized Double-Blinded Placebo Controlled Trial of Clazakizumab for the Treatment of COVID-19 Pneumonia With Hyperinflammation. Critical Care Medicine [Internet]. 2022 May 18 [cited 2022 Jun 7];Publish Ahead of Print. Available from: https://journals.lww.com/10.1097/CCM.0000000000005591

128. Song J-Y, Kim Y-S, Eom J-S, Kim J-Y, Lee J-S, Lee J, et al. Oral antiviral clevudine compared with placebo in Korean COVID-19 patients with moderate severity

[Internet]. Infectious Diseases (except HIV/AIDS); 2021 Dec [cited 2021 Dec 29]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.09.21267566

129. Altay O, Yang H, Aydin M, Alkurt G, Altunal N, Kim W, et al. Combined metabolic cofactor supplementation accelerates recovery in mild-to-moderate COVID-19 [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.10.02.20202614.

130. Altay O, Arif M, Li X, Yang H, Aydın M, Alkurt G, et al. Combined Metabolic Activators Accelerates Recovery in Mild-to-Moderate COVID-19. Adv Sci. 2021 Sep;8(17):2101222.

131. Hu Q, Zhang Q-Y, Peng C-F, Ma Z, Han Y-L. Efficiency of Nicotinamide-based Supportive Therapy in Lymphopenia for Patients With COVID-19: A Randomized Controlled Trial [Internet]. In Review; 2022 Jan [cited 2022 Jan 18]. Available from: https://www.researchsquare.com/article/rs-1173313/v1

132. Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: The GRECCO-19 randomized clinical trial. JAMA Netw Open 2020;3(6):e2013136. Available from: https://doi.org/10.1001/jamanetworkopen.2020.13136.

133. Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Dib SM, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. RMD Open. 2021 Feb;7(1):e001455.

134. Farhad S, Pourfarzi F, Ataei S. The impact of colchicine on the COVID-19 patients: a clinical trial study [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-69374/v1.

135. Tardif J-C, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. The Lancet Respiratory Medicine. 2021 May;S2213260021002228.

136. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet Respiratory Medicine. 2021 Oct;S2213260021004355.

137. Pascual-Figal DA, Roura-Piloto AE, Moral-Escudero E, Bernal E, Albendin-Iglesias H, Pérez-Martínez MT, et al. Colchicine in Recently Hospitalized Patients with

COVID-19: A Randomized Controlled Trial (COL-COVID). IJGM. 2021 Sep;Volume 14:5517–26.

138. Dorward J, Yu LM, Hayward G, Saville BR, Gbinigie O, Van Hecke O, et al. Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. Br J Gen Pract. 2022 Mar 23;BJGP.2022.0083.

139. Diaz R, Orlandini A, Castellana N, Caccavo A, Corral P, Corral G, et al. Effect of Colchicine vs Usual Care Alone on Intubation and 28-Day Mortality in Patients Hospitalized With COVID-19: A Randomized Clinical Trial. JAMA Netw Open. 2021 Dec 29;4(12):e2141328.

140. Alsultan M, Obeid A, Alsamarrai O, Anan MT, Bakr A, Soliman N, et al. Efficacy of Colchicine and Budesonide in Improvement Outcomes of Patients with Coronavirus Infection 2019 in Damascus, Syria: A Randomized Control Trial. Lanzafame M, editor. Interdisciplinary Perspectives on Infectious Diseases. 2021 Dec 31;2021:1–7.

141. Pourdowlat G, Saghafi F, Mozafari A, Sahebnasagh A, Abedini A, Nabi Meybodi M, et al. Efficacy and safety of colchicine treatment in patients with COVID -19: A prospective, multicenter, randomized clinical trial. Phytotherapy Research. 2022 Feb 2;ptr.7319.

142. Gorial FI, Maulood MF, Abdulamir AS, Alnuaimi AS, abdulrrazaq MK, Bonyan FA. Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection. Annals of Medicine and Surgery. 2022 Apr;103593.

143. Pimenta Bonifácio L, Ramacciotti E, Agati LB, Vilar FC, Tojal da Silva AC, Louzada-Junior P, et al. Efficacy and Safety of Ixekizumab vs. Low-Dose IL-2 vs. Colchicine *vs.* Standard of Care on the Treatment of Patients Hospitalized with Moderate to Critical Covid-19: A Pilot Randomized Clinical Trial (STRUCK: Survival Trial Using Cyto kine Inhibitors). SSRN Journal [Internet]. 2022 [cited 2022 Jun 8]; Available from: https://www.ssrn.com/abstract=4095747

144. Cecconi A, Martinez-Vives P, Vera A, Lavilla Olleros C, Barrios A, Fonseca Aizpuru E, et al. Efficacy of short-course colchicine treatment in hospitalized patients with moderate to severe COVID-19 pneumonia and hyperinflammation: a randomized clinical trial. Sci Rep. 2022 Dec;12(1):9208.

145. Rabbani A, Rafique A, Wang X, Campbell D, Wang D, Brownell N, et al. Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients With Coronavirus Disease-19. Front Cardiovasc Med. 2022 Jun 17;9:876718.

146. Gaitán-Duarte HG, Álvarez-Moreno C, Rincón-Rodríguez CJ, Yomayusa-González N, Cortés JA, Villar JC, et al. Effectiveness of Rosuvastatin plus Colchicine, Emtricitabine/Tenofovir and a combination of them in Hospitalized Patients with SARS Covid-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Aug 2]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.06.21260085

147. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324(5):460-70. Available from: https://doi.org/10.1001/jama.2020.10044.

148. Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema PN, et al. Convalescent plasma for COVID-19: a randomized clinical trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.07.01.20139857.

149. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, Ruiz-Antoran B, de Molina RM, Torres F, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.08.26.20182444.

150. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate COVID-19 in India: an open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial) [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.09.03.20187252.

151. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med 2020; NEJMoa2031304. Available from: https://doi.org/10.1056/NEJMoa2031304.

152. Bajpai M, Kumar S, Maheshwari A, Chabra K, Kale P, Gupta A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.10.25.20219337.

153. AlQahtani M, Abdulrahman A, AlMadani A, Yousif AlAli S, Al Zamrooni AM, Hejab A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease [Preprint]. 2020 MedRxiv 2020. Available from: https://doi.org/10.1101/2020.11.02.20224303.

154. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021 Jan 6;NEJMoa2033700.

155. Ray, Yogiraj, Shekhar Ranjan Paul, Purbita Bandopadhyay, Ranit D'Rozario, Jafar Sarif, Deblina Raychaudhuri, Debaleena Bhowmik, et al. 2022. "A Phase 2 Single Center Open Label Randomised Control Trial for Convalescent Plasma Therapy in Patients with Severe COVID-19." *Nature Communications* 13 (1): 383. https://doi.org/10.1038/s41467-022-28064-7.

156. Horby PW, Estcourt L, Peto L, Emberson JR, Staplin N, Spata E, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Mar 11]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.09.21252736

157. Baklaushev V, Averyanov AV, Sotnikova AG, Perkina AS, Ivanov A, Yusubalieva GM, et al. Safety and Efficacy of Convalescent Plasma for COVID-19: The First Results of a Clinical Study. Journal of Clinical Practice [Internet]. 2020 Jul 17 [cited 2021 Feb 14]; Available from: https://journals.eco-vector.com/clinpractice/article/view/35168

158. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. Journal of Clinical Investigation [Internet]. 2021 May 11 [cited 2021 May 17]; Available from: http://www.jci.org/articles/view/150646

159. Gonzalez JLB, González Gámez M, Mendoza Enciso EA, Esparza Maldonado RJ, Palacios DH, Campos SD, et al. Efficacy and safety of convalescent plasma and intravenous immunoglobulin in critically ill COVID-19 patients. A controlled clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Apr 5]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.28.21254507

160. Pouladzadeh M, Safdarian M, Eshghi P, Abolghasemi H, Bavani AG, Sheibani B, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. Internal and emergency medicine [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1996674ceda1dbb24d8246a2f7b3b4f651353693

161. Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Convalescent Plasma Versus Standard Plasma in Coronavirus Disease 2019 Infected Hospitalized Patients in New York: A Double-Blind Randomized Trial. Critical Care Medicine [Internet]. 2021 Apr 16 [cited 2021 Apr 27];Publish Ahead of Print. Available from: https://journals.lww.com/10.1097/CCM.0000000000005066

162. Hamdy Salman O, Ail Mohamed HS. Efficacy and safety of transfusing plasma from COVID-19 survivors to COVID-19 victims with severe illness. A double-blinded controlled preliminary study. Egyptian Journal of Anaesthesia. 2020 Jan 1;36(1):264–72.

163. Körper S, Weiss M, Zickler D, Wiesmann T, Zacharowski K, M.Corman V, et al. High Dose Convalescent Plasma in COVID-19: Results from the Randomized Trial CAPSID [Internet]. Infectious Diseases (except HIV/AIDS); 2021 May [cited 2021 May 20]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.10.21256192

164. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, McQuilten ZK, McVerry BJ, Al-Beidh F, et al. Effect of Convalescent Plasma on Organ Support-Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2021 Oct 4;

165. The CONCOR-1 Study Group, CONCOR-1 writing committee, Bégin P, Callum J, Jamula E, Cook R, et al. Convalescent plasma for hospitalized patients with COVID-19 and the effect of plasma antibodies: a randomized controlled, open-label trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Jul 6]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.06.29.21259427

166. Sekine L, Arns B, Fabro BR, Cipolatt MM, Machado RRG, Durigon EL, et al. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. Eur Respir J. 2021 Jul 8;2101471.

167. Kirenga B, Byakika-Kibwika P, Muttamba W, Kayongo A, Loryndah NO, Mugenyi L, et al. Efficacy of convalescent plasma for treatment of COVID-19 in Uganda. BMJ Open Resp Res. 2021 Aug;8(1):e001017.

168. Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, et al. Early Convalescent Plasma for High-Risk Outpatients with Covid-19. N Engl J Med. 2021 Aug 18;NEJMoa2103784.

169. Devos T, Van Thillo Q, Compernolle V, Najdovski T, Romano M, Dauby N, et al. Early high antibody-titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma. Eur Respir J. 2021 Aug 26;2101724.

170. Bar KJ, Shaw PA, Choi GH, Aqui N, Fesnak A, Yang JB, et al. A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia. Journal of Clinical Investigation [Internet]. 2021 Nov 17 [cited 2021 Dec 13]; Available from: http://www.jci.org/articles/view/155114

171. Menichetti F, Popoli P, Puopolo M, Spila Alegiani S, Tiseo G, Bartoloni A, et al. Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Netw Open. 2021 Nov 29;4(11):e2136246.

172. Millat-Martinez P, Gharbharan A, Alemany A, Rokx C, Geurtsvankessel C, Papageourgiou G, et al. Convalescent plasma for outpatients with early COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Dec [cited 2021 Dec 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.11.30.21266810

173. Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, et al. Early Outpatient Treatment for Covid-19 with Convalescent Plasma. N Engl J Med. 2022 Mar 30;NEJMoa2119657.

174. Holm K, Lundgren MN, Kjeldsen-Kragh J, Ljungquist O, Böttiger B, Wikén C, et al. Convalescence plasma treatment of COVID-19: results from a prematurely terminated randomized controlled open-label study in Southern Sweden. BMC Res Notes. 2021 Dec;14(1):440.

175. Ortigoza MB, Yoon H, Goldfeld KS, Troxel AB, Daily JP, Wu Y, et al. Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial. JAMA Intern Med [Internet]. 2021 Dec 13 [cited 2022 Jan 6]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2787090

176. Baldeón ME, Maldonado A, Ochoa-Andrade M, Largo C, Pesantez M, Herdoiza M, et al. Effect of convalescent plasma as complementary treatment in patients with moderate COVID -19 infection. Transfusion Medicine. 2022 Jan 9;tme.12851.

177. De Santis GC, Oliveira LC, Garibaldi PMM, Almado CEL, Croda J, Arcanjo GGA, et al. High-Dose Convalescent Plasma for Treatment of Severe COVID-19. Emerg Infect Dis [Internet]. 2022 Mar [cited 2022 Feb 14];28(3). Available from: https://wwwnc.cdc.gov/eid/article/28/3/21-2299_article.htm

178. van den Berg K, Glatt TN, Vermeulen M, Little F, Swanevelder R, Barrett C, et al. Convalescent plasma in the treatment of moderate to severe COVID-19 pneumonia: a randomized controlled trial (PROTECT-Patient Trial). Sci Rep. 2022 Dec;12(1):2552.

179. Axfors C, Janiaud P, Schmitt AM, van't Hooft J, Smith ER, Haber NA, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. BMC Infect Dis. 2021 Dec;21(1):1170.

180. Fernández-Sánchez V, Ventura-Enríquez Y, Cabello-Gutiérrez C, Pérez-Calatayud ÁA, Rosa ECD la, Fareli-González CJ, et al. Convalescent Plasma to Treat Covid-19: a Randomized Double Blind 2 Centers Trial [Internet]. In Review; 2022 Apr [cited 2022 Apr 25]. Available from: https://www.researchsquare.com/article/rs-1277990/v1

181. Song ATW, Rocha V, Mendrone-Júnior A, Calado RT, De Santis GC, Benites BD, et al. Treatment of severe COVID-19 patients with either low- or high-volume of convalescent plasma versus standard of care: A multicenter Bayesian randomized open-label clinical trial (COOP-COVID-19-MCTI). The Lancet Regional Health - Americas. 2022 Jun;10:100216.

182. Bajpai M, Maheshwari A, Dogra V, Kumar S, Gupta E, Kale P, et al. Efficacy of convalescent plasma therapy in the patient with COVID-19: a randomised control trial (COPLA-II trial). BMJ Open. 2022 Apr 6;12(4):e055189.

183. Bartelt LA, Markmann AJ, Nelson B, Keys J, Root H, Henderson HI, et al. Outcomes of convalescent plasma with defined high- versus lower-neutralizing antibody titers against SARS-CoV-2 among hospitalized patients: CoronaVirus Inactivating Plasma (CoVIP), double-blind phase 2 study [Internet]. Infectious Diseases (except

HIV/AIDS); 2022 May [cited 2022 May 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.04.29.22274387

184. Shoham S, Bloch EM, Casadevall A, Hanley D, Lau B, Gebo K, et al. Transfusing convalescent plasma as post-exposure prophylaxis against SARS-CoV-2 infection: a double-blinded, phase 2 randomized, controlled trial. Clinical Infectious Diseases. 2022 May 17;ciac372.

185. Rojas M, Rodríguez Y, Hernández JC, Díaz-Coronado JC, Vergara JAD, Vélez VP, et al. Safety and efficacy of convalescent plasma for severe COVID-19: a randomized, single blinded, parallel, controlled clinical study. BMC Infect Dis. 2022 Dec;22(1):575.

186. Bargay-Lleonart J, Sarubbo F, Arrizabalaga M, Guerra JM, Borràs J, El Haji K, et al. Reinforcement of the Standard Therapy with Two Infusions of Convalescent Plasma for Patients with COVID-19: A Randomized Clinical Trial. JCM. 2022 May 27;11(11):3039.

187. Self WH, Wheeler AP, Stewart TG, Schrager H, Mallada J, Thomas CB, et al. Neutralizing COVID-19 Convalescent Plasma in Adults Hospitalized with COVID-19: A Blinded Randomized Placebo-Controlled Trial. Chest. 2022 Jul;S0012369222012016.

188. Balcells ME, Rojas L, Le Corre N, Martínez-Valdebenito C, Ceballos ME, Ferrés M, et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. PLoS Med. 2021 Mar;18(3):e1003415.

189. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc 2020;95(9):1888–97. Available from: https://doi.org/10.1016/j.mayocp.2020.06.028

190. Leucker TM, Osburn WO, Reventun P, Smith K, Claggett B, Kirwan B-A, et al. Effect of Crizanlizumab, a P-Selectin Inhibitor, in COVID-19. JACC: Basic to Translational Science. 2021 Dec;S2452302X21003156.

191. Askari G, Sahebkar A, Soleimani D, Mahdavi A, Rafiee S, Majeed M, et al. The efficacy of curcumin-piperine co-supplementation on clinical symptoms, duration, severity, and inflammatory factors in COVID-19 outpatients: a randomized double-blind, placebo-controlled trial. Trials. 2022 Dec;23(1):472.

192. Khan A, Iqtadar S, Mumtaz SU, Heinrich M, Pascual-Figal DA, Livingstone S, et al. Oral Co-Supplementation of Curcumin, Quercetin, and Vitamin D3 as an Adjuvant Therapy for Mild to Moderate Symptoms of COVID-19—Results From a Pilot Open-Label, Randomized Controlled Trial. Front Pharmacol. 2022 Jun 7;13:898062.

193. Kosiborod MN, Esterline R, Furtado RHM, Oscarsson J, Gasparyan SB, Koch GG, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes & Endocrinology. 2021 Jul;S2213858721001807.

194. Chen J, Xia L, Liu L, Xu Q, Ling Y, Huang D, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. Open Forum Infect Dis 2020;7(7):ofaa241. Available from: https://doi.org/10.1093/ofid/ofaa241.

195. Nickols NG, Mi Z, DeMatt E, Biswas K, Clise CE, Huggins JT, et al. Effect of Androgen Suppression on Clinical Outcomes in Hospitalized Men With COVID-19: The HITCH Randomized Clinical Trial. JAMA Netw Open. 2022 Apr 1;5(4):e227852.

196. Hosseinzadeh A, Emamian MH, Tavakolian A, Kia V, Ebrahimi H, Sheibani H, et al. Application of nasal spray containing dimethyl sulfoxide (DSMO) and ethanol during the COVID-19 pandemic may protect healthcare workers: A randomized controlled trials [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Jul 14]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.06.21259749

197. Porter JC, Inshaw J, Solis VJ, Denneny E, Evans R, Temkin MI, et al. Anti-inflammatory therapy with nebulised dornase alfa in patients with severe COVID-19 pneumonia [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Apr [cited 2022 Apr 28]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.04.14.22272888

198. Sobngwi E, Zemsi S, Guewo-Fokeng M, Katte J-C, Kounfack C, Mfeukeu-Kuate L, et al. Doxycycline is a safe alternative to Hydroxychloroquine + Azithromycin to prevent clinical worsening and hospitalization in mild COVID-19 patients: An open label randomized clinical trial (DOXYCOV) [Internet]. Pharmacology and Therapeutics; 2021 Jul [cited 2021 Aug 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.25.21260838

199. Butler CC, Yu L-M, Dorward J, Gbinigie O, Hayward G, Saville BR, et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of

adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet Respiratory Medicine. 2021 Jul;S2213260021003106.

200. Dhar R, Kirkpatrick J, Gilbert L, Khanna A, Modi MM, Chawla RK, et al. Doxycycline for the prevention of progression of COVID-19 to severe disease requiring intensive care unit (ICU) admission: a randomized, controlled, open-label, parallel group trial (DOXPREVENT.ICU) [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Feb [cited 2022 Feb 15]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.01.30.22269685

201. Stambouli N, Driss A, Gargouri F, Bahrini K, Arfaoui B, Abid R, et al. COVID-19 prophylaxis with Doxycycline and Zinc in Health Care Workers: A prospective randomized double-blind clinical trial. International Journal of Infectious Diseases. 2022 Jun;S1201971222003496.

202. Sasson J, Donlan AN, Ma JZ, Haughey H, Coleman R, Nayak U, et al. Safety and Efficacy of Dupilumab for the Treatment of Hospitalized Patients with Moderate to Severe COVID 19: A Phase IIa Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Apr [cited 2022 Apr 27]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.03.30.22273194

203. Cadegiani FA, McCoy J, Wambier CG, Goren A. 5-alpha-reductase inhibitors reduce remission time of COVID-19: results from a randomized double blind placebo controlled interventional trial in 130 SARS-CoV-2 positive men [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.11.16.20232512.

204. Cadegiani FA, McCoy J, Gustavo Wambier C, Goren A. Early Antiandrogen Therapy With Dutasteride Reduces Viral Shedding, Inflammatory Responses, and Time-to-Remission in Males With COVID-19: A Randomized, Double-Blind, Placebo-Controlled Interventional Trial (EAT-DUTA AndroCoV Trial – Biochemical). Cureus [Internet]. 2021 Feb 1 [cited 2021 Feb 14]

205. Moslemi M, Hejazian SM, Shaddelan M, Javanali F, Mirghaffari A, Sadeghi A, et al. Evaluating the effect of Edaravone on clinical outcome of patients with severe COVID-19 admitted to ICU: a randomized clinical trial. Inflammopharmacol [Internet]. 2022 Jun 20 [cited 2022 Jul 5]; Available from: https://link.springer.com/10.1007/s10787-022-01001-2

206. Delgado-Enciso I, Paz-Garcia J, Barajas-Saucedo CE, Mokay-Ramírez KA, Meza-Robles C, Lopez-Flores R, et al. Patient-reported health outcomes after treatment of COVID-19 with nebulized and/or intravenous neutral electrolyzed saline combined with usual medical care versus usual medical care alone: a randomized, open-label, controlled trial [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-68403/v1.

207. Gutiérrez-García R, De La Cerda-Angeles JC, Cabrera-Licona A, Delgado-Enciso I, Mervitch-Sigal N, Paz-michel B. Nasopharyngeal and oropharyngeal rinses with neutral electrolyzed water prevents COVID-19 in front-line health professionals: A randomized, open-label, controlled trial in a general hospital in Mexico City. Biomed Rep. 2021 Dec 15;16(2):11.

208. Matli K, Al Kotob A, Jamaleddine W, Al Osta S, Salameh P, Tabbikha R, et al. Managing Endothelial Dysfunction in COVID -19 with Statins, Beta Blockers, Nicorandil and Oral Supplements: A Pilot, DOUBLE-BLIND , PLACEBO-CONTROLLED , Randomized Clinical Trial. Clinical Translational Sci. 2022 Jul 8;cts.13369.

209. Olha Holubovska, Denisa Bojkova, Stefano Elli, Marco bechtel, David Boltz, Miguel Muzzio, et al. Enisamium is an inhibitor of the SARS-CoV-2 RNA polymerase and shows improvement of recovery in COVID-19 patients in an interim analysis of a clinical trial. medRxiv [Internet]. 2021.

210. Mukae H, Yotsuyanagi H, Ohmagari N, Doi Y, Sakaguchi H, Sonoyama T, et al. Efficacy and safety of ensitrelvir in patients with mild-to-moderate COVID-19: the phase 2b part of a randomized, placebo-controlled, phase 2/3 study [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jun [cited 2022 Jul 5]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.06.22.22276792.

211. ACTIV-3/TICO Study Group*. Efficacy and Safety of Ensovibep for Adults Hospitalized With COVID-19: A Randomized Controlled Trial. Ann Intern Med. 2022 Aug 9;M22-1503.

212. Welén K, Rosendal E, Gisslén M, Lenman A, Freyhult E, Fonseca-Rodríguez O, et al. A Phase 2 Trial of the Effect of Antiandrogen Therapy on COVID-19 Outcome: No Evidence of Benefit, Supported by Epidemiology and In Vitro Data. European Urology. 2021 Dec;S0302283821022247.

213. Amoushahi A, Moazam E, Reza Tabatabaei A, Ghasimi G, Salvatori P, Grant-Whyte I, et al. Efficacy and Safety of Nebulized Ethanol Inhalation in COVID-19 Treatment. A Randomized, Clinical Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jun [cited 2022 Jul 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.06.15.22276427

214. Samimagham H, Azad M, Haddad M, Arabi M, Hooshyar D, KazemiJahromi M. The Efficacy of Famotidine in improvement of outcomes in Hospitalized COVID-19 Patients: A phase III randomised clinical trial. ResearchSquare [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/a38a60b031b058f125e2d5572d2bc7678b676498

215. Brennan CM, Nadella S, Zhao X, Dima RJ, Jordan-Martin N, Demestichas BR, et al. Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial. Gut. 2022 Feb 10;gutjnl-2022-326952.

216. Pahwani S, Jadwani M, Dhanwani A, Gul M, Lal D, Rakesh F, et al. Efficacy of Oral Famotidine in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2. Cureus [Internet]. 2022 Feb 20 [cited 2022 May 2]; Available from: https://www.cureus.com/articles/78980-efficacy-of-oral-famotidine-in-patients-hospitalized-with-severe-acute-respiratory-syndrome-coronavirus-2

217. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.03.17.20037432.

218. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. Interim results of a phase II/III multicenter randomized clinical trial of AVIFAVIR in hospitalized patients with COVID-19. MedRxiv 202. Available from: https://doi.org/10.1101/2020.07.26.20154724.

219. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19. Antimicrob Agents Chemother 2020; 64:e01897-20. Available from: https://doi.org/10.1128/AAC.01897-20.

220. Dabbous HM, El-Sayed MH, El Assal G, Elghazaly H, Ebeid FFS, Sherief AF, et al. A randomized controlled study of favipiravir vs hydroxychloroquine in COVID-19 management: what have we learned so far? [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-83677/v1.

221. Zhao H, Zhu Q, Zhang C, Li J, Wei M, Qin Y, et al. Tocilizumab combined with favipiravir in the treatment of COVID-19: a multicenter trial in a small sample size. Biomed Pharmacother 2021; 133:110825. Available from: https://doi.org/10.1016/j.biopha.2020.110825.

222. Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M, Al Barwani U, et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis 2020; 102:538-43. Available from: https://doi.org/10.1016/j.ijid.2020.11.008.

223. Ruzhentsova TA, Oseshnyuk RA, Soluyanova TN, Dmitrikova EP, Mustafaev DM, Pokrovskiy KA, et al. Phase 3 trial of coronavir (favipiravir) in patients with mild to moderate COVID-19. Am J Transl Res. 2021;13(11):12575–87.

224. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial [Preprint]. Int J Infect Dis 2020. Available from: https://doi.org/10.1016/j.ijid.2020.11.142.

225. Ogarev Mordovia State University, Saransk, Russian Federation, Balykova LA, Govorov AV, A.I.Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russian Federation, Vasilyev AO, A.I.Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russian Federation, et al. Characteristics of COVID-19 and possibilities of early causal therapy. Results of favipiravir use in clinical practice. Infekc bolezni. 2020;18(3):30–40.

226. Solaymani-Dodaran M, Ghanei M, Bagheri M, Qazvini A, Vahedi E, Hassan Saadat S, et al. Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia. International Immunopharmacology. 2021 Jun;95:107522.

227. Zhao H, Zhang C, Zhu Q, Chen X, Chen G, Sun W, et al. Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A

multicenter, open-label, randomized trial. International Immunopharmacology. 2021 Aug;97:107702.

228. Bosaeed M, Mahmoud E, Alharbi A, Altayeib H, Albayat H, Alharbi F, et al. Favipiravir and Hydroxychloroquine Combination Therapy in Patients with Moderate to Severe COVID-19 (FACCT): An Open-Label, Multicentre, Randomised, Controlled Trial. SSRN Journal [Internet]. 2021 [cited 2021 May 5]; Available from: https://www.ssrn.com/abstract=3829663

229. Shinkai M, Tsushima K, Tanaka S, Hagiwara E, Tarumoto N, Kawada I, et al. Efficacy and Safety of Favipiravir in Moderate COVID-19 Pneumonia Patients without Oxygen Therapy: A Randomized, Phase III Clinical Trial. Infect Dis Ther [Internet]. 2021 Aug 27 [cited 2021 Sep 6]; Available from: https://link.springer.com/10.1007/s40121-021-00517-4

230. Atipornwanich K, Kongsaengdao S, Harnsomburana P, Nanna R, Chtuparisute C, Saengsayan P, et al. Various Combinations of Favipiravir, Lopinavir-Ritonavir, Darunavir-Ritonavir, High-Dose Oseltamivir, and Hydroxychloroquine for the Treatment of COVID-19: A Randomized Controlled Trial (FIGHT-COVID-19 Study). SSRN Journal [Internet]. 2021 [cited 2021 Oct 13]; Available from: https://www.ssrn.com/abstract=3936499

231. Shenoy S, Munjal S, Youha SA, Alghounaim M, Almazeedi S, Alshamali Y, et al. Favipiravir In Adults with Moderate to Severe COVID-19: A Phase 3 Multicentre, Randomized, Double-Blinded, Placebo-Controlled Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Nov [cited 2021 Nov 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.11.08.21265884

232. Holubar M, Subramanian A, Purington N, Hedlin H, Bunning B, Walter KS, et al. Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Nov [cited 2021 Dec 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.11.22.21266690

233. Chuah CH, Chow TS, Hor CP, Cheng JT, Ker HB, Lee HG, et al. Efficacy of Early Treatment with Favipiravir on Disease Progression among High Risk COVID-19 Patients: A Randomized, Open-Label Clinical Trial. Clinical Infectious Diseases. 2021 Nov 19;ciab962.

234. Finberg RW, Ashraf M, Julg B, Ayoade F, Marathe JG, Issa NC, et al. US201 Study: A Phase 2, Randomized Proof-of-Concept Trial of Favipiravir for the Treatment of COVID-19. Open Forum Infectious Diseases. 2021 Dec 1;8(12):ofab563.

235. Bosaeed M, Alharbi A, Mahmoud E, Alrehily S, Bahlaq M, Gaifer Z, et al. Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicenter, placebo-controlled trial clinical trial. Clinical Microbiology and Infection. 2022 Jan;S1198743X21007345.

236. Hassaniazad M, Farshidi H, Gharibzadeh A, Bazram A, Khalili E, Noormandi A, et al. Efficacy and safety of favipiravir plus interferon-beta versus lopinavir/ritonavir plus interferon-beta in moderately ill patients with COVID-19: A randomized clinical trial. Journal of Medical Virology. 2022 Mar 24;jmv.27724.

237. Lowe DM, Brown L-AK, Chowdhury K, Davey S, Yee P, Ikeji F, et al. Favipiravir, lopinavir-ritonavir or combination therapy (FLARE): a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Feb [cited 2022 Mar 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.02.11.22270775

238. Tabarsi P, Vahidi H, Saffaei A, Hashemian SMR, Jammati H, Daraei B, et al. Favipiravir Effects on the Control of Clinical Symptoms of Hospitalized COVID-19 Cases: An Experience with Iranian Formulated Dosage Form. Iran J Pharm Res. 2021;20(4):1–8.

239. AlQahtani M, Kumar N, Aljawder D, Abdulrahman A, Alnashaba F, Fayyad MA, et al. Randomized controlled trial of favipiravir, hydroxychloroquine, and standard care in patients with mild/moderate COVID-19 disease. Sci Rep. 2022 Mar 23;12(1):4925.

240. Rahman SMA, Kabir A, Abdullah ABM, Alam MB, Azad KAK, Miah MT, et al. Safety and efficacy of favipiravir for the management of COVID-19 patients: A preliminary randomized control trial. Clinical Infection in Practice. 2022 Jul;15:100145.

241. McMahon JH, Lau JSY, Coldham A, Roney J, Hagenauer M, Price S, et al. Favipiravir in Early Symptomatic COVID-19, A Randomised Placebo-Controlled Trial. SSRN Journal [Internet]. 2022 [cited 2022 Jul 6]; Available from: https://www.ssrn.com/abstract=4135325

242. Davoodi L, Abedi SM, Salehifar E, Alizadeh-Navai R, Rouhanizadeh H, Khorasani G, Hosseinimehr SJ. Febuxostat therapy in outpatients with suspected COVID-19: a clinical trial. Int J Clin Pract 2020; 74:e13600. Available from: https://doi.org/10.1111/ijcp.13600.

243. Chirinos J, Lopez-Jaramillo P, Giamarellos-Bourboulis E, Dávila-del-Carpio G, Bizri A, Andrade-Villanueva J, et al. A Randomized Trial of Lipid Metabolism Modulation with Fenofibrate for Acute Coronavirus Disease 2019 [Internet]. In Review; 2022 Aug [cited 2022 Aug 20]. Available from: https://www.researchsquare.com/article/rs-1933913/v1

244. E. Zarehoseinzade, A. Allami, M. Ahmadi, B. Bijani, N. Mohammadi. Finasteride in hospitalized adult males with Covid-19: A risk factor for severity of the disease or an adjunct treatment: A randomized controlled clinical trial. The Medical Journal of The Islamic Republic of Iran [Internet]. 2021;35(1). Available from: http://www.epistemonikos.org/documents/f3b23e45ed8faff34c8ba4b500fc9bfc82d32f81

245. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 2020 Published online November 12, 2020. Available from: https://doi.org/10.1001/jama.2020.22760.

246. Reis G, dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. The Lancet Global Health. 2021 Oct;S2214109X21004484.

247. Seo H, Kim H, Bae S, Park S, Chung H, Sung H sup, et al. Fluvoxamine Treatment of Patients with Symptomatic COVID-19 in a Community Treatment Center: A Preliminary Result of Randomized Controlled Trial. Infect Chemother. 2022;54(1):102.

248. Bramante CT, Huling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. N Engl J Med. 2022 Aug 18;387(7):599–610.

249. Strich JR, Tian X, Samour M, King CS, Shlobin O, Reger R, et al. Fostamatinib for the treatment of hospitalized adults with COVID-19 A randomized trial. Clinical Infectious Diseases. 2021 Sep 1;ciab732.

250. Soltani R, Nasirharandi S, Khorvash F, Nasirian M, Dolatshahi K, Hakamifard A. The effectiveness of gabapentin and gabapentin/montelukast combination compared with dextromethorphan in the improvement of COVID-19- related cough: A randomized, controlled clinical trial. Clinical Respiratory J. 2022 Jul 31;crj.13529.

251. Gaughan E, Sethi T, Quinn T, Hirani N, Mills A, Bruce AM, et al. GB0139, an inhaled small molecule inhibitor of galectin-3, in COVID-19 pneumonitis: a randomised, controlled, open-label, phase 2a experimental medicine trial of safety, pharmacokinetics, and potential therapeutic value [Internet]. Respiratory Medicine; 2021 Dec [cited 2021 Dec 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.21.21267983

252. Criner GJ, Lang FM, Gottlieb RL, Mathews KS, Wang TS, Rice TW, et al. Anti-GM-CSF Monoclonal Antibody Gimsilumab for COVID-19 Pneumonia: A Randomized, Double-Blind, Placebo-Controlled Trial. Am J Respir Crit Care Med. 2022 Mar 15;rccm.202108-1859OC.

253. Shogenova LV, Petrikov SS, Zhuravel SV, Gavrilov PV, Utkina II, Varfolomeev SD, et al. Thermal Helium-Oxygen Mixture as Part of a Treatment Protocol for Patients with COVID-19. Annals RAMS. 2020 Dec 4;75(5S):353–62.

254. Dupuis J, Laurin P, Tardif J-C, Hausermann L, Rosa C, Guertin M-C, et al. Fourteen-days Evolution of COVID-19 Symptoms During the Third Wave in Non-vaccinated Subjects and Effects of Hesperidin Therapy: A randomized, double-blinded, placebo-controlled study [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Oct [cited 2021 Oct 13]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.10.04.21264483

255. Jarczak D, Roedl K, Fischer M, de Heer G, Burdelski C, Frings DP, et al. Effect of Hemadsorption in Critically Ill Patients with COVID-19 (CYTOCOV-19): A Prospective Randomized Controlled Pilot Trial [Internet]. In Review; 2021 Jul [cited 2021 Nov 23]. Available from: https://www.researchsquare.com/article/rs-704552/v1

256. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open 2020;3(4):e208857. Available from: https://doi.org/10.1001/jamanetworkopen.2020.8857.

257. Huang M, Tang T, Pang P, Li M, Ma R, Lu J, et al. Treating COVID-19 with chloroquine. J Mol Cell Biol 2020;12(4):322–25. Available from: https://doi.org/10.1093/jmcb/mjaa014.

258. The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020;383:2030-40. Available from: https://doi.org/10.1056/NEJMoa2022926.

259. Mitja O, Ubals M, Corbacho M, Alemany A, Suner C, Tebe C, et al. A cluster-randomized trial of hydroxychloroquine as prevention of COVID-19 transmission and disease [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.07.20.20157651.

260. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med 2020;383:517-25. Available from: https://doi.org/10.1056/NEJMoa2016638.

261. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. N Engl J Med 2020;383:2041-52. Available from: https://doi.org/10.1056/NEJMoa2019014.

262. Kamran SM, Mirza ZH, Naseem A, Saeed F, Azam R, Ullah N, et al. Clearing the fog: is HCQ effective in reducing COVID-19 progression: a randomized controlled trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.07.30.20165365.

263. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Int Med 2020;173(8):623-31. Available from: https://doi.org/10.7326/M20-4207.

264. Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. Clin Infect Dis 2020; ciaa1009. Available from: https://doi.org/10.1093/cid/ciaa1009.

265. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised

controlled trial. BMJ 2020;369:m1849. Available from: https://doi.org/10.1136/bmj.m1849.

266. Chen Z, Hu J, Zhang Z, Jiang SS, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.03.22.20040758.

267. Chen L, Zhang Z-y, Fu J-g, Feng Z-p, Zhang S-z, Han Q-y, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.06.19.20136093.

268. Chen C-P, Lin Y-C, Chen T-C, Tseng T-Y, Wong H-L, Kuo C-Y, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19) [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.07.08.20148841.

269. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. 浙江大学学报（医学版）(Journal of Zhejiang University. Medical Sciences) 2020; 49(2):215–19. Available from: https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.

270. Abd-Elsalam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, Abd El Ghafar MS, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. Am J Trop Med Hyg 2020; 13(4):635-39. Available from: https://doi.org/10.4269/ajtmh.20-0873.

271. Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. Clin Infect Dis 2020; ciaa1571. Available from: https://doi.org/10.1093/cid/ciaa1571.

272. Ulrich RJ, Troxel AB, Carmody E, Eapen J, Bäcker M, DeHovitz JA, et al. Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind, randomized controlled trial in hospitalized patients. Open Forum Infect Dis 2020;7(10): ofaa446. Available from: https://doi.org/10.1093/ofid/ofaa446.

273. Grau-Pujol B, Camprubí D, Marti-Soler H, Fernández-Pardos M, Carreras-Abad C, et al. Pre-exposure prophylaxis with hydroxychloroquine for COVID-19: initial results

of a double-blind, placebo-controlled randomized clinical trial [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-72132/v1.

274. Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. JAMA Int Med 2020 published online September 30. Available from: https://doi.org/10.1001/jamainternmed.2020.6319.

275. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. The Lancet. 2022 May;S0140673622005190.

276. Barnabas RV, Brown ER, Bershteyn A, Stankiewicz Karita HC, Johnston C, Thorpe LE, Kottkamp A, et al. Hydroxychloroquine as Postexposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection : A Randomized Trial. Annals of Internal Medicine 2020. https://doi.org/10.7326/M20-6519.

277. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA 2020;324(21):2165-76. Available from: https://doi.org/10.1001/jama.2020.22240.

278. Brown SM, Peltan I, Kumar N, Leither L, Webb BJ, Starr N, et al. Hydroxychloroquine vs. azithromycin for hospitalized patients with COVID-19 (HAHPS): results of a randomized, active comparator trial. Ann Am Thor Soc 2020; published online 9 November 2020. Available from: https://doi.org/10.1513/AnnalsATS.202008-940OC.

279. Dubée V, Roy P-M, Vielle B, Parot-Schinkel E, Blanchet O, Darsonval A, et al. Hydroxychloroquine in mild-to-moderate COVID-19: a placebo-controlled double blind trial. Clinical Microbiology and Infection. 2021 Apr;S1198743X21001403.

280. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe COVID-19. EClinicalMedicine 2020;29: 100645. Available from: https://doi.org/10.1016/j.eclinm.2020.100645.

281. Dabbous HM, El-Sayed MH, Assal GE, Elghazaly H, Ebeid FF, Sherief AF, et al. A Randomized Controlled Study Of Favipiravir Vs Hydroxychloroquine In COVID-19

Management: What Have We Learned So Far? [Internet]. In Review; 2020 Sep [cited 2020 Oct 1]. Available from: https://www.researchsquare.com/article/rs-83677/v1

282. Hernandez-Cardenas C, Thirion-Romero I, Rivera-Martinez NE, Meza-Meneses P, Remigio-Luna A, Perez-Padilla R. Hydroxychloroquine for the Treatment of Severe Respiratory Infection by Covid-19: A Randomized Controlled Trial. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/0881ad73607247595bdf210de533bbd94651b0b4

283. Johnston C, Brown ER, Stewart J, Karita HCS, Kissinger PJ, Dwyer J, et al. Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: A randomized clinical trial. EClinicalMedicine. 2021 Feb;100773.

284. Purwati, Budiono, Rachman BE, Yulistiani, Miatmoko A, Nasronudin, et al. A Randomized, Double-Blind, Multicenter Clinical Study Comparing the Efficacy and Safety of a Drug Combination of Lopinavir/Ritonavir-Azithromycin, Lopinavir/Ritonavir-Doxycycline, and Azithromycin-Hydroxychloroquine for Patients Diagnosed with Mild to Moderate COVID-19 Infections. Huyut Z, editor. Biochemistry Research International. 2021 Feb 9;2021:1–12.

285. Beltran Gonzalez JL, González Gámez M, Mendoza Enciso EA, Esparza Maldonado RJ, Hernández Palacios D, Dueñas Campos S, et al. Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients with Severe COVID-19: A Randomized Controlled Trial. Infectious Disease Reports. 2022 Mar 3;14(2):160–8.

286. Amaravadi RK, Giles L, Carberry M, Hyman MC, Frank I, Nasta SD, et al. Hydroxychloroquine for SARS-CoV-2 positive patients quarantined at home: The first interim analysis of a remotely conducted randomized clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Feb [cited 2021 Mar 4]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.02.22.21252228

287. Galan LEB, Santos NM dos, Asato MS, Araújo JV, de Lima Moreira A, Araújo AMM, et al. Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. Pathogens and Global Health. 2021 Mar 8;1–8.

288. Seet RCS, Quek AML, Ooi DSQ, Sengupta S, Lakshminarasappa SR, Koo CY, et al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: an open-label randomized trial. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/f0a6f1dede78977943975491698 53a5d5c7c6c0e

289. Reis G, Moreira Silva EADS, Medeiros Silva DC, Thabane L, Singh G, Park JJH, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA network open. 2021;4(4):e216468.

290. Réa-Neto Á, Bernardelli RS, Câmara BMD, Reese FB, Queiroga MVO, Oliveira MC. An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients. Sci Rep. 2021 Dec;11(1):9023.

291. Syed F, Hassan M, Arif MA, Batool S, Niazi R, Laila U e, et al. Pre-exposure Prophylaxis With Various Doses of Hydroxychloroquine Among Healthcare Personnel With High-Risk Exposure to COVID-19: A Randomized Controlled Trial. Cureus [Internet]. 2021 Dec 21 [cited 2022 Feb 16]; Available from: https://www.cureus.com/articles/77806-pre-exposure-prophylaxis-with-various-doses-of-hydroxychloroquine-among-healthcare-personnel-with-high-risk-exposure-to-covid-19-a-randomized-controlled-trial

292. Sivapalan P, Suppli Ulrik C, Sophie Lapperre T, Dahlin Bojesen R, Eklöf J, Browatzki A, et al. Azithromycin and hydroxychloroquine in hospitalised patients with confirmed COVID-19–a randomised double-blinded placebo-controlled trial. Eur Respir J. 2021 Jun 3;2100752.

293. Byakika-Kibwika P, Sekaggya-Wiltshire C, Semakula JR, Nakibuuka J, Musaazi J, Kayima J, et al. Safety and efficacy of hydroxychloroquine for treatment of non-severe COVID-19 among adults in Uganda: a randomized open label phase II clinical trial. BMC Infect Dis. 2021 Dec;21(1):1218.

294. Schwartz I, Boesen ME, Cerchiaro G, Doram C, Edwards BD, Ganesh A, et al. Assessing the efficacy and safety of hydroxychloroquine as outpatient treatment of COVID-19: a randomized controlled trial. cmajo. 2021 Apr;9(2):E693–702.

295. Naggie S, Milstone A, Castro M, Collins SP, Seetha L, Anderson DJ, et al. Hydroxychloroquine for pre-exposure prophylaxis of COVID-19 in health care workers: a randomized, multicenter, placebo-controlled trial (HERO-HCQ) [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Aug [cited 2021 Aug 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.08.19.21262275

296. Rodrigues C, Freitas-Santos RS, Levi JE, Senerchia AA, Lopes ATA, Santos SR, et al. Hydroxychloroquine plus azithromycin early treatment of mild COVID-19 in outpatient setting: a randomized, double-blinded, placebo-controlled clinical trial evaluating viral clearance. International Journal of Antimicrobial Agents. 2021 Aug;106428.

297. Babalola OE, Yahaya N, Ajayi AA, Ogedengbe JO, Thairu Y, Omede O. A Randomized Controlled Trial of Ivermectin Monotherapy Versus Hydroxychloroquine, Ivermectin, and Azithromycin Combination Therapy in Covid-19 Patients in Nigeria [Internet]. In Review; 2021 Oct [cited 2021 Oct 12]. Available from: https://www.researchsquare.com/article/rs-950352/v1

298. Panda PK, Singh BO, Moirangthem B, Bahurupi YA, Saha S, Saini G, et al. Antiviral Combination Clinically Better Than Standard Therapy in Severe but Not in Non-Severe COVID-19. CPAA. 2021 Sep;Volume 13:185–95.

299. Ahmad B, ul Hassan N, Sehar B, Zeb F, e Nayab D, Siddiqui FA. Effect of Chloroquine and Hydroxychloroquine on Cytokine Release Syndrome in Patients with COVID-19. Clin Med Res. 2021 Dec;19(4):179–82.

300. McKinnon J, Wang D, Zervos M, Saval M, Marshall-Nightengale L, Kilgore P, et al. Safety and Tolerability of Hydroxychloroquine in healthcare workers and first responders for the prevention of COVID-19: WHIP COVID-19 Study. International Journal of Infectious Diseases. 2021 Dec;S1201971221012431.

301. Rojas-Serrano J, Portillo-Vásquez AM, Thirion-Romero I, Vázquez-Pérez J, Mejía-Nepomuceno F, Ramírez-Venegas A, et al. Hydroxychloroquine for prophylaxis of COVID-19 in health workers: A randomized clinical trial. Triche EW, editor. PLoS ONE. 2022 Feb 9;17(2):e0261980.

302. Polo R, García-Albéniz X, Terán C, Morales M, Rial-Crestelo D, Garcinuño MA, et al. Daily tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine for pre-exposure prophylaxis of COVID-19: a double-blind placebo controlled randomized trial in healthcare workers. Clinical Microbiology and Infection. 2022 Aug;S1198743X22003706.

303. Avezum Á, Oliveira GBF, Oliveira H, Lucchetta RC, Pereira VFA, Dabarian AL, et al. Hydroxychloroquine versus placebo in the treatment of non-hospitalised patients with COVID-19 (COPE – Coalition V): A double-blind, multicentre, randomised, controlled trial. The Lancet Regional Health - Americas. 2022 Jul;11:100243.

304. Roy-García IA, Moreno-Noguez M, Rivas-Ruiz R, Zapata-Tarres M, Perez-Rodriguez M, Ortiz-Zamora MA, et al. "Efficacy and Safety of Fixed Combination of Hydroxychloroquine with Azithromycin Versus Hydroxychloroquine and Placebo in Patients with Mild COVID-19: Randomized, double blind, Placebo controlled trial" [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Apr [cited 2022 Apr 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.04.06.22273531

305. Tirupakuzhi Vijayaraghavan BK, Jha V, Rajbhandari D, Myatra SN, Ghosh A, Bhattacharya A, et al. Hydroxychloroquine plus personal protective equipment versus personal protective equipment alone for the prevention of laboratory-confirmed COVID-19 infections among healthcare workers: a multicentre, parallel-group randomised controlled trial from India. BMJ Open. 2022 Jun;12(6):e059540.

306. Elshafie AH, Elsawah HK, Hammad M, Sweed EM, Seif AS, Abdel Ghaffar MM, et al. Ivermectin role in COVID-19 treatment (IRICT): single-center, adaptive, randomized, double-blind, placebo-controlled, clinical trial. Expert Review of Anti-infective Therapy. 2022 Jul 12;1–10.

307. Choudhary R, Ali O, Singh BK. Study on Hydroxychloroquinine Sulfate Being Given to the Admitted COVID -19 Positive Patients at Institute of JLNMCH, Bhagalpur, Bihar, India. Cureus [Internet]. 2022 Jun 28 [cited 2022 Aug 16]; Available from: https://www.cureus.com/articles/100191-study-on-hydroxychloroquinine-sulfate-being-given-to-the-admitted-covid--19-positive-patients-at-institute-of-jlnmch-bhagalpur-bihar-india

308. Hadanny A, Finci S, Catalogna M, Abu Hamed R, Korin C, Gabriella L, et al. Hyperbaric Oxygen Therapy for COVID-19 Patients: A Prospective, Randomized

Controlled Trial. SSRN Journal [Internet]. 2020 [cited 2021 Apr 19]; Available from: https://www.ssrn.com/abstract=3745115

309. Cannellotto M, Duarte M, Keller G, Larrea R, Cunto E, Chediack V, et al. Hyperbaric oxygen as an adjuvant treatment for patients with COVID-19 severe hypoxaemia: a randomised controlled trial. Emerg Med J. 2021 Dec 14;emermed-2021-211253.

310. Kjellberg A, Douglas J, Hassler A, Al-Ezerjawi S, Boström E, Abdel-Halim L, et al. COVID-19 induced acute respiratory distress syndrome treated with Hyperbaric Oxygen: Interim safety report from a multicenter, randomised, open-label phase II clinical trial (COVID-19-HBO). ResearchSquare [Internet]. 2022; Available from: http://www.epistemonikos.org/documents/db28a97c703a59e6c2ea3d021c759a1dc577c11f

311. Ali S, Uddin SM, Shalim E, Sayeed MA, Anjum F, Saleem F, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial. EClinicalMedicine. 2021 Jun;100926.

312. Parikh D, Chaturvedi A, Shah N, Patel P, Patel R, Ray S. Safety and efficacy of COVID-19 hyperimmune globulin (HIG) solution in the treatment of active COVID-19 infection- Findings from a Prospective, Randomized, Controlled, Multi-Centric Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Aug 17]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.26.21261119

313. Polizzotto MN, Nordwall J, Babiker AG, Phillips A, Vock DM, Eriobu N, et al. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. The Lancet. 2022 Feb;399(10324):530–40.

314. Huygens S, Hofsink Q, Nijhof IS, Goorhuis A, Kater AP, te Boekhorst PA, et al. SARS-CoV-2 hyperimmune globulin for severely immunocompromised patients with COVID-19: a randomised, controlled, double-blind, phase 3 trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Apr [cited 2022 Apr 27]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.04.04.22273314

315. Prasenohadi P, Burhan E, Dhunny S, Suharno W, Wabnitz P, Kim YW, et al. Double-Blind, Randomized, Placebo-Controlled Study on hzVSF-v13, a Novel Anti-

Vimentin Monoclonal Antibody Drug as Add-on Standard of Care in the Management of Patients with Moderate to Severe COVID-19. JCM. 2022 May 24;11(11):2961.

316. Coutre SE, Barnett C, Osiyemi O, Hoda D, Ramgopal M, Fort AC, et al. Ibrutinib for Hospitalized Adults With Severe Coronavirus Disease 2019 Infection: Results of the Randomized, Double-Blind, Placebo-Controlled iNSPIRE Study. Open Forum Infectious Diseases. 2022 May 1;9(5):ofac104.

317. Mansour E, Palma AC, Ulaf RG, Ribeiro LC, Bernardes AF, Nunes TA, et al. Pharmacological inhibition of the kinin-kallikrein system in severe COVID-19: a proof-of-concept study [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.08.11.20167353.

318. Kosmopoulos A, Bhatt DL, Meglis G, Verma R, Pan Y, Quan A, et al. A Randomized Trial of Icosapent Ethyl in Ambulatory Patients with COVID-19. iScience. 2021 Aug;103040.

319. Vlaar APJ, e Bruin S, Busch M, Timmermans SAMEG, van Zeggeren IE, Koning R, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. Lancet Rheumatol 2020;2(12):E764-73. Available from: https://doi.org/10.1016/S2665-9913(20)30341-6.

320. Aman J, Duijvelaar E, Botros L, Kianzad A, Schippers JR, Smeele PJ, et al. Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. The Lancet Respiratory Medicine. 2021 Jun;S221326002100237X.

321. Ravichandran R, Mohan SK, Sukumaran SK, Kamaraj D, Daivasuga SS, Ravi SOAS, et al. An open label randomized clinical trial of Indomethacin for mild and moderate hospitalised Covid-19 patients. Sci Rep. 2022 Dec;12(1):6413.

322. Fisher BA, Veenith T, Slade D, Gaskell C, Rowland M, Whitehouse T, et al. Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial. The Lancet Respiratory Medicine. 2021 Dec;S2213260021004604.

323. Lopardo G, Belloso WH, Nannini E, Colonna M, Sanguineti S, Zylberman V, et al. RBD-specific polyclonal F(ab´)2 fragments of equine antibodies in patients with

moderate to severe COVID-19 disease: A randomized, multicenter, double-blind, placebo-controlled, adaptive phase 2/3 clinical trial. EClinicalMedicine. 2021 Apr;100843.

324. Esquivel-Moynelo I, Perez-Escribano J, Duncan-Robert Y, Vazque-Blonquist D, Bequet-Romero M, Baez-Rodriguez L, et al. Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA: preliminary results of a randomized controlled clinical trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.07.29.20164251

325. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, et al. Efficacy and safety of interferon beta-1a in treatment of severe COVID-19: a randomized clinical trial [Preprint] MedRxiv 2020. Available from: https://doi.org/10.1101/2020.05.28.20116467.

326. Darazam I, Pourhoseingholi M, Shokouhi S, Irvani S, Mokhtari M, Shabani M, et al. Role of Interferon Therapy in Severe COVID-19: The COVIFERON Randomized Controlled Trial. ResearchSquare [Internet]. 2021.

327. Darazam I, Hatami F, Rabiei M, Pourhoseingholi M, Shabani M, Shokouhi S, et al. An Investigation Into the Beneficial Effects of High-Dose Interferon beta 1-a, Compared to Low-Dose Interferon Beta 1-a (the base therapeutic regimen) in moderate to severe COVID-19. ResearchSquare [Internet]. 2021.

328. Kalil AC, Mehta AK, Patterson TF, Erdmann N, Gomez CA, Jain MK, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. The Lancet Respiratory Medicine. 2021 Oct;S2213260021003842.

329. Ranieri VM, Pettilä V, Karvonen MK, Jalkanen J, Nightingale P, Brealey D, et al. Effect of Intravenous Interferon β-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2020 Feb 25;323(8):725.

330. Castro-Rodriguez JA, Fish EN, Kollmann T, Iturriaga C, Karpievitch Y, Shannon C, et al. Interferon Beta-1α ring prophylaxis to reduce household transmission of SARS-CoV-2: the Containing Coronavirus Disease-19 randomized clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jun [cited 2022 Jul 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.06.13.22276369

331. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med 2020; published online 12 November 2020. Available from: https://doi.org/10.1016/S2213-2600(20)30511-7.

332. Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, et al. Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. Int Immunopharmacol 2020;88:106903. Available from: https://doi.org/10.1016/j.intimp.2020.106903.

333. Tam AR, Zhang RR, Lung KC, Liu R, Leung KY, Liu D, et al. Early treatment of high-risk hospitalized COVID-19 patients with a combination of interferon beta-1b and remdesivir: a phase 2 open-label randomized controlled trial. Clinical Infectious Diseases. 2022 Jun 28;ciac523.

334. Myasnikov AL, Berns SA, Talyzin PA, Ershov FI. Interferon gamma in the treatment of patients with moderate COVID-19. Voprosy virusologii. 2021 Mar 7;66(1):47–54.

335. Fu W, Yan L, Liu L, Hu H, Cheng X, Liu P, et al. An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. EclinicalMedicine 2020;27:100547. Available from: https://doi.org/10.1016/j.eclinm.2020.100547.

336. Chahla RE, Medina Ruiz L, Ortega ES, Morales MF, Barreiro F, George A, et al. A Randomized Trial - Intensive Treatment Based in Ivermectin and Iota-carrageenan as Pre-exposure Prophylaxis for COVID-19 in Healthcare Agents [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Apr 2]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.26.21254398

337. Figueroa JM, Lombardo M, Dogliotti A, Flynn LP, Giugliano RP, Simonelli G, et al. Efficacy of a nasal spray containing Iota-Carrageenan in the prophylaxis of COVID-19 in hospital personnel dedicated to patients care with COVID-19 disease A pragmatic multicenter, randomized, double-blind, placebo-controlled trial (CARR-COV-02) [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 Apr 20]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.13.21255409

338. Ojeda RA. Clinical study to verify the effectiveness and safety of the modified isothymol or carvacrol compound against SARS-CoV-2 in COVID-19 patients [Internet]. In Review; 2022 Jul [cited 2022 Aug 30]. Available from: https://www.researchsquare.com/article/rs-1809364/v1

339. Kumar S, de Souza R, Nadkar M, Guleria R, Trikha A, Joshi SR, Loganathan S, Vaidyanathan S, Marwah A, and Athalye S. A Two-Arm, Randomized, Controlled, Multi-Centric, Open-Label Phase-2 Study to Evaluate the Efficacy and Safety of Itolizumab in Moderate to Severe ARDS Patients Due to COVID-19. [Preprint]. Allergy and Immunology 2020. https://doi.org/10.1101/2020.12.01.20239574.

340. Shouman W., Nafae M., Awad Hegazy A., et al. Use of Ivermectin as a potential chemoprophylaxis for COVID-19 in Egypt : A Randomised clinical trial Journal of Clinical and Diagnostic Research, doi:10.7860/JCDR/2020/46795.0000

341. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-38896/v1.

342. Podder C, Chowdhury N, Sina M, Haque W. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study [Internet]. IMC J Med Sci 2020;14(2):002. Available from: http://www.imcjms.com/registration/journal_abstract/353

343. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.10.26.20219345.

344. Mahmud R, Rahman MdM, Alam I, Ahmed KGU, Kabir AKMH, Sayeed SKJB, et al. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. J Int Med Res. 2021 May;49(5):030006052110135.

345. Elgazzar A, Hany B, Youssef SA, Hafez M, Moussa H. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-100956/v1.

346. Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso DF, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial. EClinicalMedicine. 2021 Jul;37:100959.

347. Niaee MS, Gheibi N, Namdar P, Allami A, Zolghadr L, Javadi A, Amin Karampour, et al. 2020. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial [Preprint]. ResearchSquare 2020. https://doi.org/10.21203/rs.3.rs-109670/v1.

348. Sabeena A, Karim MM, Ross ag, Hossain ms, Clemens jd, Sumiya MK, Phru CS, et al. A Five Day Course of Ivermectin for the Treatment of COVID-19 May Reduce the Duration of Illness. International Journal of Infectious Diseases 2020. S1201971220325066. https://doi.org/10.1016/j.ijid.2020.11.191.

349. Chaccour C, Casellas A, Blanco-Di Matteo A, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine. 2021 Jan;100720.

350. Zeeshan Khan Chachar A, Ahmad Khan K, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. ijSciences. 2020;9(09):31–5.

351. Babalola OE, Bode CO, Ajayi AA, Alakaloko FM, Akase IE, Otrofanowei E, et al. Ivermectin shows clinical benefits in mild to moderate COVID19: a randomized controlled double-blind, dose-response study in Lagos. QJM: An International Journal of Medicine. 2021 Feb 18;hcab035.

352. Kirti R, Roy R, Pattadar C, Raj R, Agarwal N, Biswas B, et al. Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jan [cited 2021 Jan 11]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.01.05.21249310

353. Mohan A, Tiwari P, Suri T, Mittal S, Patel A, Jain A, et al. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial [Internet]. In Review; 2021 Feb [cited 2021 Jun 5]. Available from: https://www.researchsquare.com/article/rs-191648/v1

354. Shahbaznejad L, Davoudi A, Eslami G, Markowitz JS, Navaeifar MR, Hosseinzadeh F, et al. Effect of ivermectin on COVID-19: A multicenter double-blind

randomized controlled clinical trial. Clinical Therapeutics. 2021 May;S0149291821002010.

355. Hill A, Abdulamir A, Ahmed S, Asghar A, Babalola OE, Basri R, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection [Internet]. In Review; 2021 Jan [cited 2021 Jan 29]. Available from: https://www.researchsquare.com/article/rs-148845/v1

356. Samaha AA, Mouawia H, Fawaz M, Hassan H, Salami A, Bazzal AA, et al. Effects of a Single Dose of Ivermectin on Viral and Clinical Outcomes in Asymptomatic SARS-CoV-2 Infected Subjects: A Pilot Clinical Trial in Lebanon. Viruses. 2021 May 26;13(6):989.

357. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Feb [cited 2021 Mar 9]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.02.02.21250840

358. Okumuş N, Demirtürk N, Çetinkaya RA, Güner R, Avcı İY, Orhan S, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. BMC Infect Dis. 2021 Dec;21(1):411.

359. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2021 Mar 4 [cited 2021 Mar 9]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2777389

360. Pott-Junior H, Bastos Paoliello MM, de Queiroz Constantino Miguel A, da Cunha AF, de Melo Freire CC, Neves FF, et al. Use of ivermectin in the treatment of Covid-19: a pilot trial. Toxicology Reports. 2021 Mar;S2214750021000445.

361. Kishoria N, Mathur SL, Parmar V, Kaur RJ, Agarwal H, Parihar BS, et al. Ivermectin as Adjuvant to Hydroxycholoroquine in Patients Resistant to Standard Treatment for SARS-CoV-2: Results of an Open-label Randomized Clinical Study. PIJR. 2020 Aug 15;1–4.

362. Abd-Elsalam S, Noor RA, Badawi R, Khalaf M, Esmail ES, Soliman S, et al. Clinical Study Evaluating the Efficacy of Ivermectin in COVID-19 Treatment: A Randomized Controlled Study. J Med Virol. 2021 Jun 2;jmv.27122.

363. Biber A, Harmelin G, Lev D, Ram L, Shaham A, Nemet I, et al. The effect of ivermectin on the viral load and culture viability in early treatment of nonhospitalized

patients with mild COVID-19 – a double-blind, randomized placebo-controlled trial. International Journal of Infectious Diseases. 2022 Sep;122:733–40.

364. Faisal R, Shah SFA, Hussain M. Potential use of azithromycin alone and in combination with ivermectin in fighting against the symptoms of COVID-19. TPMJ. 2021 May 10;28(05):737–41.

365. Vallejos J, Zoni R, Bangher M, Villamandos S, Bobadilla A, Plano F, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. BMC Infect Dis. 2021 Dec;21(1):635.

366. Buonfrate D, Chesini F, Martini D, Roncaglioni MC, Fernandez MLO, Alvisi MF, et al. High dose ivermectin for the early treatment of COVID-19 (COVER study): a randomised, double-blind, multicentre, phase II, dose-finding, proof of concept clinical trial. International Journal of Antimicrobial Agents. 2022 Jan;106516.

367. Manomaipiboon A, Pholtawornkulchai K, Pupipatpab S, Suraamornkul S, Maneerit J, Ruksakul W, et al. Efficacy and safety of ivermectin in the treatment of mild-to-moderate COVID-19 infection: A randomized, double blind, placebo, controlled trial [Internet]. In Review; 2022 Feb [cited 2022 Feb 15]. Available from: https://www.researchsquare.com/article/rs-1290999/v1

368. Lim SCL, Hor CP, Tay KH, Mat Jelani A, Tan WH, Ker HB, et al. Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial. JAMA Intern Med [Internet]. 2022 Feb 18 [cited 2022 Feb 22]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2789362

369. Reis G, Silva EASM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med. 2022 Mar 30;NEJMoa2115869.

370. Rocha C de la, Cid-Lopez MA, Venegas-Lopez BI, Gómez-Mendez SC, Sánchez-Ortiz A, Pérez-Ríos AM, et al. Ivermectin compared with placebo in the clinical evolution of Mexican patients with asymptomatic and mild COVID-19: a randomized clinical trial [Internet]. In Review; 2022 May [cited 2022 Jun 8]. Available from: https://www.researchsquare.com/article/rs-1640339/v1

371. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group, Naggie S. Ivermectin for Treatment of Mild-to-Moderate COVID-19 in the Outpatient Setting: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jun [cited 2022 Jul 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.06.10.22276252

372. Rezai MS, Ahangarkani F, Hill A, Ellis L, Mirchandani M, Davoudi A, et al. Non-effectiveness of Ivermectin on Inpatients and Outpatients With COVID-19; Results of Two Randomized, Double-Blinded, Placebo-Controlled Clinical Trials. Front Med. 2022 Jun 16;9:919708.

373. Angkasekwinai N, Rattanaumpawan P, Chayakulkeeree M, Phoompoung P, Koomanachai P, Chantarasut S, et al. Safety and Efficacy of Ivermectin for the Prevention and Treatment of COVID-19: A Double-Blinded Randomized Placebo-Controlled Study. Antibiotics. 2022 Jun 12;11(6):796.

374. Mirahmadizadeh A, Semati A, Heiran A, Ebrahimi M, Hemmati A, Karimi M, et al. Efficacy of single-dose and double-dose ivermectin early treatment in preventing progression to hospitalization in mild COVID -19: A multi-arm, parallel-group randomized, double-blind, placebo-controlled trial. Respirology. 2022 Jun 23;resp.14318.

375. George B, Moorthy M, Kulkarni U, Selvarajan S, Rupali P, Christopher DJ, et al. Single Dose of Ivermectin is not Useful in Patients with Hematological Disorders and COVID-19 Illness: A Phase II B Open Labelled Randomized Controlled Trial. Indian J Hematol Blood Transfus [Internet]. 2022 May 27 [cited 2022 Jul 1]; Available from: https://link.springer.com/10.1007/s12288-022-01546-w

376. Schilling WH, Jittamala P, Watson JA, Ekkapongpisit M, Siripoon T, Ngamprasertchai T, et al. Pharmacometric assessment of the *in vivo* antiviral activity of ivermectin in early symptomatic COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jul [cited 2022 Jul 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.07.15.22277570

377. Nimitvilai S, Suputtamongkol Y, Poolvivatchaikarn U, Rassamekulthana D, Rongkiettechakorn N, Mungaomklang A, et al. A randomized controlled trial of combined ivermectin and zinc sulfate versus combined hydroxychloroquine,

darunavir/ritonavir, and zinc sulfate among adult patients with asymptomatic or mild coronavirus-19 infection. J Global Infect Dis. 2022;14(2):69.

378. Aref ZF, Bazeed SEES, Hassan MH, Hassan AS, Rashad A, Hassan RG, et al. Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19. Int J Nanomedicine. 2021;16:4063–72.

379. Sakoulas G, Geriak M, Kullar R, Greenwood K, Habib M, Vyas A, et al. Intravenous immunoglobulin (IVIG) significantly reduces respiratory morbidity in COVID-19 pneumonia: a prospective randomized trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.07.20.20157891.

380. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi S-R, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomised placebo-controlled double-blind clinical trial [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-40899/v2.

381. Tabarsi P, Barati S, Jamaati H, Haseli S, Marjani M, Moniri A, et al. Evaluating the effects of intravenous immunoglobulin (IVIG) on the management of severe COVID-19 cases: a randomized controlled trial [Internet]. Int Immunopharmacol 2020:107205. Available from: https://doi.org/10.1016/j.intimp.2020.107205.

382. R S R, Barge VB, Darivenula AK, Dandu H, Kartha RR, Bafna V, et al. A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in COVID-19 patients with Regular Intravenous Immunoglobulin Therapy. The Journal of Infectious Diseases. 2021 Feb 15;jiab098.

383. Haran JP, Zheng Y, Knobil K, Palma NA, Lawrence JF, Wingertzahn MA. Targeting the Microbiome With KB109 in Outpatients with Mild to Moderate COVID-19 Reduced Medically Attended Acute Care Visits and Improved Symptom Duration in Patients With Comorbidities [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Apr 5]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.26.21254422

384. Fiorentino G, Coppola A, Izzo R, Annunziata A, Bernardo M, Lombardi A, et al. Effects of adding L-arginine orally to standard therapy in patients with COVID-19: A randomized, double-blind, placebo-controlled, parallel-group trial. Results of the first interim analysis. EClinicalMedicine. 2021 Sep;101125.

385. Endam LM, Tremblay C, Filali A, Desrosiers MY. Intranasal Application of Lactococcus Lactis W 136 Bacteria Early in SARS-Cov-2 Infection May Have a Beneficial Immunomodulatory Effect: A Proof-of-concept Study [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 May 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.18.21255699

386. Algahtani FD, Elabbasy MT, Samak MA, Adeboye AA, Yusuf RA, Ghoniem ME. The Prospect of Lactoferrin Use as Adjunctive Agent in Management of SARS-CoV-2 Patients: A Randomized Pilot Study. Medicina. 2021 Aug 19;57(8):842.

387. Hu K, Wang M, Zhao Y, Zhang Y, Wang T, Zheng Z, et al. A small-scale medication of leflunomide as a treatment of COVID-19 in an open-label blank-controlled clinical trial [Internet]. Virol Sin 2020. Available from: https://doi.org/10.1007/s12250-020-00258-7.

388. Wang M, Zhao Y, Hu W, Zhao D, Zhang Y, Wang T, et al. Treatment of COVID-19 patients with prolonged post-symptomatic viral shedding with leflunomide -- a single-center, randomized, controlled clinical trial [Internet]. Clin Infect Dis 2020; ciaa1417. Available from: https://doi.org/10.1093/cid/ciaa1417.

389. Temesgen Z, Burger CD, Baker J, Polk C, Libertin CR, Kelley CF, et al. Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebo-controlled trial. The Lancet Respiratory Medicine. 2021 Dec;S221326002100494X.

390. Roostaei A, Meybodi Z, Mosavinasab S, Karimzadeh I, Sahebnasagh A, Gholinataj M, et al. Efficacy and Safety of Levamisole Treatment in Clinical Presentations of Patients With COVID-19: A Double-Blind, Randomized, Controlled Trial. ResearchSquare [Internet]. 2021.

391. Asgardoon MH, koochak HE, Kazemi-Galougahi MH, Dehnavi AZ, Khodaei B, Behkar A, et al. Efficacy of Levamisole with Standard Care Treatment vs Standard Care in Clinical Presentations of Non-Hospitalized Patients with COVID-19: A Randomized Clinical Trial [Internet]. In Review; 2021 Nov [cited 2021 Dec 6]. Available from: https://www.researchsquare.com/article/rs-964097/v1

392. Lomakin NV, Bakirov BA, Protsenko DN, Mazurov VI, Musaev GH, Moiseeva OM, et al. The efficacy and safety of levilimab in severely ill COVID-19 patients not requiring mechanical ventilation: results of a multicenter randomized double-blind

placebo-controlled phase III CORONA clinical study. Inflamm Res [Internet]. 2021 Sep 29 [cited 2021 Oct 12]; Available from: https://link.springer.com/10.1007/s00011-021-01507-5

393. Abuhasira R, Ayalon-Dangur I, Zaslavsky N, Koren R, Keller M, Dicker D, et al. A Randomized Clinical Trial of Linagliptin vs. Standard of Care in Patients Hospitalized With Diabetes and COVID-19. Front Endocrinol. 2021 Dec 22;12:794382.

394. Guardado-Mendoza R, Garcia-Magaña MA, Martínez-Navarro LJ, Macías-Cervantes HE, Aguilar-Guerrero R, Suárez-Pérez EL, et al. Effect of linagliptin plus insulin in comparison to insulin alone on metabolic control and prognosis in hospitalized patients with SARS-CoV-2 infection. Sci Rep. 2022 Dec;12(1):536.

395. Spuch C, López-García M, Rivera-Baltanás T, Cabrera-Alvargonzález JJ, Gadh S, Rodrigues-Amorim D, et al. Efficacy and Safety of Lithium Treatment in SARS-CoV-2 Infected Patients. Front Pharmacol. 2022 Apr 14;13:850583.

396. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; 382(19): 1787–99. Available from: https://doi.org/10.1056/NEJMoa2001282.

397. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial [Internet]. Clin Advance 2020, published online 4 May 2020. Available from: https://doi.org/10.1016/j.medj.2020.04.001.

398. RECOVERY Collaborative Group. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2020; 396 (10259): 1345-52. Available from: https://doi.org/10.1016/S0140-6736(20)32013-4.

399. Zheng F, Zhou Y, Zhou Z, Ye F, Huang B, Huang Y, et al. A novel protein drug, novaferon, as the potential antiviral drug for COVID-19 [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.04.24.20077735.

400. Chen Y-K, Huang Y-Q, Tang S-Q, Xu X-L, Zeng Y-M, He X-Q, et al. Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate novel coronavirus pneumonia: results

of a randomized, open-labeled prospective study [Preprint]. 2020. Available from SSRN: https://doi.org/10.2139/ssrn.3576905.

401. Shahnaz Sali, Davood Yadegarinia, Sara Abolghasemi, Shabnam Tehrani, Babak Gharaei, Neda Khabiri, et al. Comparison of the Efficacy of Sofosbuvir and Kaletra on Outcome of Covid-19. Is Sofosbuvir A Potential Treatment For COVID-19? Novelty in Biomedicine [Internet]. 2021

402. Purwati, Budiono, Rachman BE, Yulistiani, Miatmoko A, Nasronudin, et al. A Randomized, Double-Blind, Multicenter Clinical Study Comparing the Efficacy and Safety of a Drug Combination of Lopinavir/Ritonavir-Azithromycin, Lopinavir/Ritonavir-Doxycycline, and Azithromycin-Hydroxychloroquine for Patients Diagnosed with Mild to Moderate COVID-19 Infections. Huyut Z, editor. Biochemistry Research International. 2021 Feb 9;2021:1–12.

403. Kasgari HA, Moradi S, Shabani AM, Babamahmoodi F, Badabi ARD, Davoudi L, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. J Antimicrob Chemother 2020; 75(11):3373-78. Available from: https://doi.org/10.1093/jac/dkaa332.

404. Yadollahzadeh M, Eskandari M, Roham M, Zamani F, Laali A, Kalantari S, et al. Evaluation of Sovodak (Sofosbuvir/Daclatasvir) Treatment Outcome in COVID-19 Patient’s Compared with Kaletra (Lopinavir/ritonavir): a Randomized Clinical Trial [Internet]. In Review; 2021 Mar [cited 2021 Mar 25]. Available from: https://www.researchsquare.com/article/rs-257762/v1

405. Labhardt ND, Smit M, Petignat I, Perneger T, Marinosci A, Ustero P, et al. Efficacy of Lopinavir-Ritonavir Prophylaxis for Individuals Exposed to SARS-CoV-2: The COPEP Pragmatic Open-Label, Cluster Randomized Trial. SSRN Journal [Internet]. 2021 [cited 2021 Jul 14]; Available from: https://www.ssrn.com/abstract=3878828

406. Papachristofilou A, Finazzi T, Blum A, Zehnder T, Zellweger N, Lustenberger J, et al. Low-Dose Radiation Therapy for Severe COVID-19 Pneumonia: A Randomized Double-Blind Study. International Journal of Radiation Oncology*Biology*Physics. 2021 Mar;S036030162100239X.

407. Ganesan G, Ponniah S, Sundaram V, Kumar Marimuthu P, Pitchaikannu V, Chandrasekaran M, et al. Whole lung Irradiation as a Novel treatment for COVID-19:

Final Results of the Prospective Randomized trial (WINCOVID trial). Radiotherapy and Oncology. 2021 Dec;S0167814021090721.

408. Singh P, Mandal A, Singh D, Kumar S, Kumar A, Rakesh A, et al. Interim Analysis of Impact of Adding Low Dose Pulmonary Radiotherapy to Moderate COVID-19 Pneumonia Patients: IMpaCt-RT Study. Front Oncol. 2022 Mar 29;12:822902.

409. Cremer PC, Abbate A, Hudock K, McWilliams C, Mehta J, Chang SY, et al. Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. The Lancet Rheumatology. 2021 Mar;S2665991321000709.

410. Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, et al. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. Archives of Medical Research. 2021 Jun;S0188440921001417.

411. Davoodian N, Sharifimood F, Salarbashi D, Elyasi S, Baniasad A, Bejestani FS. The Effect of Melatonin as an Adjuvant Therapy on COVID-19: A Randomized Clinical Trial. SSRN Journal [Internet]. 2021 [cited 2021 Jul 14]; Available from: https://www.ssrn.com/abstract=3878090

412. Alizadeh Z, Keyhanian N, Ghaderkhani S, Dashti-Khavidaki S, Shokouhi Shoormasti R, Pourpak Z. A Pilot Study on Controlling Coronavirus Disease 2019 (COVID-19) Inflammation Using Melatonin Supplement. IJAAI [Internet]. 2021 Aug 11 [cited 2021 Aug 30]; Available from: https://publish.kne-publishing.com/index.php/IJAAI/article/view/6959

413. Mousavi SA, Heydari K, Mehravaran H, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, et al. Melatonin effects on sleep quality and outcomes of COVID-19 patients: An open-label, randomized, controlled trial. J Med Virol. 2021 Sep 8;jmv.27312.

414. Hasan ZT, Atrakji DrMQYMAA, Mehuaiden DrAK. The Effect of Melatonin on Thrombosis, Sepsis and Mortality Rate in COVID-19 Patients. International Journal of Infectious Diseases. 2021 Oct;S1201971221007980.

415. García-García I, Seco-Meseguer E, Ruiz-Seco P, Navarro-Jimenez G, Martínez-Porqueras R, Espinosa-Díaz M, et al. Melatonin in the Prophylaxis of SARS-CoV-2

Infection in Healthcare Workers (MeCOVID): A Randomised Clinical Trial. JCM. 2022 Feb 21;11(4):1139.

416. Alizadeh Z, Keyhanian N, Ghaderkhani S, Dashti-Khavidaki S, Shokouhi Shoormasti R, Pourpak Z. A Pilot Study on Controlling Coronavirus Disease 2019 (COVID-19) Inflammation Using Melatonin Supplement. IJAAI [Internet]. 2021 Aug 11 [cited 2021 Aug 30]; Available from: https://publish.kne-publishing.com/index.php/IJAAI/article/view/6959

417. Fogleman C, Cohen D, Mercier A, Farrell D, Rutz J, Bresz K, et al. A Pilot of a Randomized Control Trial of Melatonin and Vitamin C for Mild-to-Moderate COVID-19. J Am Board Fam Med. 2022 Jul;35(4):695–707.

418. Guzman-Esquivel J, Galvan-Salazar HR, Guzman-Solorzano HP, Cuevas-Velazquez AC, Guzman-Solorzano JA, Mokay-Ramirez KA, et al. Efficacy of the use of mefenamic acid combined with standard medical care vs. standard medical care alone for the treatment of COVID-19: A randomized double-blind placebo-controlled trial. Int J Mol Med. 2022 Mar;49(3):29.

419. Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Res Ther 2020;11(1):361. Available from: https://doi.org/10.1186/s13287-020-01875-5.

420. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. Treatment with human umbilical cord-derived mesenchymal stem cells for COVID-19 patients with lung damage: a randomised, double-blind, placebo controlled phase 2 trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.10.15.20213553.

421. Lanzoni G, Linetsky E, Correa D, Cayetano SM, Marttos AC, Alvarez RA, et al. Umbilical cord mesenchymal stem cells for COVID-19 ARDS: a double blind, phase 1/2a, randomized controlled trial [Preprint]. 2020. Available from SSRN: https://doi.org/10.2139/ssrn.3696875.

422. Dilogo IH, Aditianingsih D, Sugiarto A, Burhan E, Damayanti T, Sitompul PA, et al. Umbilical cord mesenchymal stromal cells as critical COVID -19 adjuvant therapy: A randomized controlled trial. STEM CELLS Transl Med. 2021 Jun 8;sctm.21-0046.

423. Zhu R, Yan T, Feng Y, Liu Y, Cao H, Peng G, et al. Mesenchymal stem cell treatment improves outcome of COVID-19 patients via multiple immunomodulatory

mechanisms. Cell Res [Internet]. 2021 Oct 26 [cited 2021 Nov 4]; Available from: https://www.nature.com/articles/s41422-021-00573-y

424. Fathi-Kazerooni M, Fattah-Ghazi S, Darzi M, Makarem J, Nasiri R, Salahshour F, et al. Safety and efficacy study of allogeneic human menstrual blood stromal cells secretome to treat severe COVID-19 patients: clinical trial phase I & II. Stem Cell Res Ther. 2022 Dec;13(1):96.

425. Rebelatto CLK, Senegaglia AC, Franck CL, Daga DR, Shigunov P, Stimamiglio MA, et al. Safety and long-term improvement of mesenchymal stromal cell infusion in critically COVID-19 patients: a randomized clinical trial. Stem Cell Res Ther. 2022 Dec;13(1):122.

426. Karyana M, Djaharuddin I, Rif'ati L, Arif M, Choi MK, Angginy N, et al. Safety of DW-MSC infusion in patients with low clinical risk COVID-19 infection: a randomized, double-blind, placebo-controlled trial. Stem Cell Res Ther. 2022 Dec;13(1):134.

427. Reis G, dos Santos Moreira Silva EA, Medeiros Silva DC, Thabane L, Cruz Milagres A, Ferreira TS, et al. Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial. The Lancet Regional Health - Americas. 2022 Feb;6:100142.

428. Ventura-López C, Cervantes-Luevano K, Aguirre-Sánchez JS, Flores-Caballero JC, Alvarez-Delgado C, Bernaldez-Sarabia J, et al. Treatment with metformin glycinate reduces SARS-CoV-2 viral load: An in vitro model and randomized, double-blind, Phase IIb clinical trial. Biomedicine & Pharmacotherapy. 2022 Aug;152:113223.

429. Hamidi-Alamdari D, Hafizi-Lotfabadi S, Bagheri-Moghaddam A, Safari H, Mozdourian M, Javidarabshahi Z, et al. Methylene Blue for Treatment of Hospitalized COVID-19 Patients: A Randomized, Controlled, Open-label Clinical Trial, Phase 2. Rev Invest Clin. 2021;73(3):190–8.

430. Borges M, Borges M, Borges J, Bastidas R. Estudio Experimental: Manejo del Metisoprinol en Pacientes con COVID-19. uct. 2020 Aug 10;24(103):41–50.

431. Clemente-Moragón A, Martínez-Milla J, Oliver E, Santos A, Flandes J, Fernández I, et al. Metoprolol in Critically Ill Patients With COVID-19. Journal of the American College of Cardiology. 2021 Sep;78(10):1001–11.

432. Kazempour M, Izadi H, Chouhdari A, Rezaeifard M. Anti-inflammatory Effect of Metronidazole in Hospitalized Patients with Pneumonia due to COVID-19. Iran J Pharm Res. 2021;20(3):532–40.

433. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NCJE, et al. Human Safety, Tolerability, and Pharmacokinetics of a Novel Broad-Spectrum Oral Antiviral Compound, Molnupiravir, with Activity Against SARS-CoV-2 [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Dec [cited 2020 Dec 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.12.10.20235747

434. Khoo SH, FitzGerald R, Fletcher T, Ewings S, Jaki T, Lyon R, et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase 1, dose-escalating, randomised controlled study [Internet]. Pharmacology and Therapeutics; 2021 May [cited 2021 May 14]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.03.21256309

435. Fischer WA, Eron JJ, Holman W, Cohen MS, Fang L, Szewczyk LJ, et al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med. 2021 Dec 23;eabl7430.

436. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2021 Dec 16;NEJMoa2116044.

437. Tippabhotla SK, Lahiri DrS, D RR, Kandi C, V NP. Efficacy and Safety of Molnupiravir for the Treatment of Non-Hospitalized Adults With Mild COVID-19: A Randomized, Open-Label, Parallel-Group Phase 3 Trial. SSRN Journal [Internet]. 2022 [cited 2022 Mar 7]; Available from: https://www.ssrn.com/abstract=4042673

438. Zou R, Peng L, Shu D, Zhao L, Lan J, Tan G, et al. Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial. Front Pharmacol. 2022 Jun 15;13:939573.

439. Khoo SH, FitzGerald R, Saunders G, Middleton C, Ahmad S, Edwards CJ, et al. A Randomised -Controlled Phase 2 trial of Molnupiravir in Unvaccinated and Vaccinated Individuals with Early SARS-CoV-2 [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jul [cited 2022 Aug 11]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.07.20.22277797

440. Arribas JR, Bhagani S, Lobo SM, Khaertynova I, Mateu L, Fishchuk R, et al. Randomized Trial of Molnupiravir or Placebo in Patients Hospitalized with Covid-19. NEJM Evidence [Internet]. 2022 Jan 25 [cited 2022 Aug 19];1(2). Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2100044

441. Caraco Y, Crofoot GE, Moncada PA, Galustyan AN, Musungaie DB, Payne B, et al. Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults. NEJM Evidence [Internet]. 2022 Jan 25 [cited 2022 Aug 19];1(2). Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2100043

442. Kerget B, Kerget F, Aydın M, Karaşahin Ö. Effect of montelukast therapy on clinical course, pulmonary function, and mortality in patients with COVID-19. Journal of Medical Virology. 2021 Dec 27;jmv.27552.

443. Mukhtar K, Qassim S, DanJuma MI, Mohamedali M, Al Farhan H, Khudair MF, El Tayeh AR, et al. On the Possible Beneficial Role for the Regular Use of Potent Mouthwash Solutions as a Preventive Measure for COVID19 Transmission; Invoking the Evolutionary Biology and Game Theory. [Preprint] 2020. https://doi.org/10.1101/2020.11.27.20234997.

444. Azmawati MN, Baharom N, Wan Sulaiman W, Rashid ZZ, Wong KK, Ali UK, Othman SN, et al. Early viral clearance among COVID-19 patients when gargling with povidone-iodine and essential oils: A pilot clinical trial. [Preprint] 2020. https://doi.org/10.1101/2020.09.07.20180448.

445. Guenezan J, Garcia M, Strasters D, Jousselin C, Lévêque N, Frasca D, et al. Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Nasopharyngeal Viral Load in Patients With COVID-19: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg [Internet]. 2021 Feb 4 [cited 2021 Feb 14]; Available from: https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2775984

446. Elzein R, Abdel-Sater F, Fakhreddine S, Hanna PA, Feghali R, Hamad H, et al. In vivo evaluation of the virucidal efficacy of Chlorhexidine and Povidone-iodine mouthwashes against salivary SARS-CoV-2 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Mar 22]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.07.21252302

447. Santos PS da S, Orcina B da F, Machado RRG, Vilhena FV, Alves LM da C, Zangrando MSR, et al. Beneficial effects of a mouthwash containing an antiviral

phthalocyanine derivative on the length of hospital stay for COVID-19 [Internet]. In Review; 2021 Mar [cited 2021 Mar 23]. Available from: https://www.researchsquare.com/article/rs-330173/v1

448. Carrouel, Valette, Gadea, Esparcieux, Illes, Langlois, et al. Use of an antiviral mouthwash as an additional barrier measure in the SARS-CoV-2 transmission in adults with asymptomatic to mild COVID-19: A multicenter, randomized, double-blind controlled trial [Internet]. In Review; 2021 Mar [cited 2021 Mar 25]. Available from: https://www.researchsquare.com/article/rs-315468/v1

449. Huang YH, Huang JT. Use of chlorhexidine to eradicate oropharyngeal SARS-CoV-2 in COVID-19 patients. J Med Virol. 2021 Apr;jmv.26954.

450. Eduardo F de P, Corrêa L, Heller D, Daep CA, Benitez C, Malheiros Z, et al. Salivary SARS-CoV-2 load reduction with mouthwash use: A randomized pilot clinical trial. Heliyon. 2021 Jun;7(6):e07346.

451. Di Domênico MB, Collares K, dos Santos RB, Lenz U, Antunes VP, Godinho V, et al. Hydrogen peroxide as auxiliary treatment for COVID-19: A randomized double-blind clinical trial. Epidemiol Health. 2021 Aug 3;e2021051.

452. Damião Costa D, Brites C, Nunes Vaz S, Souza de Santana D, Dos Santos JN, Cury PR. Chlorhexidine mouthwash reduces the salivary viral load of SARS-CoV-2: a randomized clinical trial. Oral Dis. 2021 Nov 26

453. Ferrer MD, Barrueco ÁS, Martinez-Beneyto Y, Mateos-Moreno MV, Ausina-Márquez V, García-Vázquez E, et al. Clinical evaluation of antiseptic mouth rinses to reduce salivary load of SARS-CoV-2. Sci Rep. 2021 Dec;11(1):24392.

454. Poleti ML, Gregório D, Bistaffa AGI, Fernandes KBP, Vilhena FV, Santos PS da S, et al. The use of a mouthwash and a dentifrice containing antimicrobial phthalocyanine derivative on the reduction of clinical symptoms of COVID-19: A randomized triple-blinded clinical trial [Internet]. In Review; 2021 Dec [cited 2022 Jan 5]. Available from: https://www.researchsquare.com/article/rs-1139111/v1

455. Alemany A, Perez-Zsolt D, Raïch-Regué D, Muñoz-Basagoiti J, Ouchi D, Laporte-Villar C, et al. Cetylpyridinium Chloride Mouthwash to Reduce Shedding of Infectious SARS-CoV-2: A Double-Blind Randomized Clinical Trial. J Dent Res. 2022 Jun 21;002203452211023.

456. Barrueco ÁS, Mateos-Moreno MV, Martínez-Beneyto Y, García-Vázquez E, González AC, Ferrero JZ, et al. Effect of Oral Antiseptics in Reducing SARS-CoV-2 Infectivity: Evidence from a Randomized Double-blind Clinical Trial. Emerging Microbes & Infections. 2022 Jul 7;1–23.

457. Miller RA, Guru P, Bauer P, Robles J, Tomaszewski C, Overcash JS, et al. Clinical Results with a B Cell Activating Anti-CD73 Antibody for the Immunotherapy of COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Sep [cited 2021 Sep 29]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.09.13.21263406

458. Sehgal IS, Guleria R, Singh S, Siddiqui MS, Agarwal R. A randomised trial of *Mycobacterium w* in critically ill patients with COVID-19: ARMY-1. ERJ Open Res. 2021 Apr;7(2):00059–2021.

459. Alencar JCG de, Moreira CdL, Müller AD, Chaves CE, Fukuhara MA, Silva EA da, Miyamoto MdFS, et al. Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of Severe Acute Respiratory Syndrome caused by COVID-19. Clin Infect Dis 2020: ciaa1443. Available from: https://doi.org/10.1093/cid/ciaa1443.

460. Gaynitdinova VV, Avdeev SN, Merzhoeva ZM, Berikkhanov ZG-M, Medvedeva IV, Gorbacheva TL. N-acetylcysteine as a part of complex treatment of moderate COVID-associated pneumonia. Pul′monologiâ (Mosk). 2021 Feb 19;31(1):21–9.

461. Taher A, Lashgari M, Sedighi L, Rahimi-bashar F, Poorolajal J, Mehrpooya M. A pilot study on intravenous N-Acetylcysteine treatment in patients with mild-to-moderate COVID19-associated acute respiratory distress syndrome. Pharmacol Rep [Internet]. 2021 Jun 10 [cited 2021 Jun 21]; Available from: https://link.springer.com/10.1007/s43440-021-00296-2

462. Quinn TM, Gaughan EE, Bruce A, Antonelli J, O'Connor R, Li F, et al. Randomised Controlled Trial of Intravenous Nafamostat Mesylate in COVID pneumonitis: Phase 1b/2a Experimental Study to Investigate Safety, Pharmacokinetics and Pharmacodynamics [Internet]. Respiratory Medicine; 2021 Oct [cited 2021 Oct 18]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.10.06.21264648

463. Hassaniazad M, Eftekhar E, Inchehsablagh BR, Kamali H, Tousi A, Jaafari MR, et al. A triple-blind, placebo-controlled, randomized clinical trial to evaluate the effect of curcumin-containing nanomicelles on cellular immune responses subtypes and clinical outcome in COVID -19 patients. Phytotherapy Research. 2021 Sep 19;ptr.7294.

464. Kimura KS, Freeman MH, Wessinger BC, Gupta V, Sheng Q, Huang LC, et al. Interim analysis of an open-label randomized controlled trial evaluating nasal irrigations in non-hospitalized patients with COVID-19. Int Forum Allergy Rhinol 2020;10(12):1325-28. Available from: https://doi.org/10.1002/alr.22703.

465. Yildiz E, Koca Yildiz S, Kuzu S, Günebakan Ç, Bucak A, Kahveci OK. Comparison of the Healing Effect of Nasal Saline Irrigation with Triamcinolone Acetonide Versus Nasal Saline Irrigation alone in COVID-19 Related Olfactory Dysfunction: A Randomized Controlled Study. Indian J Otolaryngol Head Neck Surg [Internet]. 2021 Jul 10 [cited 2021 Nov 23]; Available from: https://link.springer.com/10.1007/s12070-021-02749-9

466. George CE, Scheuch G, Seifart U, Inbaraj LR, Chandrasingh S, Nair IK, et al. COVID-19 symptoms are reduced by targeted hydration of the nose, larynx and trachea. Sci Rep. 2022 Dec;12(1):4599.

467. Baxter AL, Schwartz KR, Johnson RW, Kuchinski A-M, Swartout KM, Srinivasa Rao ASR, et al. Rapid initiation of nasal saline irrigation to reduce severity in high-risk COVID+ outpatients: a randomized clinical trial compared to a national dataset observational arm [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Aug [cited 2022 Jan 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.08.16.21262044

468. Nesari TM, Bhardwaj A, ShriKrishna R, Ruknuddin G, Ghildiyal S, Das A, et al. Neem (Azadirachta Indica A. Juss) Capsules for Prophylaxis of COVID-19 Infection: A Pilot, Double-Blind, Randomized Controlled Trial. Altern Ther Health Med. 2021 Apr 23;

469. Abdulamir AS, Gorial FI, Saadi SJ, Maulood MF, Hashim HA, abdulrrazaq MK. Effectiveness and Safety of Niclosamaide as Add-on Therapy to the Standard of Care Measures in COVID-19 Management: Randomized controlled clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jun [cited 2021 Jul 9]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.06.10.21258709

470. Cairns DM, Dulko D, Griffiths JK, Golan Y, Cohen T, Trinquart L, et al. Efficacy of Niclosamide vs Placebo in SARS-CoV-2 Respiratory Viral Clearance, Viral Shedding, and Duration of Symptoms Among Patients With Mild to Moderate COVID-19: A Phase 2 Randomized Clinical Trial. JAMA Netw Open. 2022 Feb 9;5(2):e2144942.

471. Labro G, Tubach F, Belin L, Dubost JL, Osman D, Muller G, et al. Nicotine patches in patients on mechanical ventilation for severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. Intensive Care Med. 2022 Jul;48(7):876–87.

472. Ashraf S, Ashraf S, Ashraf M, Imran MA, Kalsoom L, Siddiqui UN, et al. Honey and Nigella sativa against COVID-19 in Pakistan (HNS-COVID-PK): A multi-center placebo-controlled randomized clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Nov [cited 2021 May 4]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.10.30.20217364

473. Koshak AE, Koshak EA, Mobeireek AF, Badawi MA, Wali SO, Malibary HM, et al. Nigella sativa for the treatment of COVID-19: An open-label randomized controlled clinical trial. Complementary Therapies in Medicine. 2021 Sep;61:102769.

474. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Feb 16;NEJMoa2118542.

475. Rocco PRM, Silva PL, Cruz FF, Junior MACM, Tierno PFGMM, Moura MA, et al. Early use of nitazoxanide in mild COVID-19 disease: randomized, placebo-controlled trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.10.21.20217208.

476. Vinicius Fontanesi Blum, Sérgio Cimerman, James R. Hunter, Paulo Tierno, Acioly Lacerda, Alexandre Soeiro, et al. Nitazoxanide In Vitro Efficacy Against SARS CoV-2 and In Vivo Superiority to Placebo to Treat Moderate COVID-19 – A Phase 2 Randomized Double-Blind Clinical Trial. SSRN [Internet]. 2021

477. Silva M, Espejo A, L Pereyra M, Lynch M, Thompson M, Taconelli H, et al. Efficacy of Nitazoxanide in reducing the viral load in COVID-19 patients. Randomized, placebo-controlled, single-blinded, parallel group, pilot study. [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Mar 8]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.03.21252509

478. Rossignol J-F, Bardin MC, Oaks JB, Bostick BG, Vora KN, Fulgencio J, et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization [Internet]. Infectious Diseases (except HIV/AIDS); 2021

Apr [cited 2021 Apr 29]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.19.21255441

479. Fowotade A, Bamidele F, Egbetola B, Fagbamigbe AF, Adeagbo BA, Adefuye BO, et al. Efficacy and safety of nitazoxanide combined with ritonavir-boosted atazanavir for the treatment of mild to moderate COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Feb [cited 2022 Feb 16]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.02.03.22270152
480. Medhat MA, El-Kassas M, Karam-Allah H, Al Shafie A, Abd-Elsalam S, Moustafa E, et al. Sofosbuvir/ledipasvir in combination or nitazoxanide alone are safe and efficient treatments for COVID-19 infection: A randomized controlled trial for repurposing antivirals. Arab Journal of Gastroenterology. 2022 May;S1687197922000326.
481. Sokhela S, Bosch B, Hill A, Simmons B, Woods J, Johnstone H, et al. Randomized clinical trial of nitazoxanide or sofosbuvir/daclatasvir for the prevention of SARS-CoV-2 infection. Journal of Antimicrobial Chemotherapy. 2022 Aug 12;dkac266.
482. Moni M, Madathil T, Sathyapalan DT, Menon V, Gutjahr G, Edathadathil F, et al. A Feasibility Trial to Evaluate the Composite Efficacy of Inhaled Nitric Oxide in the Treatment of Covid 19 Pneumonia : Impact on Viral Load and Clinical Outcomes [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 May 5]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.15.21255300
483. Winchester S, John S, Jabbar K, John I. Clinical Efficacy of Nitric Oxide Nasal Spray (NONS) for the Treatment of Mild COVID-19 Infection. Journal of Infection. 2021 May;S0163445321002516.
484. Strickland B, Albala L, Coffey EC, Carroll RW, Zapol WM, Ichinose F, et al. Safety and practicality of high dose inhaled nitric oxide in emergency department COVID-19 patients. The American Journal of Emergency Medicine. 2022 Aug;58:5–8.
485. Tandon M, Wu W, Moore K, Winchester S, Tu YP, Miller C, et al. SARS-CoV-2 accelerated clearance using a novel nitric oxide nasal spray (NONS) treatment: A randomized trial. The Lancet Regional Health - Southeast Asia. 2022 Jun;100036.
486. Mobarak S, Salasi M, Hormati A, Khodadadi J, Ziaee M, Abedi F, et al. Evaluation of the Effect of Sofosbuvir and Daclatasvir in Hospitalised COVID-19 Patients: A Randomized Double-Blind Clinical Trial (DISCOVER). SSRN Journal

[Internet]. 2021 [cited 2021 Mar 24]; Available from: https://www.ssrn.com/abstract=3792895

487. Eilidh B, Barlow-Pay F, Short R, Vilches-Moraga A, Price A, McGovern A, et al. Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalised patients with COVID-19. J Clin Med 2020;9(8):2586. Available from: https://doi.org/10.3390/jcm9082586.

488. Jeong HE, Lee H, Shin HJ, Choe YJ, Filion KB, Shin J-Y. Association between NSAIDs use and adverse clinical outcomes among adults hospitalised with COVID-19 in South Korea: a nationwide study [Preprint] MedRxiv 2020. Available from: https://doi.org/10.1101/2020.06.01.20119768.

489. Lund LC, Kristensen KB, Reilev M, Christensen S, Thomsen RW, Christiansen CF, et al. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: a Danish nationwide cohort study. PLOS Med 2020;17(9):e1003308. Available from: https://doi.org/10.1371/journal.pmed.1003308.

490. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. Clin Microbiol Infect 2020;26(9):1259.e5-1259.e7. Available from: https://doi.org/10.1016/j.cmi.2020.06.003.

491. Wong AYS, MacKenna B, Morton C, Schultze A, Walker AJ, Bhaskaran K, et al. OpenSAFELY: do adults prescribed non-steroidal anti-inflammatory drugs have an increased risk of death from COVID-19? [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.08.12.20171405.

492. Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020;288(4):469–76. Available from: https://doi.org/10.1111/joim.13119.

493. Esba LCA, Alqahtani RA, Thomas A, Shamas N, Alswaidan L, Mardawi G. Ibuprofen and NSAIDs use in COVID-19 infected patients is not associated with worse outcomes [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-85148/v1.

494. Alfredo CA, Noemí CR, Samuel RL, Daniel OC, Rodrigo RB, Paul MT, et al. Effect of Norelgestromin and Ethinylestradiol in Transdermal Patches on the Clinical

Outcomes and Biochemical Parameters of COVID-19 Patients: A Clinical Trial Pilot Study. Pharmaceuticals. 2022 Jun 17;15(6):757.

495. Leal F, Garcia A, Abarca L del C, Gonzalez D, Cruz G, Montell M, et al. Effect of a Nutritional Support System to Increase Survival and Reduce Mortality in Patients with COVID-19 in Stage III and Comorbidities: A Blinded Randomized Controlled Clinical Trial. SSRN Journal [Internet]. 2021 [cited 2021 Nov 4]; Available from: https://www.ssrn.com/abstract=3949424

496. Mohsen Sedighiyan, Hamed Abdollahi, Elmira Karimi, Mostafa Badeli, Reza Erfanian, Shima Raeesi, et al. Omega-3 polyunsaturated fatty acids supplementation improve clinical symptoms in patients with covid-19: A randomized clinical trial. Authorea [Internet]. 2021.

497. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. J Transl Med. 2021 Dec;19(1):128.

498. Arnardottir H, Pawelzik S-C, Sarajlic P, Quaranta A, Kolmert J, Religa D, et al. Immunomodulation by intravenous omega-3 fatty acid treatment in older subjects hospitalized for COVID-19: a single-blind randomized controlled trial [Internet]. Respiratory Medicine; 2021 Dec [cited 2022 Jan 10]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.27.21268264

499. Gusdon AM, Faraday N, Aita JS, Kumar S, Mehta I, Choi HA, et al. Dendrimer nanotherapy for severe COVID-19 attenuates inflammation and neurological injury markers and improves outcomes in a phase2a clinical trial. Sci Transl Med. 2022 Jul 20;14(654):eabo2652.

500. Winthrop KL, Skolnick AW, Rafiq AM, Beegle SH, Suszanski J, Koehne G, et al. Opaganib in Coronavirus Disease 2019 Pneumonia: Results of a Randomized, Placebo-Controlled Phase 2a Trial. Open Forum Infectious Diseases. 2022 Jul 4;9(7):ofac232.

501. Fernando Carvalho Neuenschwander, Ofra Barnett-Griness, Stefania Piconi, Yasmin Maor, Eduardo Sprinz, Nimer Assy, et al. Effect of Opaganib on Supplemental Oxygen and Mortality in Patients with Severe SARS-CoV-2 Pneumonia. medRxiv [Internet]. 2022; Available from:

http://www.epistemonikos.org/documents/f770cb51808746db8a984f4669b7473f0b8d70e3

502. Patel J, Beishuizen A, Ruiz XB, Boughanmi H, Cahn A, Criner GJ, et al. A Randomized Trial of Otilimab in Severe COVID-19 Pneumonia (OSCAR) [Internet]. Intensive Care and Critical Care Medicine; 2021 Apr [cited 2021 Apr 28]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.14.21255475

503. Araimo F, Imperiale C, Tordiglione P, Ceccarelli G, Borrazzo C, Alessandri F, et al. Ozone as adjuvant support in the treatment of COVID-19: a preliminary report of probiozovid trial [Preprint] J Med Virol 2020: jmv.26636. Available from: https://doi.org/10.1002/jmv.26636.

504. Shah M, Captain J, Vaidya V, Kulkarni A, Valsangkar K, Nair PMK, et al. Safety and efficacy of ozone therapy in mild to moderate COVID-19 patients: A phase 1/11 randomized control trial (SEOT study). International Immunopharmacology. 2021 Feb;91:107301.

505. Berger JS, Kornblith LZ, Gong MN, Reynolds HR, Cushman M, Cheng Y, et al. Effect of P2Y12 Inhibitors on Survival Free of Organ Support Among Non–Critically Ill Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2022 Jan 18;327(3):227.

506. Pandit A, Bhalani N, Bhushan BLS, Koradia P, Gargiya S, Bhomia V, et al. Efficacy and Safety of Pegylated Interferon alfa-2b in Moderate COVID-19: A phase II, randomized, controlled, open-label study. International Journal of Infectious Diseases. 2021 Mar;S1201971221002320.

507. Bushan S, Wanve S, Koradia P, Bhomia V, Soni P, Chakraborty S, et al. Efficacy and Safety of Pegylated Interferon-α2b in Moderate COVID-19: A phase 3, randomized, comparator-controlled, open-label study. International Journal of Infectious Diseases. 2021 Aug;S1201971221006779.

508. Feld JJ, Kandel C, Biondi MJ, Kozak RA, Zahoor MA, Lemieux C, et al. Peginterferon-lambda for the treatment of COVID-19 in outpatients [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.11.09.20228098.

509. Jagannathan P, Andrews J, Bonilla H, Hedlin H, Jacobson K, Balasubramanian V, et al. Peginterferon lambda-1a for treatment of outpatients with uncomplicated COVID-

19: a randomized placebo-controlled trial [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.11.18.20234161.

510. Sánchez-Conde M, Vizcarra P, Pérez-García JM, Gion M, Martialay MP, Taboada J, et al. Pembrolizumab in combination with tocilizumab in high-risk hospitalized COVID-19 patients (COPERNICO): A randomized proof-of-concept phase II study [Internet]. In Review; 2022 Feb [cited 2022 Mar 10]. Available from: https://www.researchsquare.com/article/rs-1386212/v1

511. Maldonado V, Hernandez-Ramírez C, Oliva-Pérez EA, Sánchez-Martínez CO, Pimentel-González JF, Molina-Sánchez JR, Jiménez-Villalba YZ, Chávez-Alderete J, and Loza-Mejía MA. Pentoxifylline Decreases Serum LDH Levels and Increases Lymphocyte Count in COVID-19 Patients: Results from an External Pilot Study. International Immunopharmacology 2020. 90 (January): 107209. https://doi.org/10.1016/j.intimp.2020.107209.

512. Azizi H, Rouhani N, Shaki F, Karimpour-razkenari E, Ghazaeian M, Salehifar E, et al. Pentoxifylline effects on hospitalized patients with COVID19: A randomized, double-blind clinical trial. International Immunopharmacology. 2021 Oct;108227.

513. Varona JF, Landete P, Lopez-Martin JA, Estrada V, Paredes R, Guisado-Vasco P, et al. Preclinical and randomized phase I studies of plitidepsin in adults hospitalized with COVID-19. Life Sci Alliance. 2022 Apr;5(4):e202101200.

514. Lattmann E, Bhalerao P, ShashiBhushan B, Nargundkar N, Lattmann P, Pillai KS, et al. Randomized, Comparative, Clinical Trial to Evaluate Efficacy and Safety of PNB001 in Moderate COVID-19 Patients [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 May 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.16.21255256

515. Méndez-Flores S, Priego-Ranero Á, Azamar-Llamas D, Olvera-Prado H, Rivas-Redondo KI, Ochoa-Hein E, et al. Effect of polymerized type I collagen in hyperinflammation of adult outpatients with symptomatic COVID-19: a double blind, randomised, placebo-controlled clinical trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 May [cited 2021 May 21]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.12.21257133

516. Kotfis K, Karolak I, Lechowicz K, Zegan-Barańska M, Pikulska A, Niedźwiedzka-Rystwej P, et al. Mineralocorticoid Receptor Antagonist (Potassium

Canrenoate) Does Not Influence Outcome in the Treatment of COVID-19-Associated Pneumonia and Fibrosis—A Randomized Placebo Controlled Clinical Trial. Pharmaceuticals. 2022 Feb 5;15(2):200.

517. Wang Q, Lin X, Xiang X, Liu W, Fang Y, Chen H, et al. Oropharyngeal Probiotic ENT-K12 Prevents Respiratory Tract Infections Among Frontline Medical Staff Fighting Against COVID-19: A Pilot Study. Front Bioeng Biotechnol. 2021 Jun 24;9:646184.

518. Ivashkin V, Fomin V, Moiseev S, Brovko M, Maslennikov R, Ulyanin A, et al. Efficacy of a Probiotic Consisting of Lacticaseibacillus rhamnosus PDV 1705, Bifidobacterium bifidum PDV 0903, Bifidobacterium longum subsp. infantis PDV 1911, and Bifidobacterium longum subsp. longum PDV 2301 in the Treatment of Hospitalized Patients with COVID-19: a Randomized Controlled Trial. Probiotics & Antimicro Prot [Internet]. 2021 Oct 13 [cited 2021 Oct 20]; Available from: https://link.springer.com/10.1007/s12602-021-09858-5

519. Wischmeyer PE, Tang H, Ren Y, Bohannon L, Ramirez ZE, Andermann TM, et al. Daily Lactobacillus Probiotic versus Placebo in COVID-19-Exposed Household Contacts (PROTECT-EHC): A Randomized Clinical Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jan [cited 2022 Jan 11]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.01.04.21268275

520. Gutiérrez-Castrellón P, Gandara-Martí T, Abreu Y Abreu AT, Nieto-Rufino CD, López-Orduña E, Jiménez-Escobar I, et al. Probiotic improves symptomatic and viral clearance in Covid19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial. Gut Microbes. 2022 Dec 31;14(1):2018899.

521. Saviano A, Potenza A, Siciliano V, Petruzziello C, Tarli C, Migneco A, et al. COVID-19 Pneumonia and Gut Inflammation: The Role of a Mix of Three Probiotic Strains in Reducing Inflammatory Markers and Need for Oxygen Support. JCM. 2022 Jun 28;11(13):3758.

522. Ghandehari S, Matusov Y, Pepkowitz S, Stein D, Kaderi T, Narayanan D, et al. Progesterone in addition to standard of care versus standard of care alone in the treatment of men admitted to the hospital with moderate to severe COVID-19: a randomised control phase 1 trial [Preprint]. 2020. Available from SSRN: https://doi.org/10.2139/ssrn.3709835.

523. Sigamani A, Shetty Madhavi S, Sudhishma RM, Chugani A, Chen-Walden H, Kutty T, and Platt D. Galectin Antagonist Use in Mild Cases of SARS-CoV-2 Cases; Pilot Feasibility Randomised, Open Label, Controlled Trial. [Preprint] 2020. https://doi.org/10.1101/2020.12.03.20238840.

524. Marcelo Augusto Duarte Silveira, David De Jong, Erica Batista dos Santos Galvao, Juliana Caldas Ribeiro, Thiago Cerqueira Silva, Andresa Aparecida Berretta, et al. Efficacy of propolis as an adjunct treatment for hospitalized COVID-19 patients: a randomized, controlled clinical trial. medRxiv [Internet]. 2021.

525. Johansson PI, Søe-Jensen P, Bestle MH, Clausen NE, Kristiansen KT, Lange T, et al. Prostacyclin in Mechanically Ventilated Patients with COVID-19 and Severe Endotheliopathy: A Multicenter, Randomized, Clinical Trial. Am J Respir Crit Care Med. 2021 Nov 23

526. Haeberle HA, Calov S, Martus P, Higuita LMS, Koeppen M, Goll A, et al. Inhaled Prostacyclin Improves Oxygenation in Patients with COVID-19-induced Acute Respiratory Distress Syndrome – a randomized controlled multicenter trial [Internet]. In Review; 2022 May [cited 2022 May 31]. Available from: https://www.researchsquare.com/article/rs-1652838/v1

527. Cadegiani F, McCoy J, Wambier C, Kovacevic M, Shapiro J, Sinclair R, et al. Proxalutamide (GT0918) Reduces the Rate of Hospitalization and Death in COVID-19 Male Patients: A Randomized Double-Blinded Placebo-Controlled Trial. ResearchSquare [Internet]. 2020.

528. Cadegiani FA, McCoy J, Gustavo Wambier C, Vaño-Galván S, Shapiro J, Tosti A, et al. Proxalutamide Significantly Accelerates Viral Clearance and Reduces Time to Clinical Remission in Patients with Mild to Moderate COVID-19: Results from a Randomized, Double-Blinded, Placebo-Controlled Trial. Cureus [Internet]. 2021 Feb 22 [cited 2021 Mar 4]

529. Cadegiani FA, Zimerman RA, Fonseca DN, Correia MN, Muller MP, Bet DL, et al. Final Results of a Randomized, Placebo-Controlled, Two-Arm, Parallel Clinical Trial of Proxalutamide for Hospitalized COVID-19 Patients: A Multiregional, Joint Analysis of the Proxa-Rescue AndroCoV Trial. Cureus [Internet]. 2021 Dec 25 [cited 2022 Jan 12]; Available from: https://www.cureus.com/articles/80171-final-results-of-a-randomized-placebo-controlled-two-arm-parallel-clinical-trial-of-proxalutamide-for-

[hospitalized-covid-19-patients-a-multiregional-joint-analysis-of-the-proxa-rescue-androcov-trial]()
530. Cadegiani FA, Zimerman RA, do Nascimento Fonseca D, do Nascimento Correia M, McCoy J, Wambier CG, et al. Proxalutamide (GT0918) Reduces the Rate of Hospitalization in mild-to-moderate COVID-19 Female Patients: A Randomized Double-Blinded Placebo-Controlled Two-Arm Parallel Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Jul 29]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.06.21260086
531. Fragoso-Saavedra S, Núñez I, Audelo-Cruz BM, Arias-Martínez S, Manzur-Sandoval D, Quintero-Villegas A, et al. Pyridostigmine in adults with severe SARS-CoV-2 infection: the PISCO trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 May 4]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.28.21255834
532. Önal H, Arslan B, Üçüncü Ergun N, Topuz Ş, Yilmaz Semerci S, Kurnaz ME, et al. Treatment of COVID-19 patients with quercetin: a prospective, single center, randomized, controlled trial. Turk J Biol. 2021;45(4):518–29.
533. Di Pierro F, Iqtadar S, Khan A, Ullah Mumtaz S, Masud Chaudhry M, Bertuccioli A, et al. Potential Clinical Benefits of Quercetin in the Early Stage of COVID-19: Results of a Second, Pilot, Randomized, Controlled and Open-Label Clinical Trial. Int J Gen Med. 2021;14:2807–16.
534. Shohan M, Nashibi R, Mahmoudian-Sani M-R, Abolnezhadian F, Ghafourian M, Alavi SM, et al. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: A randomized controlled trial. European Journal of Pharmacology. 2022 Jan;914:174615.
535. Rondanelli M, Perna S, Gasparri C, Petrangolini G, Allegrini P, Cavioni A, et al. Promising Effects of 3-Month Period of Quercetin Phytosome® Supplementation in the Prevention of Symptomatic COVID-19 Disease in Healthcare Workers: A Pilot Study. Life. 2022 Jan 4;12(1):66.
536. Nicastri E, Marinangeli F, Pivetta E, Torri E, Reggiani F, Fiorentino G, et al. A phase 2 randomized, double-blinded, placebo-controlled, multicenter trial evaluating the efficacy and safety of raloxifene for patients with mild to moderate COVID-19. eClinicalMedicine. 2022 Jun;48:101450.

537. Amat-Santos IJ, Santos-Martinez S, López-Otero D, Nombela-Franco L, Gutiérrez-Ibanes E, Del Valle R, et al. Ramipril in high risk patients with COVID-19. J Am Coll Cardiol 2020;76(3):268–76. Available from: https://doi.org/10.1016/j.jacc.2020.05.040.

538. Stasko N, Cockrell AS, Kocher JF, Henson I, Emerson D, Wang Y, et al. A randomized, controlled, feasibility study of RD-X19 in subjects with mild-to-moderate COVID-19 in the outpatient setting. Clin Transl Sci. 2022 Feb 8;

539. Li C, Luo F, Liu C, Xiong N, Xu Z, Zhang W, et al. Effect of a genetically engineered interferon-alpha versus traditional interferon-alpha in the treatment of moderate-to-severe COVID-19: a randomised clinical trial. Annals of Medicine. 2021 Jan 1;53(1):391–401.

540. Streinu-Cercel A, Săndulescu O, Preotescu L-L, Kim JY, Kim Y-S, Cheon S, et al. Efficacy and Safety of Regdanvimab (CT-P59): A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial in Outpatients With Mild-to-Moderate Coronavirus Disease 2019. Open Forum Infectious Diseases. 2022 Apr 1;9(4):ofac053.

541. Kim JY, Jang YR, Hong JH, Jung JG, Park J-H, Streinu-Cercel A, et al. Safety, Virologic Efficacy, and Pharmacokinetics of CT-P59, a Neutralizing Monoclonal Antibody Against SARS-CoV-2 Spike Receptor-Binding Protein: Two Randomized, Placebo-Controlled, Phase I Studies in Healthy Individuals and Patients With Mild SARS-CoV-2 Infection. Clinical Therapeutics. 2021 Aug;S0149291821003088.

542. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2020 Dec 17;NEJMoa2035002.

543. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2022 Feb;399(10325):665–76.

544. O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan K-C, et al. Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA [Internet]. 2022 Jan 14 [cited 2022 Jan 18]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2788256

545. Herman GA, O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, et al. Efficacy and safety of a single dose of casirivimab and imdevimab for the prevention of COVID-19 over an 8-month period: a randomised, double-blind, placebo-controlled trial. The Lancet Infectious Diseases. 2022 Jul;S1473309922004169.

546. Somersan-Karakaya S, Mylonakis E, Menon VP, Wells JC, Ali S, Sivapalasingam S, et al. Casirivimab and Imdevimab for the Treatment of Hospitalized Patients With COVID-19. The Journal of Infectious Diseases. 2022 Jul 27;jiac320.

547. Portal-Celhay C, Forleo-Neto E, Eagan W, Musser BJ, Davis JD, Turner KC, et al. Phase 2 dose-ranging study of the virologic efficacy and safety of the combination COVID-19 antibodies casirivimab and imdevimab in the outpatient setting [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Nov [cited 2021 Dec 13]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.11.09.21265912

548. Isa F, Forleo-Neto E, Meyer J, Zheng W, Rasmussen S, Armas D, et al. Repeat Subcutaneous Administration of REGEN-COV ® in Adults is Well-Tolerated and Prevents the Occurrence of COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Nov [cited 2021 Dec 1]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.11.10.21265889

549. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients [Internet]. Infectious Diseases (except HIV/AIDS); 2021 May [cited 2021 May 24]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.19.21257469

550. Huang DT, McCreary EK, Bariola JR, Minnier TE, Wadas RJ, Shovel JA, et al. Effectiveness of casirivimab and imdevimab, and sotrovimab during Delta variant surge: a prospective cohort study and comparative effectiveness randomized trial [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Dec [cited 2022 Jan 10]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.12.23.21268244

551. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 — final report. N Engl J Med 2020;383:1813-26. Available from: https://doi.org/10.1056/NEJMoa2007764.

552. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med 2020;383:1827-37. Available from: https://doi.org/10.1056/NEJMoa2015301.

553. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569–78. Available from: https://doi.org/10.1016/S0140-6736(20)31022-9.

554. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Viladomiu AS, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020;324(11):1048-57. Available from: https://doi.org/10.1001/jama.2020.16349.

555. Mahajan L, Singh A, Gifty. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. Indian J Anaesth. 2021;65(13):41.

556. Abd-Elsalam S, Ahmed OA, Mansour NO, Abdelaziz DH, Salama M, Fouad MHA, et al. Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial. The American Journal of Tropical Medicine and Hygiene [Internet]. 2021 Sep 10 [cited 2021 Oct 19]; Available from: https://www.ajtmh.org/view/journals/tpmd/aop/article-10.4269-ajtmh.21-0606/article-10.4269-ajtmh.21-0606.xml

557. Sarhan RM, Harb HS, Abou Warda AE, Salem-Bekhit MM, Shakeel F, Alzahrani SA, et al. Efficacy of the early treatment with tocilizumab-hydroxychloroquine and tocilizumab-remdesivir in severe COVID-19 Patients. Journal of Infection and Public Health. 2021 Nov;S1876034121003452.

558. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2021 Dec 22;NEJMoa2116846.

559. Ali K, Azher T, Baqi M, Binnie A, Borgia S, Carrier FM, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. CMAJ. 2022 Jan 19;cmaj.211698.

560. Landoni G, Piemonti L, Monforte A d'Arminio, Grossi P, Zangrillo A, Bucci E, et al. A Multicenter Phase 2 Randomized Controlled Study on the Efficacy and Safety of Reparixin in the Treatment of Hospitalized Patients with COVID-19 Pneumonia. Infect Dis Ther [Internet]. 2022 May 26 [cited 2022 Jun 6]; Available from: https://link.springer.com/10.1007/s40121-022-00644-6

561. McCreary MR, Schnell PM, Rhoda DA. Randomized double-blind placebo-controlled proof-of-concept trial of resveratrol for outpatient treatment of mild coronavirus disease (COVID-19). Sci Rep. 2022 Dec;12(1):10978.

562. Kaplan HG, Wang K, Reeves KM, Scanlan JM, Nunn CC, Kieper DA, et al. Resveratrol and Zinc in the Treatment of Outpatients With COVID-19 – The Reszinate Study - A Phase 1/2 Randomized Clinical Trial Utilizing Home Patient-Obtained Nasal and Saliva Viral Sampling. SSRN Journal [Internet]. 2021 [cited 2021 Oct 13]; Available from: https://www.ssrn.com/abstract=3934228

563. Cheng L-l, Guan W-j, Duan C-y, Zhang N-f, Lei C-l, Hu Y, et al. Effect of recombinant human granulocyte colony–stimulating factor for patients with coronavirus disease 2019 (COVID-19) and lymphopenia: a randomized clinical trial. JAMA Intern Med 2020; published online 10 September 2020. Available from: https://doi.org/10.1001/jamainternmed.2020.5503.

564. Bosteels C, Damme KV, De Leeuw E, Declercq J, Maes B, Bosteels V, et al. Early treatment with inhaled GM-CSF improves oxygenation and anti-viral immunity in COVID-19 induced lung injury – a randomized clinical trial [Internet]. In Review; 2021 Oct [cited 2021 Oct 21]. Available from: https://www.researchsquare.com/article/rs-959220/v1

565. DiNubile MJ, Parra S, Salomó AC, Levinson SL. Adjunctive Recombinant Human Plasma Gelsolin for Severe Coronavirus Disease 2019 Pneumonia. Open Forum Infectious Diseases. 2022 Aug 2;9(8):ofac357.

566. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395(10238):1695–1704. Available from: https://doi.org/10.1016/S0140-6736(20)31042-4.

567. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol 2020;146(1):137-46.E3. Available from: https://doi.org/10.1016/j.jaci.2020.05.019.

568. Han MK, Antila M, Ficker JH, Gordeev I, Guerreros A, Bernus AL, et al. Ruxolitinib in addition to standard of care for the treatment of patients admitted to

hospital with COVID-19 (RUXCOVID): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Rheumatology. 2022 Mar;S2665991322000443.

569. Barnette KG, Gordon MS, Rodriguez D, Bird TG, Skolnick A, Schnaus M, et al. Oral Sabizabulin for High-Risk, Hospitalized Adults with Covid-19: Interim Analysis. NEJM Evidence [Internet]. 2022 Jul 6 [cited 2022 Jul 13]; Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2200145

570. The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Feb 25;NEJMoa2100433.

571. Lescure F-X, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Respiratory Medicine. 2021 Mar;S2213260021000990.

572. Sivapalasingam S, Lederer DJ, Bhore R, Hajizadeh N, Criner G, Hossain R, et al. A Randomized Placebo-Controlled Trial of Sarilumab in Hospitalized Patients with Covid-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 May [cited 2021 May 20]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.13.21256973

573. Mariette X, Hermine O, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, et al. Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial. The Lancet Rheumatology. 2022 Jan;4(1):e24–32.

574. Hermine O, Mariette X, Porcher R, Resche-Rigon M, Tharaux P-L, Ravaud P. Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: two Randomised Controlled Trials of the CORIMUNO-19 Collaborative Group. Eur Respir J. 2022 Feb 3;2102523.

575. García-Vicuña R, Rodriguez-García SC, Abad-Santos F, Bautista Hernández A, García-Fraile L, Barrios Blandino A, et al. Subcutaneous IL-6 Inhibitor Sarilumab vs. Standard Care in Hospitalized Patients With Moderate-To-Severe COVID-19: An Open Label Randomized Clinical Trial. Front Med. 2022 Feb 23;9:819621.

576. Merchante N, Cárcel S, Garrido-Gracia JC, Trigo-Rodríguez M, Esteban Moreno MÁ, León-López R, et al. Early Use of Sarilumab in Patients Hospitalised with COVID-19 Pneumonia and Features of Systemic Inflammation. Antimicrob Agents Chemother. 2021 Dec 13;AAC.02107-21.

577. Sancho-López A, Caballero-Bermejo AF, Ruiz-Antorán B, Múñez Rubio E, García Gasalla M, Buades J, et al. Efficacy and Safety of Sarilumab in patients with COVID19 Pneumonia: A Randomized, Phase III Clinical Trial (SARTRE Study). Infect Dis Ther [Internet]. 2021 Oct 17 [cited 2021 Nov 2]; Available from: https://link.springer.com/10.1007/s40121-021-00543-2

578. Branch-Elliman W, Ferguson R, Doros G, Woods P, Leatherman S, Strymish J, et al. Subcutaneous sarilumab for the treatment of hospitalized patients with moderate to severe COVID19 disease: A pragmatic, embedded randomized clinical trial. De Socio GV, editor. PLoS ONE. 2022 Feb 25;17(2):e0263591.

579. Resende GG, da Cruz Lage R, Lobê SQ, Medeiros AF, Costa e Silva AD, Nogueira Sá AT, et al. Blockade of Interleukin Seventeen (IL-17A) with Secukinumab in Hospitalized COVID-19 patients – the BISHOP study [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Jul [cited 2021 Aug 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.21.21260963

580. Granfeldt A, Andersen LW, Vallentin MF, Hilberg O, Hasselstrøm JB, Sørensen LK, et al. Senicapoc treatment in COVID -19 Patients with Severe Respiratory Insufficiency – A Randomized, OPEN-LABEL , Phase II Trial. Acta Anaesthesiol Scand. 2022 Apr 11;aas.14072.

581. Panatto D, Orsi A, Bruzzone B, Ricucci V, Fedele G, Reiner G, et al. Efficacy of the Sentinox Spray in Reducing Viral Load in Mild COVID-19 and Its Virucidal Activity against Other Respiratory Viruses: Results of a Randomized Controlled Trial and an In Vitro Study. Viruses. 2022 May 12;14(5):1033.

582. Tian F, Wang J, Xi X, He M, Zhao C, Feng F, et al. Efficacy and safety of short-wave diathermy treatment for moderate COVID-19 patients: a prospective, double-blind, randomized controlled clinical study. European journal of physical and rehabilitation medicine [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/356ba654e07f6231b50fd2a20e44ae587685ad91

583. Santamarina MG, Beddings I, Lomakin FM, Boisier Riscal D, Gutiérrez Claveria M, Vidal Marambio J, et al. Sildenafil for treating patients with COVID-19 and perfusion mismatch: a pilot randomized trial. Crit Care. 2022 Dec;26(1):1.

584. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Domingo P, Mur I, Mateo GM, Gutierrez M del M, Pomar V, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA [Internet]. 2021 Jul 6 [cited 2021 Jul 13]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2781880

585. Aryan H, Farahani RH, Chamanara M, Elyasi S, Jaafari MR, Haddad M, et al. Evaluation of the efficacy of oral nano-silymarin formulation in hospitalized patients with COVID-19: A double-blind placebo-controlled clinical trial. Phytotherapy Research. 2022 Jul 20;ptr.7537.

586. Asadipooya K, Abbasi F, Adatorwovor R, Davarpanah MA, Mansoori Y, Hajiani M, et al. A Randomized Single Blind Controlled Trial of Combination Therapy (Spironolactone and Sitagliptin) in Hospitalized Adult Patients with Covid-19. SSRN Journal [Internet]. 2021 [cited 2021 Aug 3]; Available from: https://www.ssrn.com/abstract=3889411

587. Sadeghi A, Asgari AA, Norouzi A, Kheiri Z, Anushirvani A, Montazeri M, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. J Antimicrob Chemother 2020;75(11):3379-85. Available from: https://doi.org/10.1093/jac/dkaa334.

588. Yakoot M, Eysa B, Gouda E, Hill A, Helmy SA, Elsayed MR, et al. Efficacy and safety of sofosbuvir/daclatasvir in the treatment of COVID-19: a randomized, controlled study [Preprint]. 2020. Available from SSRN: https://doi.org/10.2139/ssrn.3705289.

589. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, et al. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. Journal of Antimicrobial Chemotherapy. 2020 Dec 18;dkaa501.

590. Mobarak S, Salasi M, Hormati A, Khodadadi J, Ziaee M, Abedi F, et al. Evaluation of the Effect of Sofosbuvir and Daclatasvir in Hospitalised COVID-19 Patients: A Randomized Double-Blind Clinical Trial (DISCOVER). SSRN Journal [Internet]. 2021 [cited 2021 Mar 24]; Available from: https://www.ssrn.com/abstract=3792895

591. Alavi-moghaddam M, Haghighi M, Sabaghian T, Soroureddin Z, Chaboki BG. Safety and Efficacy of Sofosbuvir in Hospitalized Adult Patients with SARS-CoV-2: A Preliminary Report. SSRN Journal [Internet]. 2021 [cited 2021 Mar 24]; Available from: https://www.ssrn.com/abstract=3790463

592. Khalili H, Nourian A, Ahmadinejad Z, Emadi Kouchak H, Jafari S, Dehghan Manshadi SA, et al. Efficacy and safety of sofosbuvir/ ledipasvir in treatment of patients with COVID-19; A randomized clinical trial. Acta Biomed. 2020 Nov 10;91(4):e2020102.

593. Elgohary MA-S, Hasan EM, Ibrahim AA, Ahmed Abdelsalam MF, Abdel-Rahman RZ, Zaki AI, et al. Efficacy of Sofosbuvir plus Ledipasvir in Egyptian patients with COVID-19 compared to standard treatment: Randomized controlled trial [Internet]. Epidemiology; 2021 May [cited 2021 May 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.05.19.21257429

594. Sayad B, Khodarahmi R, Najafi F, Miladi R, Mohseni Afshar Z, Mansouri F, et al. Efficacy and safety of sofosbuvir/velpatasvir versus the standard of care in adults hospitalized with COVID-19: a single-centre, randomized controlled trial. Journal of Antimicrobial Chemotherapy. 2021 May 25;dkab152.

595. El-Bendary M, Abd-Elsalam S, Elbaz T, El-Akel W, Cordie A, Elhadidy T, et al. Efficacy of combined Sofosbuvir and Daclatasvir in the treatment of COVID-19 patients with pneumonia: a multicenter Egyptian study. Expert Review of Anti-infective Therapy. 2021 Jul 15;1–5.

596. Abbass S, Salama M, Salman T, Sabry A, Abdel-Razek W, Kamal E, et al. fficacy and safety of Sofosbuvir plus Daclatasvir or Ravidasvir in patients with COVID-19, A Randomized Controlled Trial. J Med Virol. 2021 Aug 11;jmv.27264.

597. Medhat MA, El-Kassas M, Karam-Allah H, Al Shafie A, Abd-Elsalam S, Moustafa E, et al. Sofosbuvir/ledipasvir in combination or nitazoxanide alone are safe and efficient treatments for COVID-19 infection: A randomized controlled trial for repurposing antivirals. Arab Journal of Gastroenterology. 2022 May;S1687197922000326.

598. Bozorgmehr R, Amiri F, Hosein Zadeh M, Ghorbani F, Khameneh Bagheri A, Yazdi E, et al. Effect of Sofosbuvir on Length of Hospital Stay in Moderate COVID-19 Cases; a Randomized Controlled Trial. Arch Acad Emerg Med. 2022;10(1):e46.

599. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Rodrigues Falci D, et al. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA [Internet]. 2022 Mar 14 [cited 2022 Mar 28]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2790246

600. Wadhwa B, Malhotra V, Kerai S, Husain F, Pandey NB, Saxena KN, et al. Phase 2 randomised placebo-controlled trial of spironolactone and dexamethasone versus dexamethasone in COVID-19 hospitalised patients in Delhi [Internet]. Respiratory Medicine; 2022 Jul [cited 2022 Jul 21]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.07.01.22277163

601. INSPIRATION-S Investigators. Atorvastatin versus placebo in patients with covid-19 in intensive care: randomized controlled trial. BMJ. 2022 Jan 7;376:e068407.

602. Ghafoori M, Saadati H, Taghavi M, Azimian A, Alesheikh P, Mohajerzadeh MS, et al. Survival of the hospitalized patients with COVID-19 receiving atorvastatin: A randomized clinical trial. J Med Virol. 2022 Mar 10;

603. Carmenate YV, Alkaabi FM, Aleman YMC, Valverde CAV, Ahmed YM, Sanna P, et al. Safety and Efficacy of Autologous Non-Hematopoietic Enriched Stem Cell Nebulization in Covid-19 Patients. A Randomized Clinical Trial, Abu Dhabi 2020. [Internet]. In Review; 2021 Jun [cited 2021 Jun 18]. Available from: https://www.researchsquare.com/article/rs-558653/v1

604. GLUCOCOVID investigators, Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: An open-label randomized trial (GLUCOCOVID). Wien Klin Wochenschr [Internet]. 2021 Feb 3 [cited 2021 Feb 11]; Available from: http://link.springer.com/10.1007/s00508-020-01805-8

605. Jeronimo CMP, Farias MEL, Almeida Val FF, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2020: ciaa1177. Available from: https://doi.org/10.1093/cid/ciaa1177.

606. Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report [Preprint] MedRxiv 2020. Available from: https://doi.org/10.1101/2020.06.22.20137273.

607. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic Corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020;324:1330-41. Available from: https://doi.org/10.1001/jama.2020.17023.

608. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020; 324(13):1307-16. Available from: https://doi.org/10.1001/jama.2020.17021.

609. The Writing Committee for the REMAP-CAP Investigators, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020; 324(13):1317-29. https://doi.org/10.1001/jama.2020.17022.

610. Dequin P-F, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. JAMA 2020;324(13):1298-1306. Available from: https://doi.org/10.1001/jama.2020.16761.

611. Farahani RH, Mosaed R, Nezami-Asl A, Chamanara N, Soleiman-Meigooni S, Kalantar S, et al. Evaluation of the efficacy of methylprednisolone pulse therapy in treatment of Covid-19 adult patients with severe respiratory failure: randomized, clinical trial [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-66909/v1.

612. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial [Preprint]. Eur Respir J 2020; published online 17 September 2020. Available from: https://doi.org/10.1183/13993003.02808-2020.

613. Tang X, Feng Y-M, Ni J-X, Zhang J-Y, Liu L-M, Hu K, et al. Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial. Respiration. 2021 Jan 22;1–11.

614. Jamaati H, Hashemian SM, Farzanegan B, Malekmohammad M, Tabarsi P, Marjani M, et al. No clinical benefit of high dose corticosteroid administration in patients with COVID-19: A preliminary report of a randomized clinical trial. European Journal of Pharmacology. 2021 Apr;897:173947.

615. Rashad A, Mousa S, Nafady-Hego H, Nafady A, Elgendy H. Short term survival of critically ill COVID-19 Egyptian patients on assisted ventilation treated by either Dexamethasone or Tocilizumab. Sci Rep. 2021 Dec;11(1):8816.

616. Les I, Loureiro-Amigo J, Capdevila F, Oriol I, Elejalde I, Aranda-Lobo J, et al. Methylprednisolone Pulses in Hospitalized COVID-19 Patients Without Respiratory Failure: A Randomized Controlled Trial. Front Med (Lausanne). 2022;9:807981.

617. Ranjbar K, Shahriarirad R, Erfani A, Khodamoradi Z, Saadi MHG, Mirahmadizadeh A, et al. Methylprednisolone or Dexamethasone, Which One Is the Superior Corticosteroid in the Treatment of Hospitalized&nbsp;COVID-19 Patients: A Triple-Blinded Randomized Controlled Trial [Internet]. In Review; 2021 Feb [cited 2021 Feb 14]. Available from: https://www.researchsquare.com/article/rs-148529/v1

618. Munch MW, Myatra SN, Tirupakuzhi Vijayaraghavan BK, Saseedharan S, Benfield T, Wahlin RR, et al. Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxia: an international, randomized, blinded trial [Internet]. Intensive Care and Critical Care Medicine; 2021 Jul [cited 2021 Jul 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.07.22.21260755

619. Maskin LP, Bonelli I, Olarte GL, Palizas F, Velo AE, Lurbet MF, et al. High- Versus Low-Dose Dexamethasone for the Treatment of COVID-19-related Acute Respiratory Distress Syndrome: A Multicenter and Randomized Open-label Clinical Trial [Internet]. Intensive Care and Critical Care Medicine; 2021 Sep [cited 2021 Sep 24]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.09.15.21263597

620. Toroghi N, Abbasian L, Nourian A, Davoudi-Monfared E, Khalili H, Hasannezhad M, et al. Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: a three-arm randomized clinical trial. Pharmacol Rep [Internet]. 2021 Nov 27 [cited 2021 Dec 1]; Available from: https://link.springer.com/10.1007/s43440-021-00341-0

621. Taboada M, Rodríguez N, Varela PM, Rodríguez MT, Abelleira R, González A, et al. Effect of high *versus* low dose of dexamethasone on clinical worsening in patients

hospitalised with moderate or severe COVID-19 Pneumonia: an open-label, randomised clinical trial. Eur Respir J. 2021 Dec 16;2102518.

622. Naik NB, Puri GD, Kajal K, Mahajan V, Bhalla A, Kataria S, et al. High-Dose Dexamethasone Versus Tocilizumab in Moderate to Severe COVID-19 Pneumonia: A Randomized Controlled Trial. Cureus [Internet]. 2021 Dec 11 [cited 2022 Jan 24]; Available from: https://www.cureus.com/articles/78251-high-dose-dexamethasone-versus-tocilizumab-in-moderate-to-severe-covid-19-pneumonia-a-randomized-controlled-trial

623. Salvarani C, Massari M, Costantini M, Franco Merlo D, Lucia Mariani G, Viale P, et al. Intravenous methylprednisolone pulses in hospitalised patients with severe COVID-19 pneumonia, A double-blind, randomised, placebo-controlled trial. Eur Respir J. 2022 Mar 31;2200025.

624. Bouadma L, Mekontso-Dessap A, Burdet C, Merdji H, Poissy J, Dupuis C, et al. High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. JAMA Intern Med. 2022 Jul 5;

625. Dastenae ZH, Bahadori A, Dehghani M, Asadi-Samani M, Izadi I, Shahraki HR. Comparison of the effect of intravenous dexamethasone and methylprednisolone on the treatment of hospitalized patients with COVID-19: A randomized clinical trial. International Journal of Infectious Diseases. 2022 Jul;S1201971222004131.

626. Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. The Lancet Respiratory Medicine. 2021 Apr;S2213260021001600.

627. Yu L-M, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet. 2021 Aug;S014067362101744X.

628. Song J-Y, Yoon J-G, Seo Y-B, Lee J, Eom J-S, Lee J-S, et al. Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial. JCM. 2021 Aug 12;10(16):3545.

629. Clemency BM, Varughese R, Gonzalez-Rojas Y, Morse CG, Phipatanakul W, Koster DJ, et al. A randomized controlled trial of inhaled ciclesonide for outpatient treatment of symptomatic COVID-19 infections [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Sep [cited 2021 Sep 13]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.09.07.21261811

630. Ezer N, Belga S, Daneman N, Chan A, Smith BM, Daniels S-A, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. BMJ. 2021 Nov 2;e068060.

631. Duvignaud A, Lhomme E, Onaisi R, Sitta R, Gelley A, Chastang J, et al. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). Clin Microbiol Infect. 2022 Mar 15;S1198-743X(22)00108-2.

632. Agustí A, De Stefano G, Levi A, Muñoz X, Romero-Mesones C, Sibila O, et al. Add-on inhaled budesonide in the treatment of hospitalised patients with COVID-19: a randomised clinical trial. Eur Respir J. 2022 Mar;59(3):2103036.

633. Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group, Naggie S. Inhaled Fluticasone for Outpatient Treatment of Covid-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jul [cited 2022 Jul 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.07.12.22277548

634. Gonzalez Ochoa AJ, Raffetto JD, Hernandez AG, Zavala NA, Gutierrez O, Vargas A, and Loustaunau J. Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomised Controlled Trial. MedRxiv 2020. https://doi.org/10.1101/2020.12.04.20242073.

635. Dow GS, Smith BL. A phase II, double blind, placebo-controlled, randomized evaluation of the safety and efficacy of tafenoquine in patients with mild-moderate COVID-19 disease. New Microbes and New Infections. 2022 Apr;47:100986.

636. Singh D, Bogus M, Moskalenko V, Lord R, Moran EJ, Crater GD, et al. A phase 2 study of the inhaled pan-JAK inhibitor TD-0903 in severe COVID-19: Part 1 [Internet]. Respiratory Medicine; 2021 Mar [cited 2021 Mar 24]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.09.21252944

637. Parienti J-J, Prazuck T, Peyro-Saint-Paul L, Fournier A, Valentin C, Brucato S, et al. Effect of Tenofovir Disoproxil Fumarate and Emtricitabine on nasopharyngeal SARS-CoV-2 viral load burden amongst outpatients with COVID-19: A pilot, randomized, open-label phase 2 trial. EClinicalMedicine. 2021 Jun;100993.

638. Arruda EAG, Pires-Neto RJ, Medeiros MS, Quirino-Filho J, Clementino M, Gondim RNDG, et al. Clinical Trial of Efficacy and Toxicity of Disoproxil Tenofovir Fumarate and Emtricitabine for Mild to Moderate SARS-CoV-2 Infections [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Sep [cited 2021 Oct 12]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.09.28.21264242

639. Amra B, Ashrafi F, Soltaninejad F, Feizi A, Salmasi M. Thalidomide for the treatment of severe Covid-19: A randomized clinical trial [Internet]. In Review; 2021 Apr [cited 2021 Apr 8]. Available from: https://www.researchsquare.com/article/rs-379635/v1

640. Shirin Haghighi, Soodeh Ramezaninejad, Atousa Hakamifard, et al. The Effects of Thalidomide as an Adjuvant Treatment Besides of Dexamethasone and Remdesivir on Patients with Moderate COVID-19. Available online at: https://ssrn.com/abstract=3941711

641. Bencheqroun H, Ahmed Y, Kocak M, Villa E, Barrera C, Mohiuddin M, et al. A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of ThymoQuinone Formula (TQF) for Treating Outpatient SARS-CoV-2. Pathogens. 2022 May 7;11(5):551.

642. Barrett CD, Moore HB, Moore EE, Wang DJ, Hajizadeh N, Biffl WL, et al. STudy of Alteplase for Respiratory failure in SARS-Cov2 COVID-19 (STARS): A Vanguard Multicenter, Rapidly Adaptive, Pragmatic, Randomized, Controlled Trial. Chest. 2021 Sep;S0012369221040630.

643. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, et al. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19. N Engl J Med. 2022 Apr 20;NEJMoa2116620.

644. Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-

blind, placebo-controlled trial. The Lancet Respiratory Medicine. 2022 Jun;S2213260022001801.

645. Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. The Lancet Respiratory Medicine. 2022 Jul;S2213260022002156.

646. Rosas IO, Bräu N, Waters M, Go RC, Malhotra A, Hunter BD, et al. Tocilizumab in patients hospitalised with COVID-19 pneumonia: Efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA). eClinicalMedicine. 2022 May;47:101409.

647. Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. Tocilizumab ameliorates the hypoxia in COVID-19 moderate patients with bilateral pulmonary lesions: a randomized, controlled, open-label, multicenter trial [Preprint]. 2020. Available from SSRN: https://doi.org/10.2139/ssrn.3667681.

648. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial [Preprint]. JAMA Int Med 2020; published online 20 October 2020. Available from: https://doi.org/10.1001/jamainternmed.2020.6615.

649. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19 [Preprint]. N Engl J Med 2020; published online 21 October 2020. Available from: https://doi.org/10.1056/NEJMoa2028836.

650. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, and the CORIMUNO-19 Collaborative Group. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial [Preprint]. JAMA Int Med 2020; published online 20 October 2020. Available from: https://doi.org/10.1001/jamainternmed.2020.6820.

651. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2020 Dec 17;NEJMoa2030340.

652. Veiga VC, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021 Jan 20;n84.

653. Horby PW, Campbell M, Staplin M, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2021 May;397(10285):1637–45.

654. Rutgers A, Westerweel PE, van der Holt B, Postma S, van Vonderen MGA, Piersma DP, et al. Timely Administration of Tocilizumab Improves Survival of Hospitalized COVID-19 Patients. SSRN Journal [Internet]. 2021 [cited 2021 May 12]; Available from: https://www.ssrn.com/abstract=3834311

655. Talaschian M, Akhtari M, Mahmoudi M, Mostafaei S, Jafary M, Husseini AS, et al. Tocilizumab Failed to Reduce Mortality in Severe COVID-19 Patients: Results From a Randomized Controlled Clinical Trial [Internet]. In Review; 2021 May [cited 2021 May 14]. Available from: https://www.researchsquare.com/article/rs-463921/v1

656. Hamed DM, Belhoul KM, Al Maazmi NA, Ghayoor F, Moin M, Al Suwaidi M, et al. Intravenous methylprednisolone with or without tocilizumab in patients with severe COVID-19 pneumonia requiring oxygen support: A prospective comparison. Journal of Infection and Public Health. 2021 Aug;14(8):985–9.

657. Broman N, Feuth T, Vuorinen T, Valtonen M, Hohenthal U, Löyttyniemi E, et al. Early administration of tocilizumab in hospitalized COVID-19 patients with elevated inflammatory markers; COVIDSTORM – A prospective, randomized, single center, open label study. Clinical Microbiology and Infection. 2022 Mar;S1198743X22001045.

658. Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med [Internet]. 2021 Oct 5 [cited 2021 Oct 12]; Available from: https://link.springer.com/10.1007/s00134-021-06507-x

659. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. The Lancet Respiratory Medicine. 2021 May;9(5):511–21.

660. Hermine O, Mariette X, Porcher R, Djossou F, Nguyen Y, Arlet JB, et al. Tocilizumab plus dexamethasone versus dexamethasone in patients with moderate-to-severe COVID-19 pneumonia: A randomised clinical trial from the CORIMUNO-19 study group. eClinicalMedicine. 2022 Apr;46:101362.

661. Karampitsakos T, Papaioannou O, Tsiri P, Katsaras M, Katsimpris A, Kalogeropoulos AP, et al. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jun [cited 2022 Jul 6]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.06.13.22276211

662. Kumar PN, Hernández-Sánchez J, Nagel S, Feng Y, Cai F, Rabin J, et al. Safety and Efficacy of Tocilizumab 4 or 8 mg/kg in Hospitalized Patients With Moderate to Severe Coronavirus Disease 2019 Pneumonia: A Randomized Clinical Trial. Open Forum Infectious Diseases. 2022 Jan 1;9(1):ofab608.

663. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021 Jun 16;NEJMoa2101643.

664. Murugesan H, Cs G, Nasreen HS, Santhanam S, M G, Ravi S, et al. An Evaluation of Efficacy and Safety of Tofacitinib, A JAK Inhibitor in the Management of Hospitalized Patients with Mild to Moderate COVID-19 - An Open-Label Randomized Controlled Study. J Assoc Physicians India. 2022 Dec;69(12):11–2.

665. Saeedi-Boroujeni A, Nashibi R, Ghadiri AA, Nakajima M, Salmanzadeh S, Mahmoudian-Sani MR, et al. Tranilast as an Adjunctive Therapy in Hospitalized Patients with Severe COVID- 19: A Randomized Controlled Trial. Archives of Medical Research. 2022 Mar;S0188440922000248.

666. Wu X, Yu K, Wang Y, Xu W, Ma H, Hou Y, et al. Efficacy and safety of triazavirin therapy for coronavirus disease 2019: a pilot randomized controlled trial. Engineering 2020;6(10):1185-91. Available from: https://doi.org/10.1016/j.eng.2020.08.011.

667. Wagener G, Goldklang MP, Gerber A, Elisman K, Eiseman KA, Fonseca LD, et al. A randomized, placebo-controlled, double-blinded pilot study of angiotensin 1–7 (TXA-127) for the treatment of severe COVID-19. Crit Care. 2022 Dec;26(1):229.

668. Lau FH, Powell CE, Adonecchi G, Danos DM, DiNardo AR, Chugden RJ, et al. Pilot phase results of a prospective, randomized controlled trial of narrowband ultraviolet B phototherapy in hospitalized COVID -19 patients. Experimental Dermatology. 2022 Jun 13;exd.14617.

669. Nojomi M, Yasin Z, Keyvani H, Makiani MJ, Roham M, Laali A, et al. Effect of arbidol on COVID-19: a randomized controlled trial [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-78316/v1.

670. Yethindra V, Tagaev T, Uulu MS, Parihar Y. Efficacy of umifenovir in the treatment of mild and moderate COVID-19 patients. Int J Res Pharm Sci 2020;11(SPL1):506–09. Available from: https://doi.org/10.26452/ijrps.v11iSPL1.2839.

671. Ghaderkhani S, Khaneshan AS, Salami A, Alavijeh PE, Kouchak HE, Khalili H, et al. Efficacy and safety of arbidol in treatment of patients with COVID-19 infection: a randomized clinical trial [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-91430/v1.

672. Alavi Darazam I, Shokouhi S, Mardani M, Pourhoseingholi MA, Rabiei MM, Hatami F, et al. Umifenovir in hospitalized moderate to severe COVID-19 patients: A randomized clinical trial. International Immunopharmacology. 2021 Oct;99:107969.

673. Ramachandran R, Bhosale V, Reddy H, Atam V, Faridi M, Fatima J, et al. Phase III, Randomized, Double-Blind, Placebo Controlled Trial of Efficacy, Safety and Tolerability of Antiviral Drug Umifenovir vs Standard Care of Therapy in Non-Severe Covid-19 Patients. SSRN Journal [Internet]. 2021 [cited 2021 Sep 29]; Available from: https://www.ssrn.com/abstract=3919585

674. Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, et al. High-dose vitamin C infusion for the treatment of critically ill COVID-19 [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-52778/v1.

675. Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, et al. The Role of Vitamin C as Adjuvant Therapy in COVID-19. Cureus [Internet]. 2020 Nov 30 [cited 2021 Jan 11]; Available from: https://www.cureus.com/articles/45284-the-role-of-vitamin-c-as-adjuvant-therapy-in-covid-19

676. Jamali Moghadam Siahkali S, Zarezade B, Koolaji S, Alinaghi S, Zendehdel A, Tabarestani M, et al. Safety and Effectiveness of High-Dose Vitamin C in Patients with

COVID-19; A Randomized Controlled open-label Clinical Trial . ResearchSquare [Internet]. 2021.

677. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. JAMA Netw Open. 2021 Feb 12;4(2):e210369.

678. Tehrani S, Yadegarynia D, Abrishami A, Moradi H, Gharaei B, Rauofi M, et al. An investigation into the Effects of Intravenous Vitamin C on Pulmonary CT Findings and Clinical Outcomes of Patients with COVID 19 Pneumonia A Randomized Clinical Trial. Urology Journal. 2021 Nov 8;(Instant 2021):6863.

679. Beigmohammadi MT, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Soltani D. The effect of supplementation with vitamins A, B, C, D, and E on disease severity and inflammatory responses in patients with COVID-19: a randomized clinical trial. Trials. 2021 Dec;22(1):802.

680. Majidi N, Rabbani F, Gholami S, Gholamalizadeh M, BourBour F, Rastgoo S, et al. The Effect of Vitamin C on Pathological Parameters and Survival Duration of Critically Ill Coronavirus Disease 2019 Patients: A Randomized Clinical Trial. Front Immunol. 2021 Dec 15;12:717816.

681. Ried K, BinJemain T, Sali A. Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, and Vitamin D3 With or Without Intravenous Vitamin C: An International, Multicenter, Randomized Trial. Cureus [Internet]. 2021 Nov 25 [cited 2022 Jan 10]; Available from: https://www.cureus.com/articles/76496-therapies-to-prevent-progression-of-covid-19-including-hydroxychloroquine-azithromycin-zinc-and-vitamin-d3-with-or-without-intravenous-vitamin-c-an-international-multicenter-randomized-trial

682. Coppock D, Violet PC, Vasquez G, Belden K, Foster M, Mullin B, et al. Pharmacologic Ascorbic Acid as Early Therapy for Hospitalized Patients with COVID-19: A Randomized Clinical Trial. Life. 2022 Mar 19;12(3):453.

683. Castillo ME, Costa LME, Barrios JMV, Díaz JFA, Miranda JL, Bouillon R, Gomez JMQ. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study [Preprint]. J Steroid

Biochem Mol Biol 2020;203:105751. Available from: https://doi.org/10.1016/j.jsbmb.2020.105751.

684. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE Study) [Preprint]. Postgrad Med J 2020; published online 12 November 2020. Available from: https://doi.org/10.1136/postgradmedj-2020-139065.

685. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. JAMA. 2021 Feb 17

686. Lakkireddy M, Gadiga SG, Malathi RD, Karra ML, Raju ISSVPM, Ragini, et al. Impact of Pulse D Therapy on The Inflammatory Markers in Patients With COVID-19. [Internet]. In Review; 2021 Feb [cited 2021 Mar 8]. Available from: https://www.researchsquare.com/article/rs-152494/v1

687. Sabico S, Enani MA, Sheshah E, Aljohani NJ, Aldisi DA, Alotaibi NH, et al. Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with Mild to Moderate Covid-19: A Randomized Clinical Trial. Nutrients. 2021 Jun 24;13(7):2170.

688. Maghbooli Z, Sahraian MA, Jamalimoghadamsiahkali S, Asadi A, Zarei A, Zendehdel A, et al. Treatment With 25-Hydroxyvitamin D3 (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial. Endocrine Practice. 2021 Oct;S1530891X21012593.

689. Gaborit B, Dailly E, Vanhove B, Josien R, Lacombe K, Dubee V, et al. Pharmacokinetics and safety of XAV-19, a swine glyco-humanized polyclonal anti-SARS-CoV-2 antibody, for COVID-19-related moderate pneumonia: a randomized, double-blind, placebo-controlled, phase IIa study [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 Apr 28]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.15.21255549

690. Bishop CW, Ashfaq A, Melnick JZ, Vazquez-Escarpanter E, Fialkow JA, Strugnell SA, et al. Results From the REsCue Trial: A Randomized Controlled Trial with

Extended-Release Calcifediol in Symptomatic Outpatients with COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Feb [cited 2022 Feb 17]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.01.31.22270036

691. Karonova TL, Chernikova AT, Golovatyuk KA, Bykova ES, Grant WB, Kalinina OV, et al. Vitamin D Intake May Reduce SARS-CoV-2 Infection Morbidity in Health Care Workers. Nutrients. 2022 Jan 24;14(3):505.

692. Cannata-Andía JB, Díaz-Sottolano A, Fernández P, Palomo-Antequera C, Herrero-Puente P, Mouzo R, et al. A single-oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve outcomes in the COVID-19 disease: the COVID-VIT-D—a randomised multicentre international clinical trial. BMC Med. 2022 Dec;20(1):83.

693. Jolliffe DA, Holt H, Greenig M, Talaei M, Perdek N, Pfeffer P, et al. Vitamin D Supplements for Prevention of Covid-19 or other Acute Respiratory Infections: a Phase 3 Randomized Controlled Trial (CORONAVIT) [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Mar [cited 2022 Apr 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.03.22.22271707

694. Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, Zurita-Cruz JN, Barrada-Vázquez AS, González-Ibarra J, et al. Efficacy and Safety of Vitamin D Supplementation to Prevent COVID-19 in Frontline Healthcare Workers. A Randomized Clinical Trial. Archives of Medical Research. 2022 Jun;53(4):423–30.

695. Mariani J, Antonietti L, Tajer C, Ferder L, Inserra F, Sanchez Cunto M, et al. High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: Multicentre randomized controlled clinical trial. Putzu A, editor. PLoS ONE. 2022 May 27;17(5):e0267918.

696. Annweiler C, Beaudenon M, Gautier J, Gonsard J, Boucher S, Chapelet G, et al. High-dose versus standard-dose vitamin D supplementation in older adults with COVID-19 (COVIT-TRIAL): A multicenter, open-label, randomized controlled superiority trial. Cannegieter SC, editor. PLoS Med. 2022 May 31;19(5):e1003999.

697. Karonova TL, Golovatyuk KA, Kudryavtsev IV, Chernikova AT, Mikhaylova AA, Aquino AD, et al. Effect of Cholecalciferol Supplementation on the Clinical Features and Inflammatory Markers in Hospitalized COVID-19 Patients: A Randomized, Open-Label, Single-Center Study. Nutrients. 2022 Jun 23;14(13):2602.

698. Romero-Ibarguengoitia ME, Gutiérrez-González D, Cantú-López C, Sanz-Sánchez MA, González-Cantú A. Effect of Vitamin D $_3$ supplementation vs. dietary-hygienic measures on SARS-COV-2 infection rates in hospital workers with 25-hydroxyvitamin D3 [25(OH)D3] levels ≥20 ng/mL [Internet]. Infectious Diseases (except HIV/AIDS); 2022 Jul [cited 2022 Jul 22]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.07.12.22277450

699. Cervero M, López-Wolf D, Casado G, Novella-Mena M, Ryan-Murua P, Taboada-Martínez ML, et al. Beneficial Effect of Short-Term Supplementation of High Dose of Vitamin D3 in Hospitalized Patients With COVID-19: A Multicenter, Single-Blinded, Prospective Randomized Pilot Clinical Trial. Front Pharmacol. 2022 Jul 4;13:863587.

700. Abroug H, Maatouk A, Bennasrallah C, Dhouib W, Fredj MB, Zemni I, et al. Effect of vitamin D supplementation versus placebo on recovery delay among COVID-19 patients: A randomized-controlled clinical trial [Internet]. In Review; 2022 Jul [cited 2022 Jul 26]. Available from: https://www.researchsquare.com/article/rs-1276203/v1

701. De Niet S, Trémège M, Coffiner M, Rousseau AF, Calmes D, Frix AN, et al. Positive Effects of Vitamin D Supplementation in Patients Hospitalized for COVID-19: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients. 2022 Jul 26;14(15):3048.

702. Gaborit B, Dailly E, Vanhove B, Josien R, Lacombe K, Dubee V, et al. Pharmacokinetics and safety of XAV-19, a swine glyco-humanized polyclonal anti-SARS-CoV-2 antibody, for COVID-19-related moderate pneumonia: a randomized, double-blind, placebo-controlled, phase IIa study [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Apr [cited 2021 Apr 28]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.04.15.21255549

703. De Leeuw E, Van Damme KFA, Declercq J, Bosteels C, Maes B, Tavernier SJ, et al. Efficacy and safety of the investigational complement C5 inhibitor zilucoplan in patients hospitalized with COVID-19: an open-label randomized controlled trial. Respir Res. 2022 Aug 9;23(1):202.

704. Hassan M, Abdelmaksoud A, Ghweil A, Rashad A, Aref Z, Khodeary A, et al. Olfactory disturbances as presenting manifestation among Egyptian patients with

COVID-19: possible role of zinc [Preprint]. ResearchSquare 2020. Available from: https://doi.org/10.21203/rs.3.rs-107577/v1.

705. Abd-Elsalam S, Soliman S, Esmail ES, Khalaf M, Mostafa EF, Medhat MA, Ahmed OA, El Ghafar MSA, Alboraie M, and Hassany SM. Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: A Randomized, Multicenter Trial. Biological Trace Element Research 2020. https://doi.org/10.1007/s12011-020-02512-1.

706. Abdelmaksoud AA, Ghweil AA, Hassan MH, Rashad A, Khodeary A, Aref ZF, et al. Olfactory Disturbances as Presenting Manifestation Among Egyptian Patients with COVID-19: Possible Role of Zinc. Biol Trace Elem Res [Internet]. 2021 Jan 7 [cited 2021 Jan 11]; Available from: http://link.springer.com/10.1007/s12011-020-02546-5

707. Patel O, Chinni V, El-Khoury J, Perera M, Neto AS, McDonald C, et al. A pilot double-blind safety and feasibility randomised controlled trial of high-dose intravenous zinc in hospitalised COVID-19 patients. J Med Virol. 2021 Feb 25;jmv.26895.

708. Zhong M, Sun A, Xiao T, Yao G, Sang L, Zheng X, Zhang J, et al. A randomized, single-blind, group sequential, active-controlled study to evaluate the clinical efficacy and safety of α-lipoic acid for critically ill patients with coronavirus disease 2019 (COVID-19) [Preprint]. MedRxiv 2020. Available from: https://doi.org/10.1101/2020.04.15.20066266.