COVID-19

Ongoing Living Update of COVID-19 Therapeutic Options:

Summary of Evidence

Rapid Review, 11 March 2021

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

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PAHO/IMS/EIH/COVID-19/21-0005

Disclaimer

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

Contents

Executive summary

Background

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

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

Summary of evidence

Tables 1 and 2, which divide the total group of identified studies into randomized (Table 1) and non-randomized (Table 2) designs, indicate the primary outcome measures used for each investigation and the level of certainty. Table 3, below, summarizes the status of evidence for the 85 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=233)

Intervention		Overall number of studies including the intervention, n=233	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)
Hydroxychloroquine or Chloroquine	NEW	38	10	7	7	6	10
Ivermectin	NEW	26	4 (*)	3	2 (*)	3	4
Glucocorticoids	NEW	14	12	6	5		6
Convalecent plasma	NEW	12	11	7	5		3
Favipiravir		11	1		6		1
Lopinavir-Ritonavir		10	3	3	2		1
Tocilizumab		10	8	8	4		8
Azithromycin	NEW	7	3	3	3		1
Remdesivir		6	4 (#)	4	3		3
Umifenovir		5					
Zinc	NEW	5	2	1	2		
Colchicine		4	3	2			1
Interferon beta-1a		4	3	3	2		
IVIG	NEW	4	4	2			1
Sofosbuvir +/- Daclatasvir		4	2	2	2		
Vitamin C		4	4	4	2		
Vitamin D	NEW	4	2	1			1
Bamlanivimab		3	1		2		3
Bromhexine Hydrochloride		3	1	1	1	1	1
Mesenchimal cell tranplantation		3	1		1		1
ACEIs or ARBs (continuation)		2	2	2			
ACEIs or ARBs (treatment)	NEW	2	2	2			
Dutasteride		2			1		
Leflunomide		2					
Mouthwash (povidone iodine or essential oils)		2					
Nitazoxanide		2	1	1	1		1
Ozone		2	2		1		1
Proxalutide	NEW	2	1	1	1		
Sarilumab		2	2	1	1		1
99mTc-MDP		1					
Anakinra		1	1	1	1		1
Anticoagulants		1	1				
Aprepitant		1					
Artemisinin		1			1		1
Auxora		1	1	1			
Azvudine		1					
Baloxavir		1			1		
Bamlanivimab + etesevimab		1	1		1		1
Baricitinib		1	1	1	1		1
BCG		1	1				
Chloroquine nasal drops		1					
Clarithromycin		1					
CIGB-325		1			1		1
Cofactors		1			1		1
Darunavir-Cobicistat		1					
Electrolyzed saline		1	1		1		
Enisamium		1			1		
Febuxostat		1					
Flebuxamine		1	1	1			1
Helium (inhaled)		1					
Icatibant		1	1				
iC1e/K		1	1				
IFN-alpha2b + IFN-gamma		1					
IFX-1		1	1				1
INM005 (equine antibodies)		1	1	1	1		1
Interferon beta-1b		1	1	1	1		

Interferon beta-1a (inhaled)	1	1	1	1		1
Interferon kappa + TFF2	1	1				1
Itolizumab	1	1	1			1
Levamizole	1			1		
Lincomecin	1					
Melatonin	1	1		1		
Metisoprinol	1					
Molnupiravir	1					1
Mouthwash (hydrogen peroxide)	1	1	1	1		
N-acetylcysteine	1	1	1			1
Nasal hypertonic saline	1			1		
Novaferon	1					
Omega-3 fatty acids	1					
Peg-IFN lambda	1					1
Progesterone	1	1	1			1
Prolectin-M	1	1	1			1
Propolis	1	1	1	1		
Querceritin	1	1		1		
Ramipril	1	1			1	
Recombinant Super-Compound IFN	1	1		1		
REGN-COV2 (Regeneron)	1					1
Ribavirin	1					
Ribavirin + Interferon beta-1b	1					
Ruxolitinib	1			1		
rhG-CSF	1	1		1		1
Sofosbuvir/ledipasvir	1	1	1	1		
Steroids (inhaled)	1			1		
Sulodexide	1	1	1			1
Telmisartan	1	1	1			
Triazavirin	1	1		1		1
α-Lipoic acid	1	1				

(*) Although pooled estimates suggest significant benefits with ivermectin, included studies methodological limitations and a small overall number of events results in very low certainty of the evidence. Based on the results reported by the only four RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality and probably does not improve time to symptom resolution. Further research is needed to confirm or discard those findings; (#) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-statitically significant mortality reduction (RR 0.94, 95%CI 0.82 - 1.08).

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

Table 2. List of non-RCTs of interventions for COVID-19 with primary outcome measures and certainty (n=27)

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)
Anticoagulants	17	13				
NSAID	7	7				
Famotidine	3	3				

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

Table 3. Summary of findings on potential therapeutic options for COVID-19 (n=85), as of 11 March 2021

	Intervention	Summary of findings
1	**99mTc-MDP**	Uncertainty in potential benefits and harms. Further research is needed.
2	**ACEIs or ARBs**	Continuing ACEIS or ARBs in patients with COVID-19 may not increase mortality nor mechanical ventilation requirements
3	**Anakinra**	Anakinra may not improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. Further research is needed.
4	**Anticoagulants**	There are specific recommendations on the use of antithrombotic agents. Studies are ongoing to evaluate the preventive and therapeutic use of antithrombotic agents to mitigate the thrombotic and hemorrhagic events and assess the potential drug interactions with investigational drugs.
5	**Aprepitant**	Uncertainty in potential benefits and harms. Further research is needed.
6	**Artemisinin**	Uncertainty in potential benefits and harms. Further research is needed.
7	**Auxora**	Uncertainty in potential benefits and harms. Further research is needed.
8	**Azithromycin**	Azithromycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
9	**Azvudine**	Uncertainty in potential benefits and harms. Further research is needed.
10	**Baricitinib**	Baricitinib may reduce mortality, mechanical ventilation requirements and may improve time to symptom resolution. However certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.

	Intervention	Summary of findings
11	**Baloxavir**	Uncertainty in potential benefits and harms. Further research is needed.
12	**Bamlanivimab (monoclonal antibody)**	Bamlanivimab probably does not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. Further research is needed.
13	**Bamlanivimab + etesevimab (monoclonal antibodies)**	Bamlanivimab + etesevimab probably does not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. Further research is needed.
14	**BCG**	Uncertainty in potential benefits and harms. Further research is needed.
15	**Bromhexine hydrochloride**	Uncertainty in potential benefits and harms. Further research is needed.
16	**Chloroquine nasal drops**	Uncertainty in potential benefits and harms. Further research is needed.
17	**CIGB-325**	Uncertainty in potential benefits and harms. Further research is needed.
18	**Clarithromycin**	Uncertainty in potential benefits and harms. Further research is needed.
19	**Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)**	Uncertainty in potential benefits and harms. Further research is needed.
20	**Colchicine**	Colchicine may reduce mortality and mechanical ventilation requirements. Certainty of the evidence was low because of imprecision.
21	**Convalescent plasma**	Convalescent plasma probably does not reduce mortality nor significantly reduces mechanical ventilation requirements or improves time to symptom resolution with moderate to high certainty of the evidence. Infusion related severe adverse events are probably exceptional.

	Intervention	Summary of findings
22	**Darunavir-cobicistat**	Uncertainty in potential benefits and harms. Further research is needed.
23	**Dutasteride**	Uncertainty in potential benefits and harms. Further research is needed**.**
24	**Electrolyzed saline**	Uncertainty in potential benefits and harms. Further research is needed.
25	**Enisamium**	Uncertainty in potential benefits and harms. Further research is needed.
26	**Famotidine**	Uncertainty in potential benefits and harms. Further research is needed.
27	**Favipiravir**	Favipiravir may improve time to symptom resolution. It is uncertain if favipiravir affects mortality or mechanical ventilation requirements. Further research is needed.
28	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
29	**Flevuxamine**	Uncertainty in potential benefits and harms. Further research is needed.
30	**Helium (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
31	**Hydroxychloroquine and chloroquine**	Hydroxychloroquine or chloroquine probably does not reduce mortality, invasive mechanical ventilation nor significantly improves time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19 it may not significantly reduce the risk of infection. However, certainty of the evidence is low because of risk of bias and imprecision. HCQ/CQ may also be associated with a small increase in severe adverse events.
32	**Icatibant/iC1e/K**	Uncertainty in potential benefits and harms. Further research is needed.
33	**IFX-1**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
34	**INM005 (polyclonal fragments of equine antibodies)**	Uncertainty in potential benefits and harms. Further research is needed.
35	**Interferon alpha-2b and Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
36	**Interferon beta-1a**	IFN beta-1a probably does not reduce mortality nor invasive mechanical ventilation requirements. Inhaled interferon beta-1a may improve time to symptom resolution.
37	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
38	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.
39	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
40	**Ivermectin**	Although pooled estimates suggest significant benefits with ivermectin, included studies methodological limitations and a small overall number of events results in very low certainty of the evidence. Based on the results reported by the only four RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality and probably does not improve time to symptom resolution. Further research is needed to confirm or discard those findings.
41	**Intravenous immunoglobulin**	Uncertainty in potential benefits and harms. Further research is needed.
42	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
43	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.
44	**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.

	Intervention	Summary of findings
45	**Melatonin**	Uncertainty in potential benefits and harms. Further research is needed.
46	**Mesenchymal stem-cell transplantation**	Uncertainty in potential benefits and harms. Further research is needed.
47	**Molnupiravir**	Uncertainty in potential benefits and harms. Further research is needed.
48	**Mouthwash (hydrogen peroxide)**	Uncertainty in potential benefits and harms. Further research is needed.
49	**Mouthwash (povidone iodine or essential oils)**	Uncertainty in potential benefits and harms. Further research is needed.
50	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.
51	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
52	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.
53	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
54	**Non-steroidal anti-inflammatory drugs (NSAIDs)**	Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However, certainty of the evidence is very low because of risk of bias. Further research is needed.
55	**Omega-3 fatty acids**	Uncertainty in potential benefits and harms. Further research is needed

	Intervention	Summary of findings
56	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
57	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
58	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.
59	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed
60	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed
61	**Propolis**	Uncertainty in potential benefits and harms. Further research is needed
62	**Proxalutide**	Proxalutide may improve time to symptom resolution. However certainty of the evidence is low because of risk of bias. Further research is needed.
63	**Quercetin**	Uncertainty in potential benefits and harms. Further research is needed
64	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
65	**Recombinant super-Compound Interferon**	Uncertainty in potential benefits and harms. Further research is needed.
66	**REGN-COV2 (Regeneron)**	Uncertainty in potential benefits and harms. Further research is needed.
67	**Remdesivir**	Remdesivir may slightly reduce mortality and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.

	Intervention	Summary of findings
68	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.
69	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.
70	**Ribavirin + Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
71	**Ruxolitinib**	Uncertainty in potential benefits and harms. Further research is needed.
72	**Sarilumab**	Sarilumab may reduce mortality and mechanical ventilation requirements. However, the certainty is low because of imprecision and inconsistency.
73	**Sofosbuvir +/- daclatasvir**	Uncertainty in potential benefits and harms. Further research is needed.
74	**Sofosbuvir/ledipasvir**	Uncertainty in potential benefits and harms. Further research is needed.
75	**Steroids**	Steroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Steroids may not significantly increase the risk of severe adverse events.
76	**Steroids (inhaled)**	Uncertainty in potential benefits and harms. Further research is needed.
77	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
78	**Telmisartan**	Uncertainty in potential benefits and harms. Further research is needed.

	Intervention	Summary of findings
79	**Tocilizumab**	Tocilizumab may not reduce mortality but probably reduces mechanical ventilation requirements without possibly increasing severe adverse events.
80	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.
81	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
82	**Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
83	**Vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
84	**Zinc**	Uncertainty in potential benefits and harms. Further research is needed.
85	**α-Lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.

Key findings

• **Therapeutic options:** More than 200 therapeutic options or their combinations are being investigated in more than 1,700 clinical trials. In this review, we examined 85 therapeutic options.

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

• **Remdesivir:** In the WHO SOLIDARITY trial, remdesivir resulted in little or no effect on overall mortality, initiation of ventilation and duration of hospital stay among hospitalized patients. When

combining those findings with those from five other RCTs, remdesivir may slightly reduce mortality and invasive mechanical ventilation requirements and may improve time to symptom resolution. However, overall certainty of the evidence is low and further research is needed to confirm these findings.

• **Hydroxychloroquine, lopinavir–ritonavir and interferon beta-1a**: The body of evidence on hydroxychloroquine, lopinavir-ritonavir and interferon beta-1a, including anticipated findings from the RECOVERY and SOLIDARITY trials, showed no benefit in terms of mortality reduction, invasive mechanical ventilation requirements or time to clinical improvement. Furthermore, the analysis showed probable mortality increment in those patients treated with hydroxychloroquine. Six studies assessed hydroxychloroquine in exposed individuals and showed a non-statistically significant trend towards reduction in symptomatic infection. Further research is needed to confirm these findings.

• **Convalescent plasma:** The results of twelve RCTs assessing convalescent plasma in COVID-19, including the RECOVERY trial with 11558 hospitalized patients, showed no mortality reduction, significant mechanical ventilation requirement reduction or time to symptom resolution improvement with moderate to high certainty of the evidence. Infusion related severe adverse events were exceptional. No significant differences were observed between patients treated early (<4 days since symptom onset) or with more advanced disease.

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

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

• **Ivermectin:** Although 26 RCTs assessed ivermectin in patients with COVID-19, only ten of those studies reported on clinical important outcomes. Pooled estimates suggest mortality reduction with ivermectin but the certainty of the evidence was very low because of methodological limitations and small number of events. Based on the results reported by the only four RCTs classified as low risk of bias, ivermectin may not significantly reduce mortality and

probably does not improve time to symptom resolution. Further research is needed to confirm these findings.

• **Baricitinib:** The results of one RCT show that, in patients with moderate to severe disease, baricitinib may reduce mortality, mechanical ventilation requirements and time to symptom resolution. However the certainty of the evidence was low because of risk of bias and a small number of events. Further research is needed to confirm or discard these findings.

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

• **Bamlinivimab:** The results of three RCTs suggest thas bamlinivimab may not significantly improve time to symptom resolution. Its effects on other relevant outcomes are uncertain. Further research is needed.

• **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.

• **Thromboembolic complications:** 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.

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

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

Changes since previous edition

• **IVIG:** New evidence included without significant changes

• **Steroids:** New evidence included without significant changes

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

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

• **Zinc:** New evidence included without significant changes

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

• **ACEIs or ARBs:** New evidence included without significant changes

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

• **Azithromycin:** New evidence included without significant changes

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

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

Concluding remarks

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

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

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

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

Hallazgos clave

Opciones terapéuticas: Se están investigando más de 200 intervenciones terapéuticas o sus combinaciones en más de 1700 estudios clínicos. En esta revisión se incluyen 85 intervenciones para el manejo de pacientes con COVID-19.

• **Esteroides:** El conjunto de evidencia sobre los esteroides incluye doce ensayos clínicos controlados aleatorizados (ECCA) y muestra que la administración de dosis bajas y moderadas (la dosis utilizada en el estudio RECOVERY fue dexametasona 6 mg diarios por vía oral o endovenosa durante 10 días) probablemente reducen la mortalidad en pacientes con infección grave por COVID-19. Los resultados se mantuvieron uniformes tras agregar al análisis estudios en los que pacientes con SDRA de otras etiologías recibieron corticosteroides o manejo estándar de forma aleatoria.

• **Remdesivir:** En el estudio SOLIDARITY de la OMS, el remdesivir no tuvo un efecto clínicamente relevante sobre la mortalidad global, la necesidad de ventilación mecánica invasiva o el tiempo de estadía hospitalaria. Tras combinar dichos resultados con otros tres ECCA, se observó que el remdesivir podría reducir la mortalidad, la necesidad de ventilación mecánica invasiva y mejorar el tiempo hasta la resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estos hallazgos.

• **Hidroxicloroquina, interferón beta 1-a y lopinavir-ritonavir:** El conjunto de evidencia sobre hidroxicloroquina, interferón beta 1-a y lopinavir-ritonavir, incluidos los resultados preliminares de los estudios RECOVERY y SOLIDARITY, no muestra beneficios en la reducción de la mortalidad, necesidad de ventilación mecánica invasiva o el plazo necesario para la mejoría clínica. Incluso la evidencia sobre hidroxicloroquina sugiere que su utilización probablemente genere un incremento en la mortalidad. Seis estudios que evaluaron la hidroxicloroquina en personas expuestas a la COVID-19 mostraron una tendencia hacia una reducción en el riesgo de infección, pero esta no resulta estadísticamente significativa. Se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estos hallazgos.

• **Plasma de convalecientes:** Los resultados de doce ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19, incluyendo el estudio RECOVERY que reclutó 11558 pacientes, mostraron ausencia de reducción de la mortalidad, ausencia de reducción significativa en los requerimientos de ventilación mecánica invasiva y ausencia de mejoría en el tiempo a la resolución de síntomas con moderada a alta certeza. Los eventos adversos severos relacionados a la infusión fueron excepcionales. Adicionalmente, no se observó un efecto diferencial entre aquellos pacientes tratados rápidamente (<4 días de inicio de los síntomas) y aquellos con enfermedad más avanzada al iniciar dicho tratamiento.

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

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

• **Ivermectina:** A pesar de que 26 ECCA evaluaron ivemectina en pacientes con COVID-19, solo diez de estos estudios reportaron sobre desenlaces clínicamente importantes. Los resultados combinados de estos estudios sugieren una reducción en la mortalidad con ivermectina, sin embargo la certeza en la evidencia resultó muy baja por limitaciones metodológicas y un número pequeño de eventos. Considerando la información aportada por los únicos cuatro estudios con bajo riesgo de sesgo, ivermectina podría no reducir significativamente la mortalidad y probablemente no se asocie a una mejoría en la velocidad de resolución de los síntomas. Se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• **Baricitinib:** Los resultados de un ECCA muestran que, en pacientes con enfermedad moderada a severa, baricitinib podría reducir la mortalidad, los requerimientos de ventilación mecánica invasiva y mejorar el tiempo a resolución de los síntomas. Sin embargo la certeza en la evidencia

resultó baja por riesgo de sesgo y un número pequeño de eventos. Se necesita más información para confirmar o descartar estas conclusiones.

• **Proxalutide:** Los resultados de un ECCA muestran que, en pacientes con enfermedad leve a moderada, proxalutide podría mejorar el tiempo a resolución de los síntomas. Sin embargo la certeza en la evidencia resultó baja por riesgo de sesgo. Se necesita más información para confirmar o descartar estas conclusiones.

• **Bamlinivimab:** Los resultados de tres ECCA sugieren que bamlinivimab podría no mejorar significativamente el tiempo a resolución de los síntomas. Sus efectos sobre otros desenlaces importantes son inciertos. Se necesita más información para confirmar o descartar estas conclusiones.

• **INM005 (fragmentos policlonales de anticuerpos equinos):** Hasta el momento, la evidencia sobre los efectos de INM005 es de muy baja certeza. Se necesita más información procedente de estudios con un diseño adecuado para evaluar su eficacia.

• **Famotidina:** Hasta el momento, la evidencia sobre los efectos de la famotidina es de muy baja certeza. Se necesita más información procedente de estudios con un diseño adecuado para evaluar su eficacia y seguridad.

• **Complicaciones tromboembólicas:** Las complicaciones tromboembólicas en pacientes con COVID-19 son frecuentes. Al igual que en pacientes hospitalizados por afecciones médicas graves, las directrices de práctica clínica vigentes indican que los pacientes hospitalizados por COVID-19 sean tratados con medidas tromboprofilácticas.

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

• **IECA y ARB:** La continuación del tratamiento con IECA y ARB en pacientes con COVID-19 podría no aumentar la mortalidad ni los requerimientos de ventilación mecánica invasiva. Sin embargo, la certeza en la evidencia es baja, por lo que se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

Cambios respecto a la anterior versión

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

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

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

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

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

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

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

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

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

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

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

Conclusiones

• La Organización Panamericana de la Salud (OPS) hace seguimiento en todo momento de la evidencia en relación con cualquier posible intervención terapéutica. A medida que se disponga de nueva evidencia, la OPS la incorporará con rapidez y actualizará sus recomendaciones,

especialmente si dicha evidencia se refiere a grupos en situación de vulnerabilidad como los niños, las mujeres embarazadas, adultos mayores o los pacientes inmunocomprometidos, entre otros.

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

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

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

Systematic review of therapeutic options for treatment of COVID-19

Background

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

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

Methods

We used the Living OVerview of Evidence (L·OVE; https://iloveevidence.com) platform to identify studies for inclusion in this review. This platform is a system that maps PICO (Patient–Intervention–Comparison–Outcome) questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in electronic databases, preprint servers, trial registries, and other resources relevant to COVID-19. The last version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on the L·OVE website.[2]

Search strategy

We systematically searched in L·OVE for COVID-19. The search terms and databases covered are described on the L·OVE search strategy methods page available at: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?question_domain=undefined&section=methods. The repository is continuously updated, and the information is transmitted in real-time to the L·OVE platform, however, it was last checked for this review on March 11, 2021. The searches covered the period from the inception date of each database, and no study design, publication status or language restriction was applied.

Study selection

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

Inclusion criteria

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

Living evidence synthesis

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

The focus has been on RCTs studies for all included therapeutic pharmacological interventions (adults and children). Adults and children exposed to or with confirmed or suspected COVID-19 were and will be included. Trials that compare interventions head-to-head or against no intervention or placebo is the focus. We have focused on comparative effectiveness studies that provide evidence on patient-important outcomes (mortality, invasive mechanical ventilation, symptom resolution or improvement, infection (prophylaxis studies) and severe adverse events).[3] No electronic database search restrictions were imposed.

For any meta-analytical pooling, if and when data allow, we pool all studies and present the combined analysis with relative and absolute effect sizes. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). We extracted mortality and invasive mechanical ventilation baseline risks from the ISARIC cohort as of December 18, 2020.[5,6] For baseline infection risk in exposed to COVID-19 we used estimates from a SR on physical distancing and mask utilization,[7] and for adverse events and symptom resolution/improvement we used the mean risk in the control groups from included RCTs until December 18, 2020. For 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.

A risk of bias assessment was applied to RCTs focusing on randomization, allocation concealment, blinding, attrition, or other biases relevant to the estimates of effect.[8] For non-RCTs, potential residual confounding was assumed in all cases and certainty of the evidence was downgraded twice for risk of bias. The GRADE approach was used to assess the certainty on the body of evidence for every comparison on an outcome basis (Table 5).[9] Risk of bias judgments were compared against other similar projects (Drug treatments for covid-19: living systematic review and network meta-analysis and The COVID-NMA initiative). Significant discrepancies were discussed until a final decision was reached.

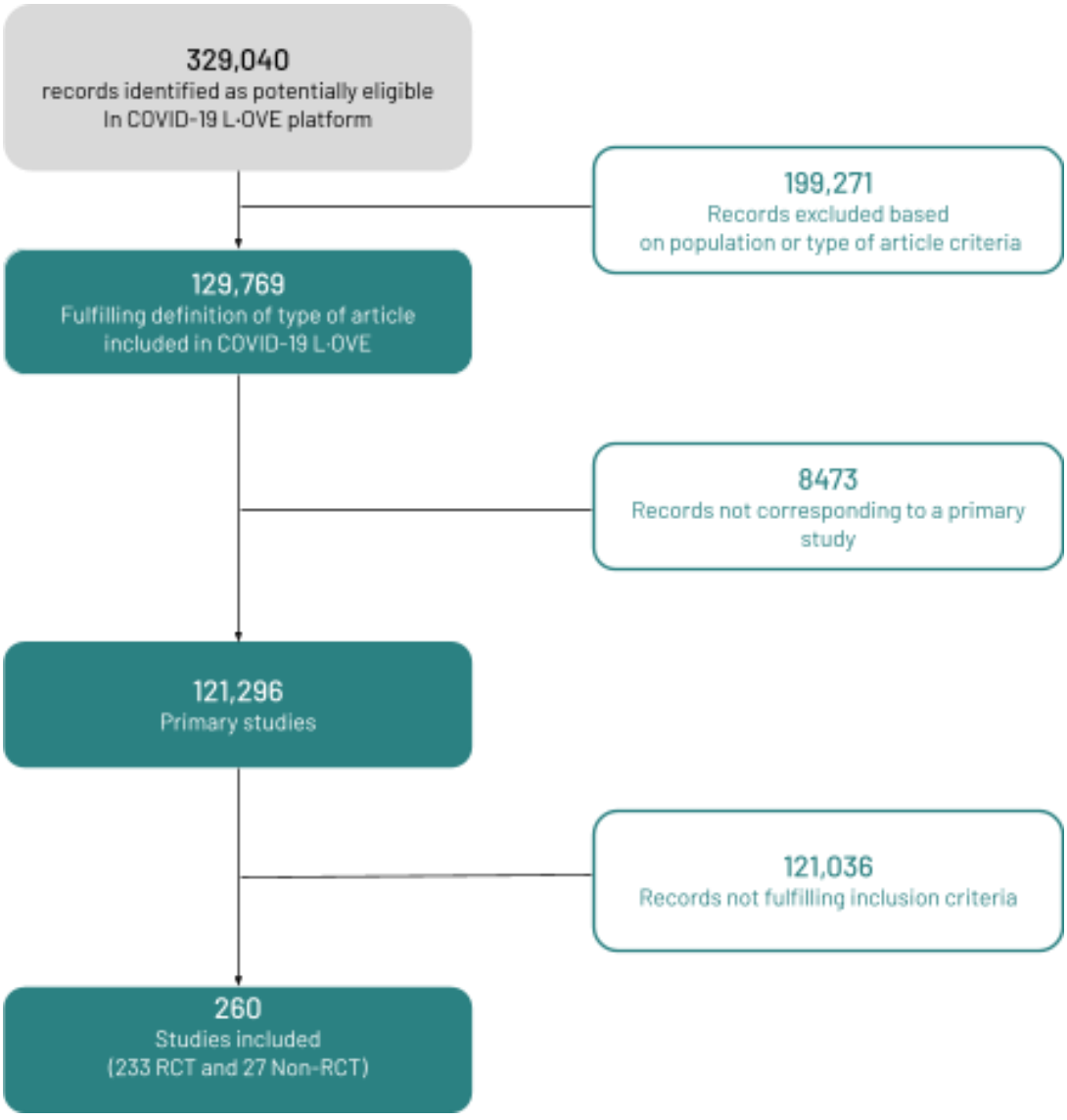
We used MAGIC authoring and publication platform (https://app.magicapp.org/) to generate the tables summarizing our findings, which are included in Appendix 1.

Results

Studies identified and included

Study identification and selection process is described in figure 1. A total of 260 studies were selected for inclusion, 233 RCT and 27 non-RCT. List of excluded studies is available upon request.

Figure 1. Study identification and selection process



Risk of bias

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

Table 4. Risk of bias of included RCTs

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

Podder CS et al	High	Some Concerns	Low	Some Concerns	Low	High	High
HESACOVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
TEACH	High	Low	Low	Some Concerns	Low	High	High
Nojomi et al (Iran University of Medical Sciences)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PrEP_COVID	Low	Low	Low	Low	Low	Low	Low
de Alencar JCG et al (Universidade de São Paulo)	Low	Low	Low	Low	Low	Low	Low
Fu W et al (Shanghai Public Health Clinical Center)	High	Some Concerns	Low	Some Concerns	Low	High	High
Salehzadeh F (Ardabil University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
Dabbous H et al (Ain Shams University)	High	Some Concerns	Low	Some Concerns	Low	High	High
PATCH	Low	Low	Low	Low	Low	Low	Low
Zhao H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
PLASM-AR	Low	Low	Low	Low	Low	Low	Low
COVID-19-MCS	Low	Low	Low	Some Concerns	High	Low	High
Ansarin K (Tabriz University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
WHO SOLIDARITY - HCQ	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - LPV/r	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - remdesivir	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - IFN	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
WHO SOLIDARITY - IFN	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Yethindra V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Shi L et al	Low	Low	Low	Low	Low	Low	Low
RCT-TCZ-COVID-19	Low	Some Concerns	Low	Some Concerns	Low	Low	High
BACC Bay Tocilizumab Trial	Low	Low	Low	Low	Low	Low	Low
SARITA-2	Low	Some Concerns	Some Concerns	Some Concerns	Low	Low	High
Ghaderkhani S et al (Tehran University of Medical Sciences)	High	Some Concerns	Low	Some Concerns	Low	High	High
COVID-19 PEP (University of Washington)	Low	Low	Low	Low	Low	NA	Low
Hashim HA et a (Alkarkh Health Directorate-Baghdad)	High	Some Concerns	Low	Some Concerns	Low	High	High
ILBS-COVID-02	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PROBIOZOVID	High	Some Concerns	Low	Some Concerns	Low	High	High
Padmanabhan U et al (Medical Education and Drugs 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 A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgazzar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Elgazzar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Tabarsi P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FAV052020 (Promomed, LLC)	High	Some Concerns	Low	Some Concerns	Low	High	High
Murai IH et al (University of Sao Paulo)	Low	Low	Low	Low	Low	Low	Low
Udwadia ZF et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
CORIMUNO-TOCI 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
EMPACTA	Low	Low	Low	Low	Low	Low	Low
HYCOVID	Low	Low	Low	Low	Low	Low	Low
Krolewiecki A et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ILIAD	Low	Low	Low	Low	Low	Low	Low
AB-DRUG-SARS-004	High	Low	Low	Low	Low	High	High
Q-PROTECT	Low	Low	Low	Low	Low	Low	Low
Hassan M et al	High	Low	Low	Low	Low	High	High
FundacionINFANT-Plasma	Low	Low	Low	Low	Low	Low	Low
COVID-Lambda	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Niaee MS et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
PICP19	High	Some Concerns	Low	Some Concerns	Low	High	High
Mukhtar K et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Ahmed S et al	High	Low	Low	Low	Low	High	High
ITOLI-C19-02-I-00	High	Some Concerns	Low	Some Concerns	Low	High	High
Abd-Elsalam S et al (Tanta University)	High	Some Concerns	Low	Some Concerns	Low	High	High
Prolectin-M	High	Some Concerns	Low	Some Concerns	Low	High	High
Maldonado V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
GARGLES	High	Some Concerns	Low	Some Concerns	Low	High	High
ERSul	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
SAINT	Low	Low	Low	Low	Low	Low	Low
ACTT-2	Low	Low	Some Concerns	Low	Low	Some Concerns	Some Concerns
RECOVERY	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
EIDD-2801-1001	Low	Low	Low	Low	Low	Low	Low
Weinreich	Low	Low	Low	Low	Low	Low	Low
Roozbeh F et al	Low	Some Concerns	Low	Some Concerns	Low	Low	High
ACTIV-3/TICO	Low	Low	Some Concerns	Low	Low	Low	High
Chachar AZ et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Balykova LA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Babalola et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REMAP-CAP - tocilizumab	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Abdelmaksoud AA et al	High	Some Concerns	Low	Some Concerns	Low	High	High
REPLACE COVID	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Kirti R et al	Low	Low	Low	Low	Low	Low	Low
Kumari P et al	High	Some Concerns	Low	Some Concerns	Low	High	High
FK/FAV00A-CoV/2020	High	Low	Low	Low	Low	High	High
IVERCAR-TUC	High	Some Concerns	Low	Some Concerns	Low	High	High
COVIFERON	Low	Some Concerns	Low	Some Concerns	Low	Low	High
RECOVERY-Plasma	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Interferon in COVID (Alavi Darazam I et al)	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AB-DRUG-SARS-004 (Cadegiani FA et al)	High	Some Concerns	Low	Some Concerns	Low	High	High
JamaliMoghadamSiahkali S et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Sedighiyan M et al	High	Some Concerns	Low	Some Concerns	Low	High	High

Roostaei A et al	High	Low	Low	Low	Low	High	High
Bee-Covid	Low	Some Concerns	Low	Some Concerns	Low	Low	High
SEOT	High	Some Concerns	Low	Some Concerns	Low	High	High
RIVET-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Rezai M et al	Low	Low	Low	Low	Low	Low	Low
Spoorthi V et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Raad H et al	High	Low	Low	Low	Low	High	High
IVE-COV	High	Some Concerns	Low	Some Concerns	Low	High	High
Okumus	High	Some Concerns	Low	Some Concerns	Low	High	High
Veiga	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
Gottlieb	Low	Low	Low	Low	Low	Low	Low
BRACE CORONA	Low	Some Concerns	Some Concerns	Low	Low	Some Concerns	Some Concerns
CORIMUNO-ANA-1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Thakar A et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Onal H et al	High	High	Low	Some Concerns	Low	High	High
Tang X et al	Low	Some Concerns	Low	Low	Low	Low	Low
COLCORONA	Low	Some Concerns	Low	Low	Low	Low	Low
Lopardo	Low	Low	Low	Low	High	Low	High
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
COVIDAtoZ - Vit C	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
COVID-19 Early Treatment	Low	Some Concerns	Low	Low	Low	Low	Low
Shogenova LV et al	High	Some Concerns	Low	Some Concerns	Low	High	High
EFC16844	Low	Some Concerns	Low	Low	Low	Low	Low
ARTI-19	High	Some Concerns	Low	Some Concerns	Low	High	High
Purwati	High	Some Concerns	Low	Some Concerns	Low	High	High
VB-N-IVIG-COVID-19/2020-CT2	High	Some Concerns	Low	Some Concerns	Low	High	High
Jamaati H et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Beltran-HCQ	High	Some Concerns	Low	Some Concerns	Low	High	High
Beltran-Ivermectin	High	Some Concerns	Low	Some Concerns	Low	High	High
ZINC COVID	Low	Some Concerns	Low	Low	Low	Low	Low
PATCH 1	Low	Some Concerns	Low	Some Concerns	Low	Low	High
AB-DRUG-SARS-004	High	Some Concerns	Low	Some Concerns	Low	High	High
Nouri-Vaskeh M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Lopez-Medina	Low	Some Concerns	Low	Low	Low	Low	Low
Lakkireddy M et al	High	Some Concerns	Low	Some Concerns	Low	High	High
Silva	High	Some Concerns	Low	Some Concerns	Low	High	High
PRINCIPLE	Low	Some Concerns	Some Concerns	Some Concerns	Low	Some Concerns	High
Bermejo Galan	Low	Some Concerns	Low	Low	Low	Low	Low
Pott-Junior	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Mikhaylov	Low	Some Concerns	Low	Some Concerns	Low	Low	High

Main findings

Corticosteroids

See Summary of findings Table 1, Appendix 1

We identified 14 RCTs including 8115 participants in which systemic steroids (dexamethasone, methylprednisolone or hydrocortisone) were compared against standard of care or other treatments. Ten of these trials provided information on relevant outcomes. The RECOVERY trial was the biggest with 2,104 patients assigned to dexamethasone and 4,321 to standard of care. All ten studies included patients with severe to critical disease, as shown by the fact that mortality in the control groups ranged from 14.2% to 61.4%. In the RECOVERY trial, a subgroup analysis

which stratified patients by the amount of baseline respiratory support they received, showed significant differences favoring those with oxygen requirements. However, as mortality was high in the subgroup of patients that did not receive baseline oxygen treatment (14%), we decided to adopt a conservative approach and include the primary analysis considering all randomized patients. Our results showed:

- Steroids probably reduce mortality, RR 0.90 (95%CI 0.80 to 1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕◯ (Figure 1.)
- Steroids probably reduce invasive mechanical ventilation requirement, RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕◯
- Steroids may improve time-to-symptom resolution, RR 1.27 (95%CI 0.98 to 1.65); RD 16.3% (95%CI -1.2% to 39.4%); Low certainty ⊕⊕◯◯
- Steroids may not significantly increase the risk of severe adverse events, RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕◯◯
- Results were consistent with trials in which steroids were used to treat non COVID-19 patients with ARDS. No significant differences between subgroups of studies using different steroids were observed. (Figures 2. and 3.)

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

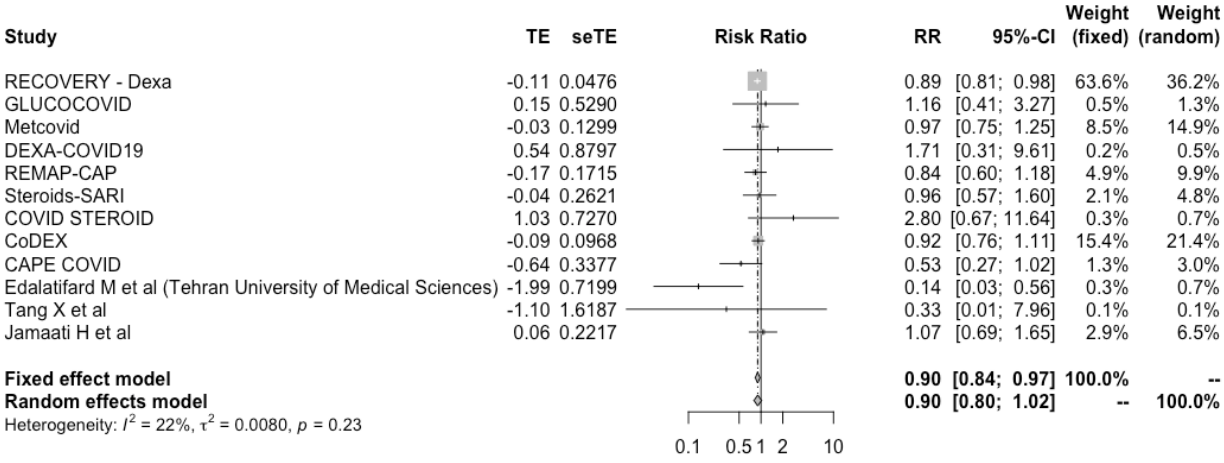


Figure 2. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

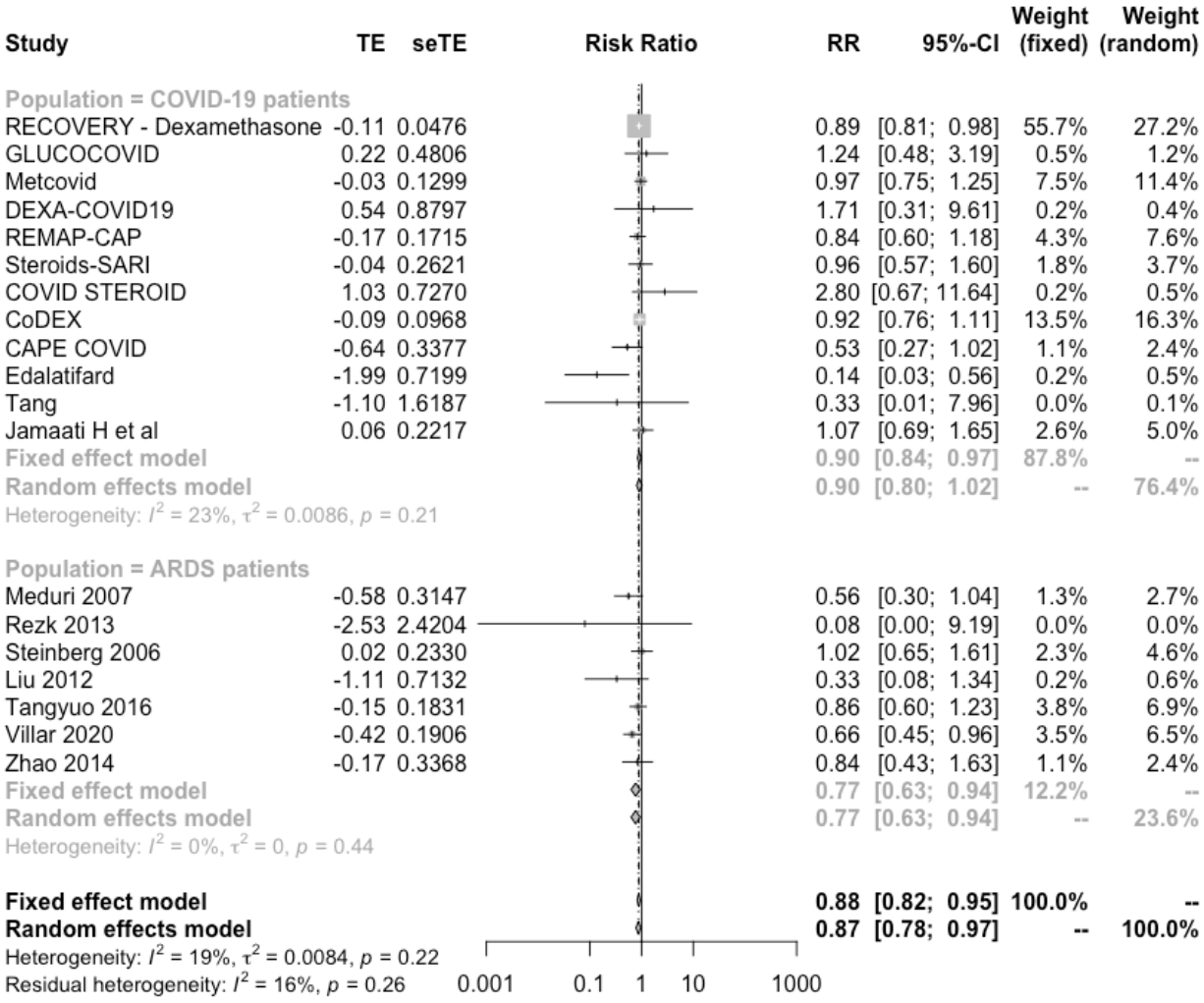
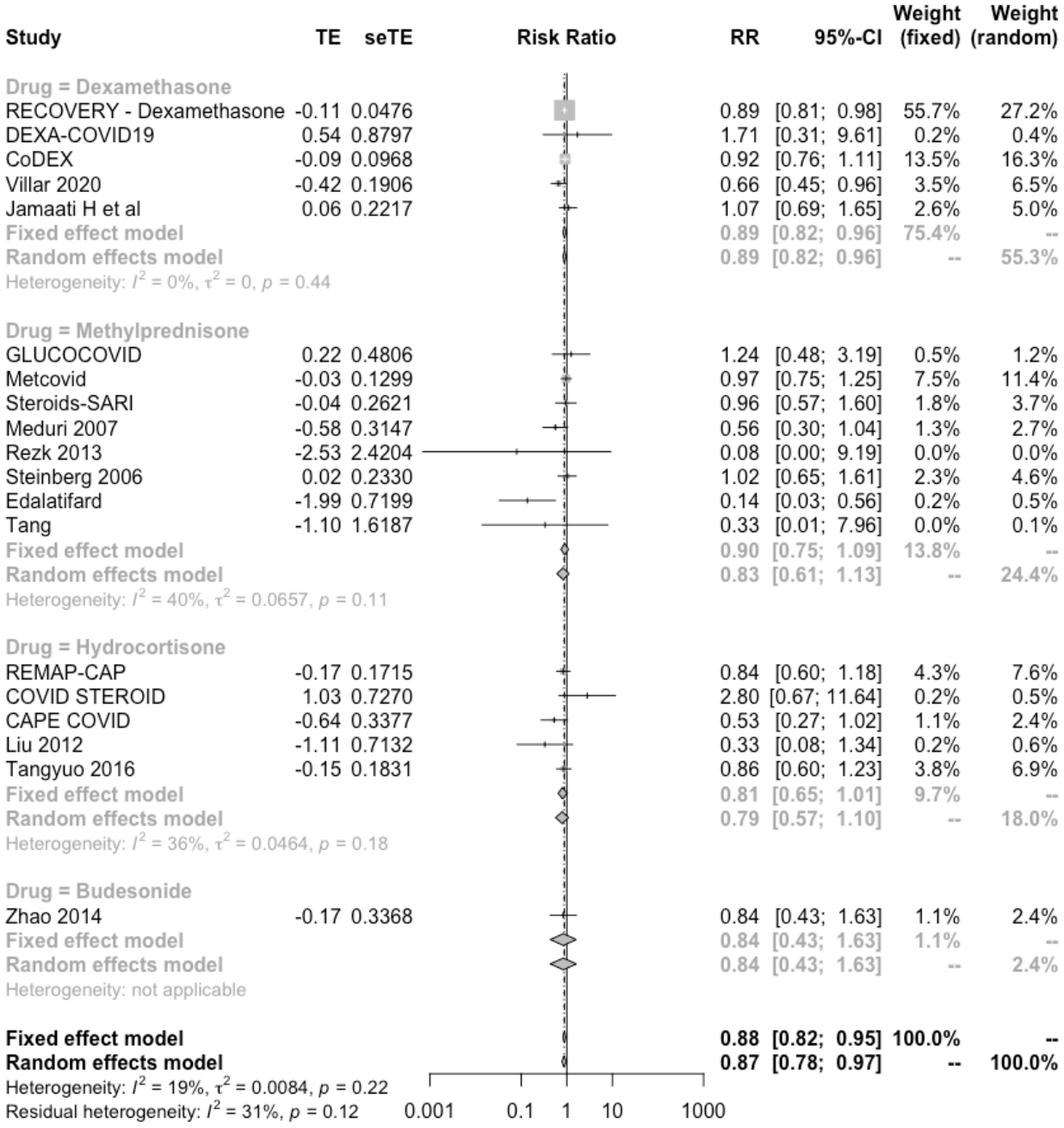


Figure 3. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19



Remdesivir

See Summary of findings Table 2, Appendix 1

We identified six RCTs including 15,057 patients in which remdesivir was compared against standard of care or other treatments. In addition, we identified one study that compared different remdesivir dosage schemes. The WHO SOLIDARITY trial was the biggest with 2,734 patients assigned to remdesivir and 2,708 to standard of care. Three studies included patients with severe disease as shown by the fact that mortality in the control groups ranged from 10.3% to 12.6%, and one study included non-severe patients with 2% mortality in the control arm. Our results showed:

- Remdesivir may slightly reduce mortality, RR 0.94 (95%CI 0.82 to 1.08); RD -1% (95%CI -2.9% to 1.3%); Low certainty ⊕⊕◯◯ (figure 4.)
- Remdesivir may reduce invasive mechanical ventilation requirement RR 0.65 (95%CI 0.39 to 1.11); RD -6% (95%CI -10.6% to 1.9%); Low certainty ⊕⊕◯◯ (Figure 5.)
- Remdesivir may improve time to symptom resolution, RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⊕⊕◯◯ (Figure 6.)
- Remdesivir may not significantly increase the risk of severe adverse events, RR 0.8 (95%CI 0.48 to 1.33); RD -2% (95%CI -5.3% to 3.4%); Low certainty ⊕⊕◯◯

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

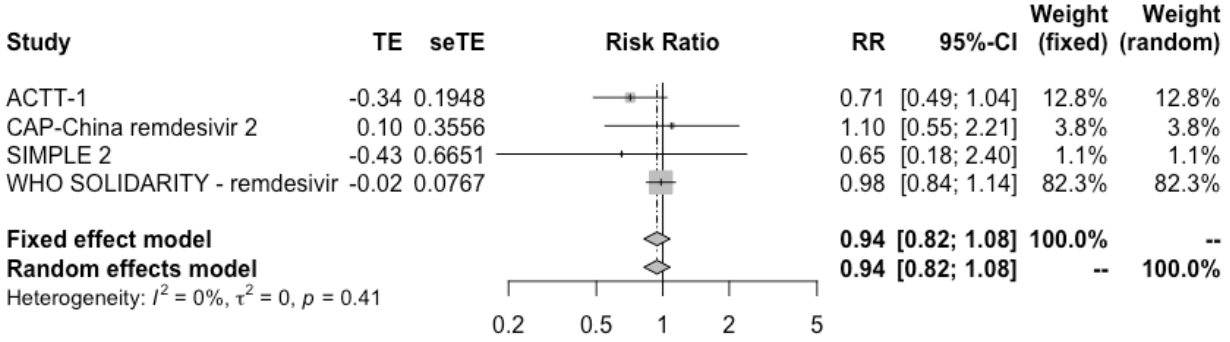


Figure 5. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

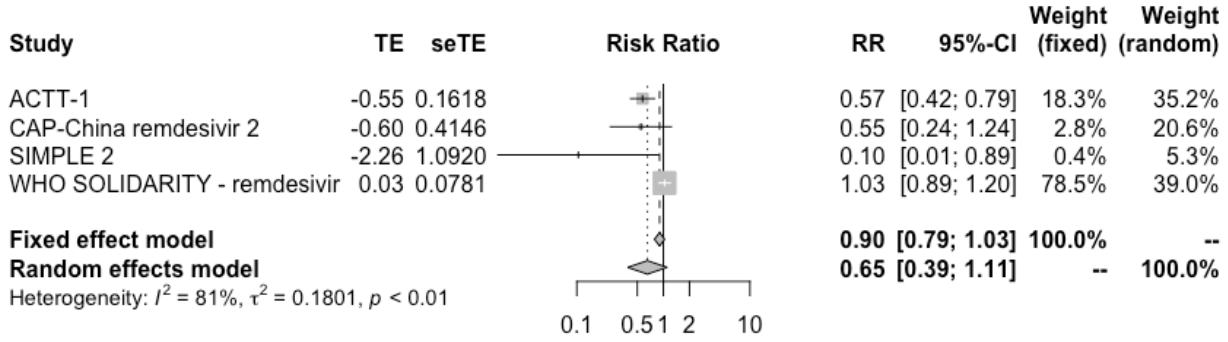
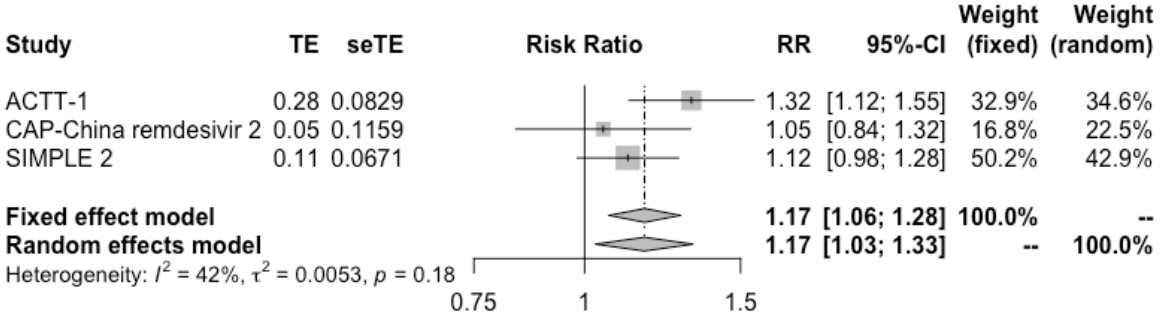


Figure 6. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 38 RCTs including 18,102 patients in which hydroxychloroquine or chloroquine were compared against standard of care or other treatments. The RECOVERY trial was the biggest with 1,561 patients assigned to dexamethasone and 3,155 to standard of care. In both the RECOVERY and SOLIDARITY trials, patients had severe disease as shown by the high mortality risk in control arms (24.9% and 9.2%, respectively). The remaining studies included patients with non-severe disease, as shown by the lower mortality risk in control arms, ranging from 0 to 5.2%.

Additionally, we identified six studies in which hydroxychloroquine was used in healthy persons to prevent COVID-19 infection. Our results showed:

- Hydroxychloroquine or chloroquine probably increase mortality, RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕◯ (Figure 7.)
- Hydroxychloroquine or chloroquine probably does not reduce invasive mechanical ventilation requirement; RR 1.05 (95%CI 0.9 to 1.22); RD 0.9% (95%CI -1.7% to 3.8%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine probably does not improve time to symptom resolution, RR 1.05 (95%CI 0.95 to 1.16); RD 3% (95%CI -3% to 9.7%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine may marginally reduce COVID-19 symptomatic infection in exposed individuals, RR 0.90 (95%CI 0.73 to 1.1); RD -1.7% (95%CI -4.7% to 1.7%); Low certainty ⊕⊕◯◯ (figure 8.)
- Hydroxychloroquine or chloroquine may not significantly increase the risk of severe adverse events, RR 1.1 (95%CI 0.78 to 1.54); RD 1% (95%CI -2.2% to 5.5%); Low certainty ⊕⊕◯◯

Figure 7. All-cause mortality in RCTs comparing hydroxychloroquine or chloroquine with standard of care in patients with COVID-19

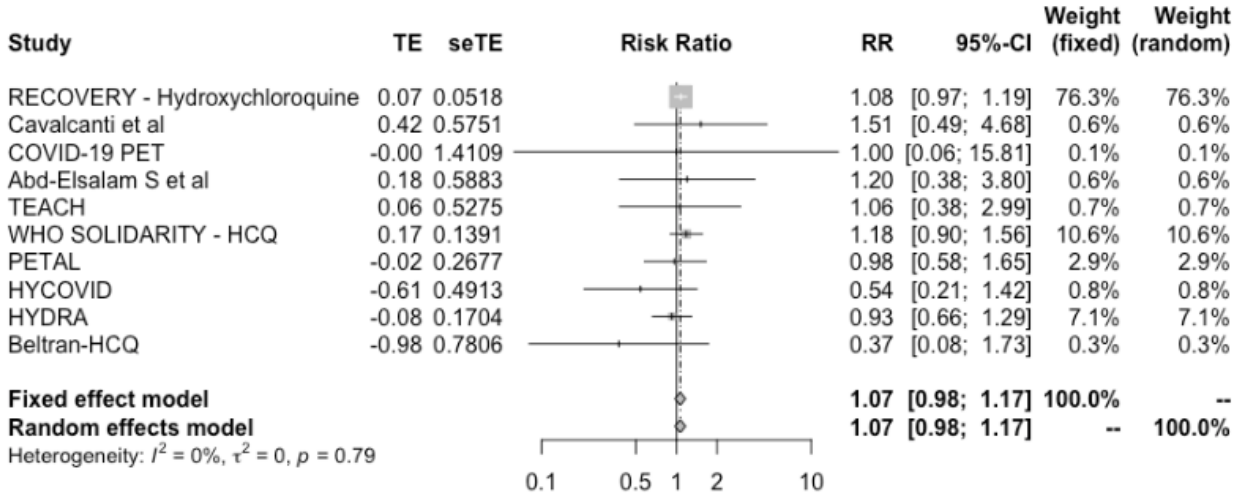
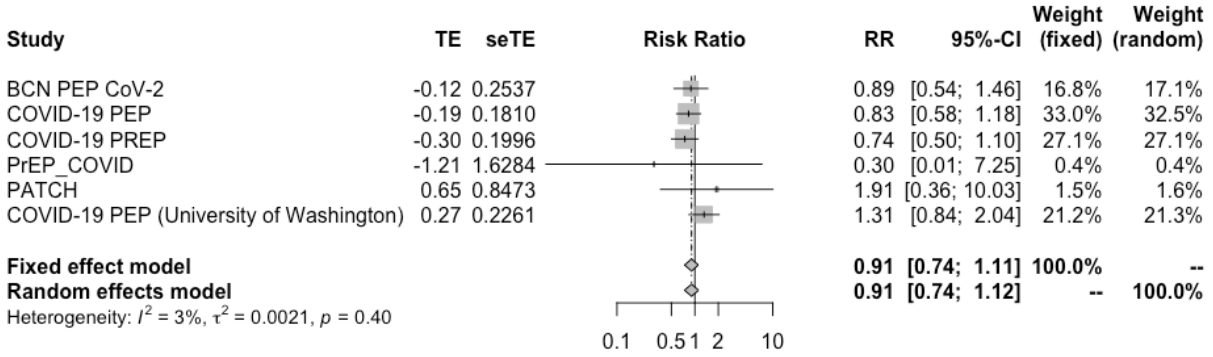


Figure 8. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



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

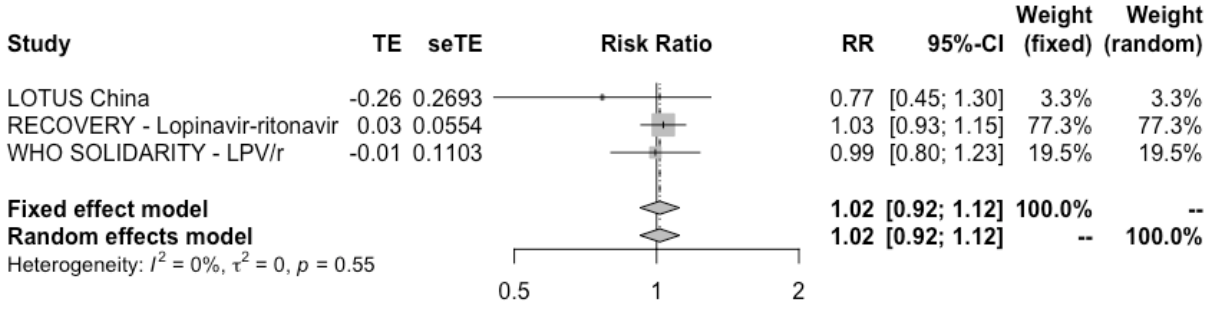
Lopinavir-Ritonavir

See Summary of findings Table 4, Appendix 1

We identified ten RCTs including 8,790 patients in which lopinavir-ritonavir was compared against standard of care or other treatments. The RECOVERY trial was the biggest with 1,616 patients assigned to dexamethasone and 3,424 to standard of care. Three studies provided information on mortality outcome, all of which included patients with severe disease, as shown by the mortality risk in control arms, which ranged from 10.6% to 25%. Our results showed:

- Lopinavir-Ritonavir probably does not reduce mortality, RR 1.02 (95%CI 0.92 to 1.22); RD 0.3% (95%CI -1.3% to 1.9%); Moderate certainty ⊕⊕⊕◯ (Figure 9.)
- Lopinavir-Ritonavir does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕
- Lopinavir-Ritonavir probably does not improve symptom resolution or improvement; RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯
- Lopinavir-ritonavir may not increase the risk of severe adverse events, RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -6.5% to -0.2%); Low certainty ⊕⊕◯◯

Figure 9. All-cause mortality in RCTs comparing lopinavir–ritonavir with standard of care for treatment of patients with COVID-19



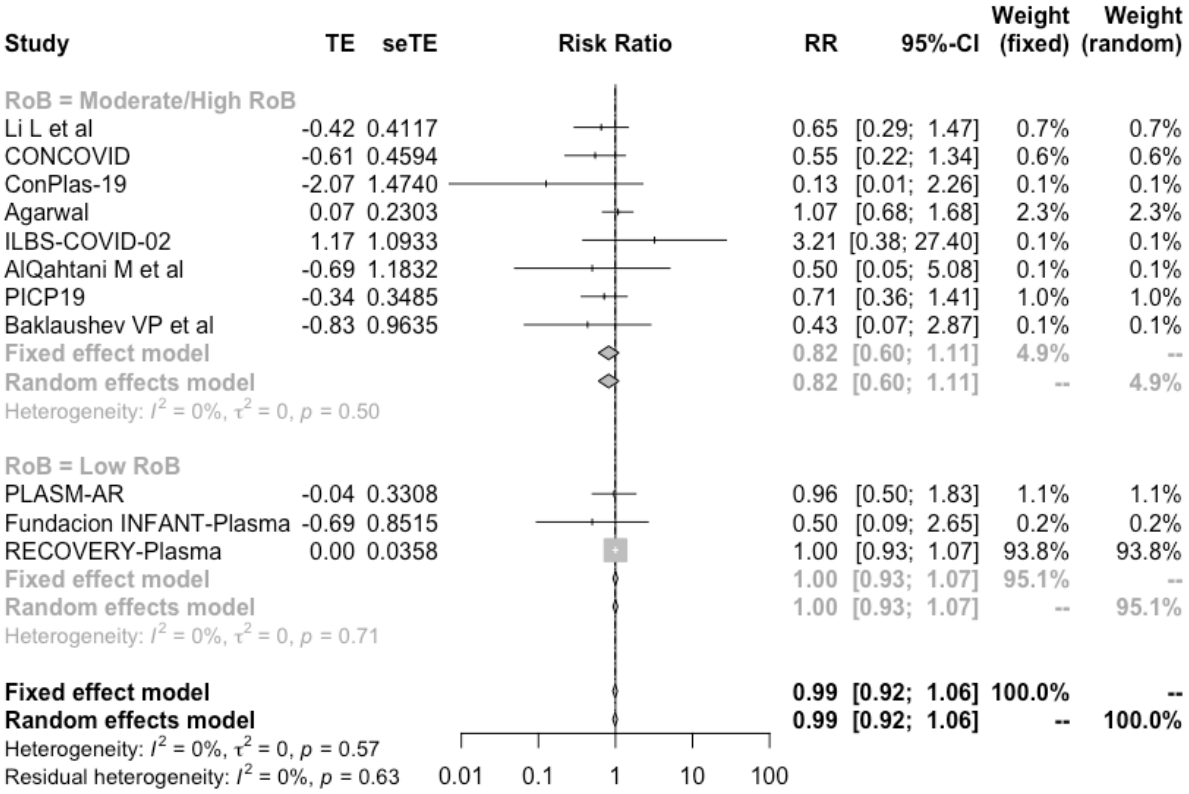
Convalescent plasma

See summary of findings table 5 in appendix 1

We identified twelve RCT including 13058 patients in which convalescent plasma was compared against standard of care or other treatments. RECOVERY was the biggest study including 11588 patients. Most studies (9/11) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 10% to 24.6%. The remaining studies included patients with recent onset symptoms and reported a control-arm mortality rate of 5% and 6.6%. Convalescent plasma was administered in one or two infusions to symptomatic patients in all cases. Our results showed:

- Convalescent plasma probably does not reduce mortality, RR 0.99 (95%CI 0.92 to 1.06); RD -0.1% (95%CI -1.3% to 1%); Moderate certainty ⊕⊕⊕◯ (figure 10.).
- Convalescent plasma probably does not significantly reduces invasive mechanical ventilation requirements, RR 0.89 (95% CI 0.76 to 1.04); RD -1.9% (95%CI -4.2% to 0.7%); Moderate certainty ⊕⊕⊕◯.
- Convalescent plasma does not improve symptom resolution or improvement, RR 1 (95% CI 0.93 to 1.08); RD 0% (95%CI -4.2% to 4.8%); High certainty ⊕⊕⊕⊕
- It is uncertain if convalescent plasma increases severe adverse events, RR 1.26 (95% CI 0.83 to 1.9); RD 2.7% (95%CI -1.7% to 9.4%); Very low certainty ⊕◯◯◯
- Specific adverse events related to convalescent plasma infusion are possibly rare: transfusion-related circulatory overload 0.18%; transfusion-related lung injury 0.10%; Severe allergic transfusion reaction 0.10%. However, we are uncertain if convalescent plasma increases severe adverse events as certainty of the evidence is very low.

Figure 10: All-cause mortality in RCTs comparing convalescent plasma with standard of care for treatment of patients with COVID-19



In one of the studies 58 patients were randomized to early administration of convalescent plasma (at the time they were randomized) or late administration (only if clinical deterioration was observed). All patients in the early arm received the treatment, while just 43.3% of patients received it in the late arm. Results showed no mortality reduction (OR 4.22, 95%CI 0.33 to 53.57) nor reduction in the need for invasive mechanical ventilation requirement reduction (OR 2.98, 95%CI 0.41 to 21.57) with early infusion. However, the certainty of the evidence was very low ⊕◯◯◯ because of imprecision. In addition, in the RECOVERY trial effect modification was suggested by a subgroup analysis performed according to time elapsed between the beginning of the symptoms and initiation of treatment with convalescent plasma.

Tocilizumab

See Summary of findings Table 6 in Appendix 1

We identified ten RCTs including 6440 patients in which tocilizumab was compared against standard of care or other interventions. Eight studies reported on mortality outcome, including

the RECOVERY study that recruited 4116 patients. All studies included severe patients but some excluded critical patients. The proportion of critical patients in those studies that included them was 16.5% to 47.5%. Our results showed:

- Tocilizumab probably reduces mortality, RR 0.90 (95%CI 0.78 to 1.03); RD -1.6% (95%CI -3.5% to 0.5%); Moderate certainty ⊕⊕⊕◯ (Figure 11.)
- Tocilizumab reduces invasive mechanical ventilation requirements, RR 0.80 (95%CI 0.71 to 0.9); RD -3.5% (95%CI -5% to -1.7%); High certainty ⊕⊕⊕⊕ (Figure 12.)
- Tocilizumab may improve time to symptom resolution, RR 1.10 (95%CI 0.99 to 1.22); RD 6% (95%CI -0.6% to 13.3%); Low certainty ⊕⊕◯◯
- Tocilizumab probably does not significantly increase severe adverse events, RR 0.89 (95%CI 0.75 to 1.07); RD -1.1% (95%CI -2.5% to 0.7%); Moderate certainty ⊕⊕⊕◯

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

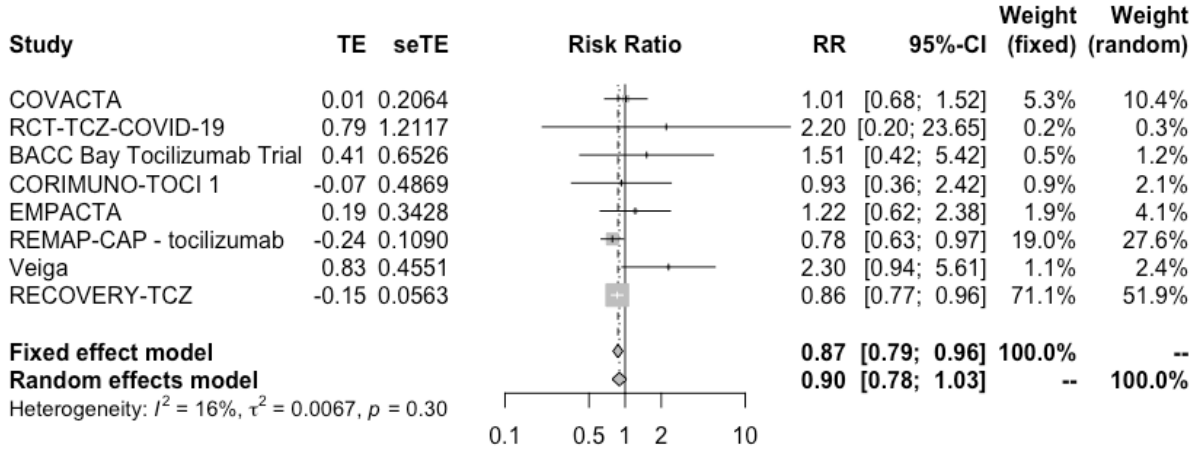
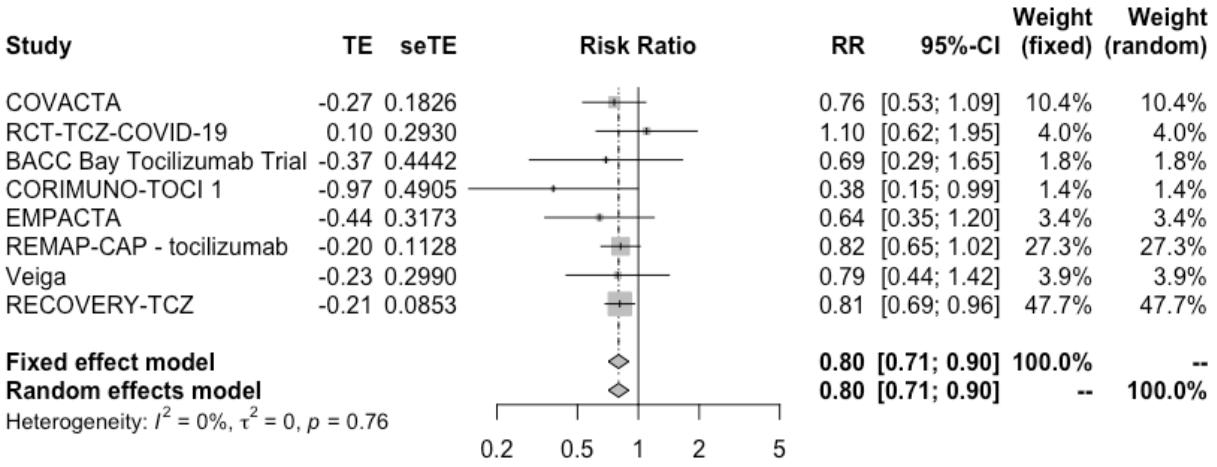


Figure 12: Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19



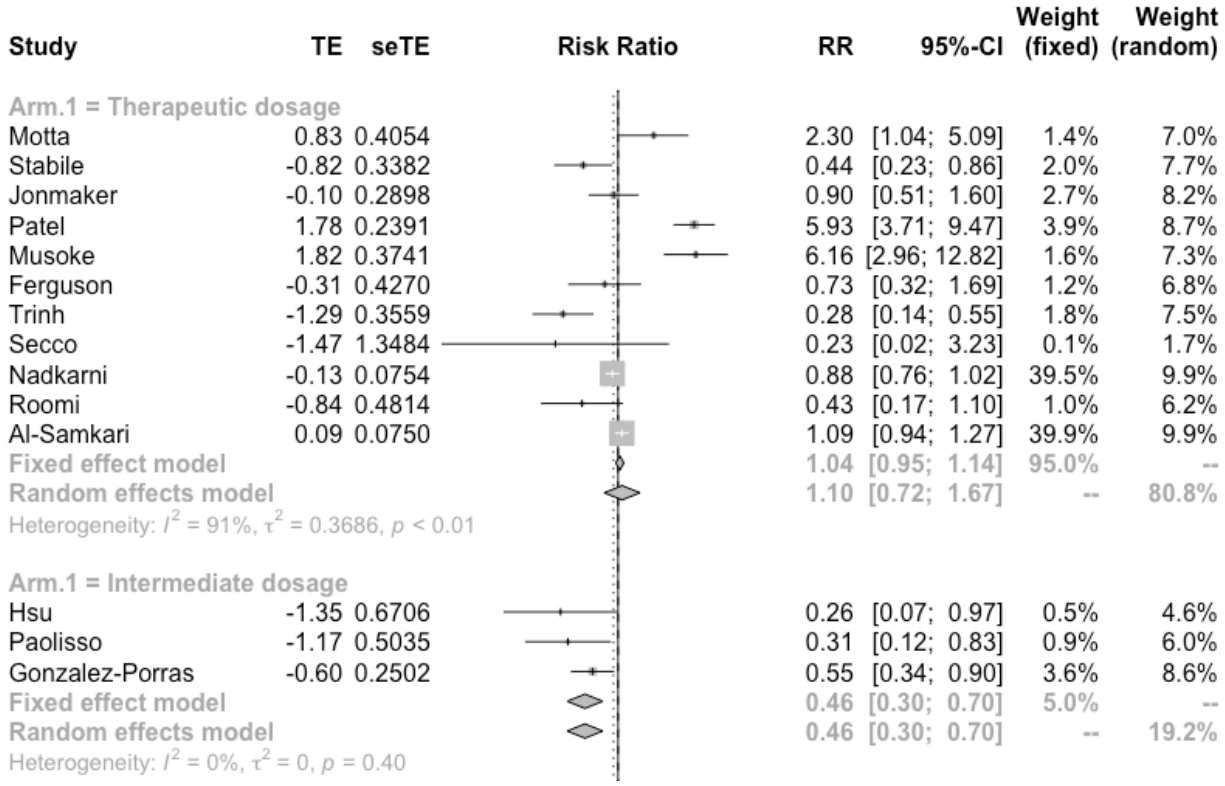
A subgroup analysis, performed in the RECOVERY trial, comparing the effect of tocilizumab in severe and critical patients, did not suggest a subgroup modification effect according to baseline disease severity (p=0.52).

Anticoagulants

See Summary of findings Table 7, Appendix 1

Thromboembolic complications in patients infected with COVID-19 are relatively frequent.[11] As for hospitalized patients with severe medical conditions, current guidelines recommend thromboprophylaxis measures should be used for inpatients with COVID-19 infection.[12] To date, not appropriately designed and powered studies comparing different prophylactic strategies have been published. Hence, optimal intervention, dose and timing remains to be determined. Results of non-RCTs suggest possible benefits with intermediate dosage anticoagulation in comparison to therapeutic or prophylactic dosage (Figure 13). However, the certainty of the evidence is very low ⊕◯◯◯, so these findings should be interpreted with extreme caution due to the risk of bias from possible baseline patient prognostic imbalances and other biases.

Figure 13: All-cause mortality in non-RCTs using anticoagulants in therapeutic doses, intermediate dose and prophylactic doses for treatment of patients with COVID-19



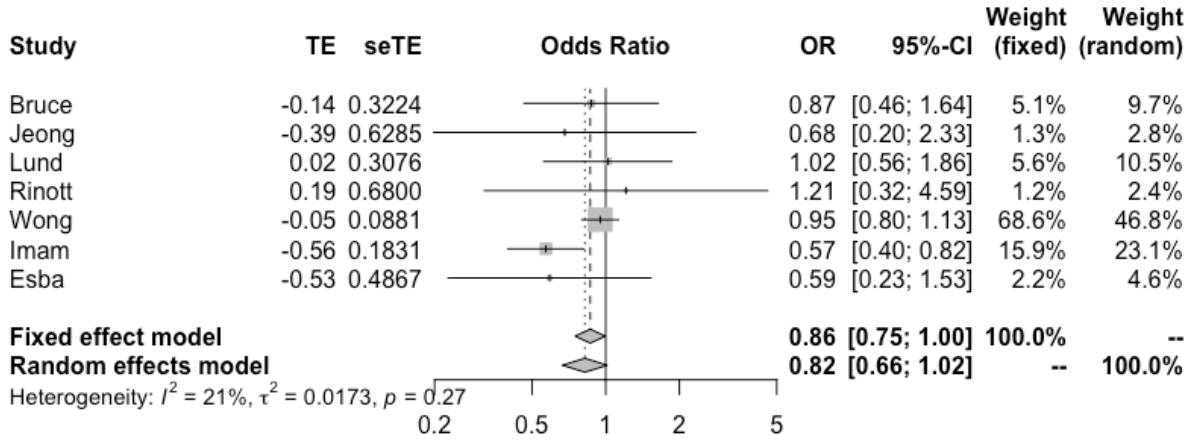
NSAIDs

See Summary of findings table 8, Appendix 1

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

- No association between NSAID exposure and mortality, OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕◯◯◯ (Figure 14.)

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



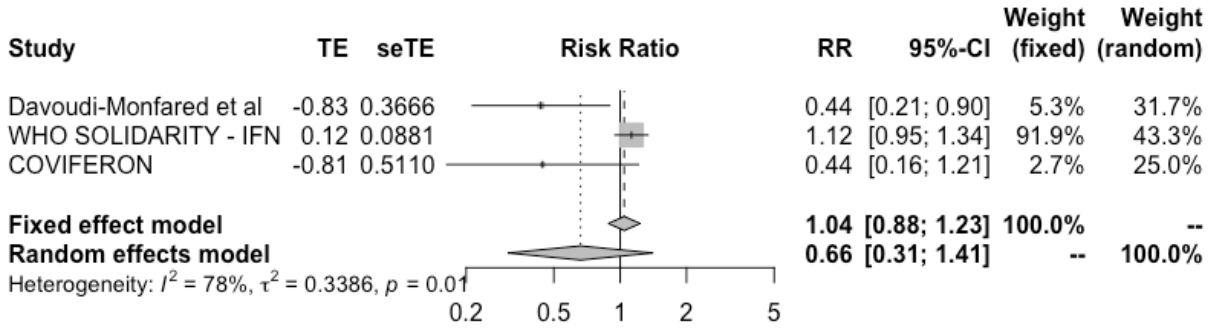
Interferon Beta-1a

See Summary of findings Table 9, Appendix 1

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

- Interferon beta-1a (subcutaneous) probably does not reduce mortality, RR 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to 3.7%); Moderate certainty ⊕⊕⊕◯ (Figure 15.)
- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕◯
- It is uncertain if interferon beta-1a (subcutaneous) affects symptom resolution or improvement; HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕◯◯◯
- Interferon beta-1a (inhaled) may increase symptom resolution or improvement, HR 2.19 (95%CI 1.03 to 4.69); RD 26.4% (95%CI 1.1% to 38.1%); Low certainty ⊕⊕◯◯

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

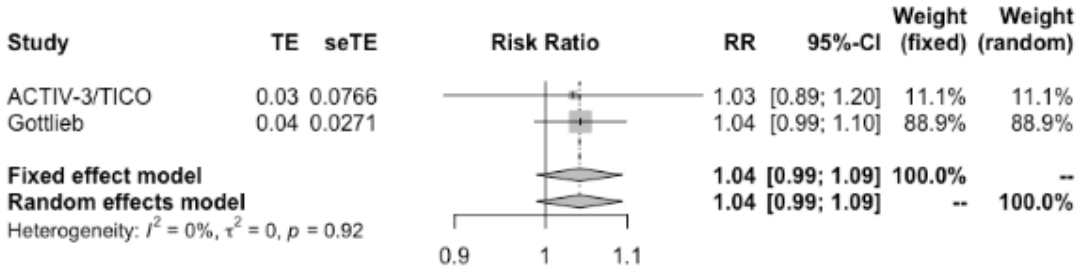


Bamlanivimab (monoclonal antibody)

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

- It is uncertain if bamlanivimab reduces mortality or mechanical ventilation requirements; Very low certainty ⊕◯◯◯
- Bamlanivimab probably does not significantly improve time to symptom resolution, RR 1.04 (95%CI 0.99 to 1.09); RD 2.4% (95%CI -0.6% to 5.4%); Moderate certainty ⊕⊕⊕◯ (Figure 16.)
- It is uncertain if bamlanivimab increases the risk of severe adverse events; Very low certainty ⊕◯◯◯

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



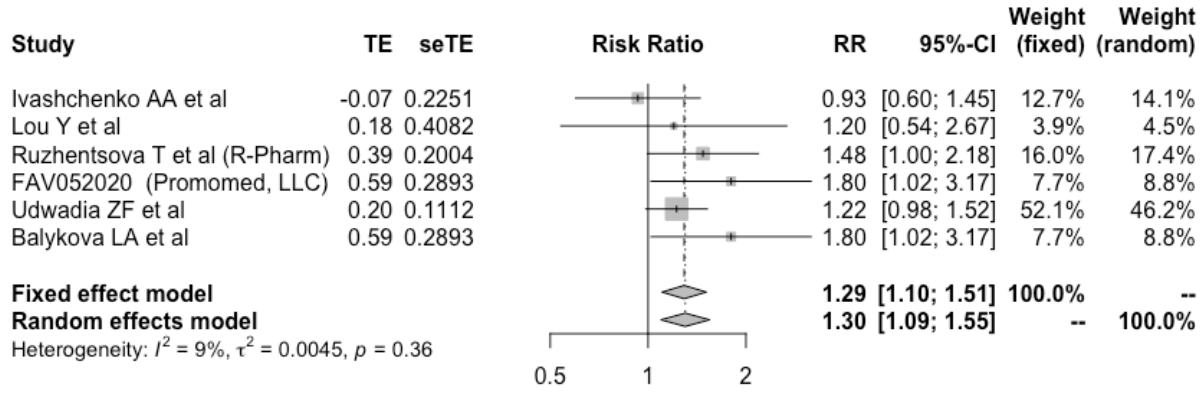
Favipiravir

See Summary of findings Table 10, Appendix 1

We identified eleven RCTs including 1346 patients in which favipiravir was compared against standard of care or other treatments. Six studies including 759 patients reported on favipiravir versus standard of care. All studies included patients with mild to moderate disease. Our results showed:

- It is uncertain if favipiravir affects mortality or mechanical ventilation requirements; Very low certainty ⊕◯◯◯
- Favipiravir may increase symptom resolution or improvement, RR 1.3 (95%CI 1.09 to 1.55); RD 18.2% (95%CI 5.5% to 33.3%); Low certainty ⊕⊕◯◯ (Figure 17.)
- It is uncertain if favipiravir increases the risk of severe adverse events; Very low certainty ⊕◯◯◯

Figure 17. Symptom resolution at 7-15 days in randomized studies comparing favipiravir with standard of care in patient with COVID-19



Ivermectin

See Summary of findings Table 11, Appendix 1

We identified twenty six RCT including 3600 patients in which ivermectin was compared against standard of care or other treatments. Studies included patients with mild to severe disease, as shown by the mortality rates in the control arms, which ranged from 0% to 21.7%. Most studies have important methodological limitations including inappropriate randomization process and lack of allocation concealment. Our results showed:

- Ivermectin may not significantly reduce mortality, RR 0.94 (95%CI 0.51 to 1.73); RD -0.96% (95%CI -7.8% to 11.7%); Low certainty ⊕⊕◯◯ (Figure 18) (based on low risk of bias studies)
- It is uncertain if ivermectin affects mechanical ventilation requirements, RR 0.89 (95%CI 0.38 to 2.07); RD -1.9% (95%CI -10.7% to 18.5%); Very low certainty ⊕◯◯◯
- Ivermectin probably does not improve symptom resolution or improvement, RR 1 (95%CI 0.9 to 1.11); RD 0% (95%CI -6% to 6.6%); Moderate certainty ⊕⊕⊕◯ (based on low risk of bias studies)
- It is uncertain if ivermectin affects symptomatic infection, RR 0.14 (95%CI 0.09 to 0.21); RD -15% (95%CI -13.7% to -15.8%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects severe adverse events, RR 1.04 (95%CI 0.32 to 3.38); RD 0.4% (95%CI -6.9% to 24.2%); Very low certainty ⊕◯◯◯

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

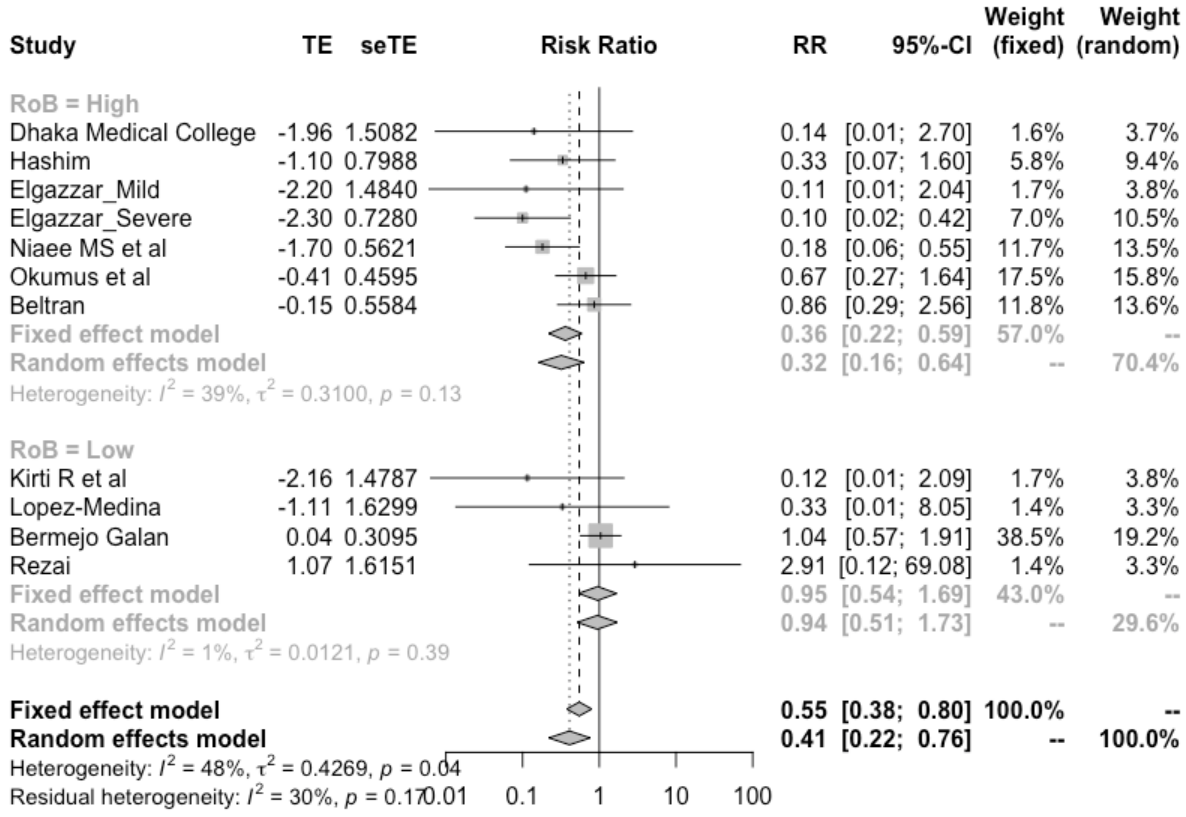
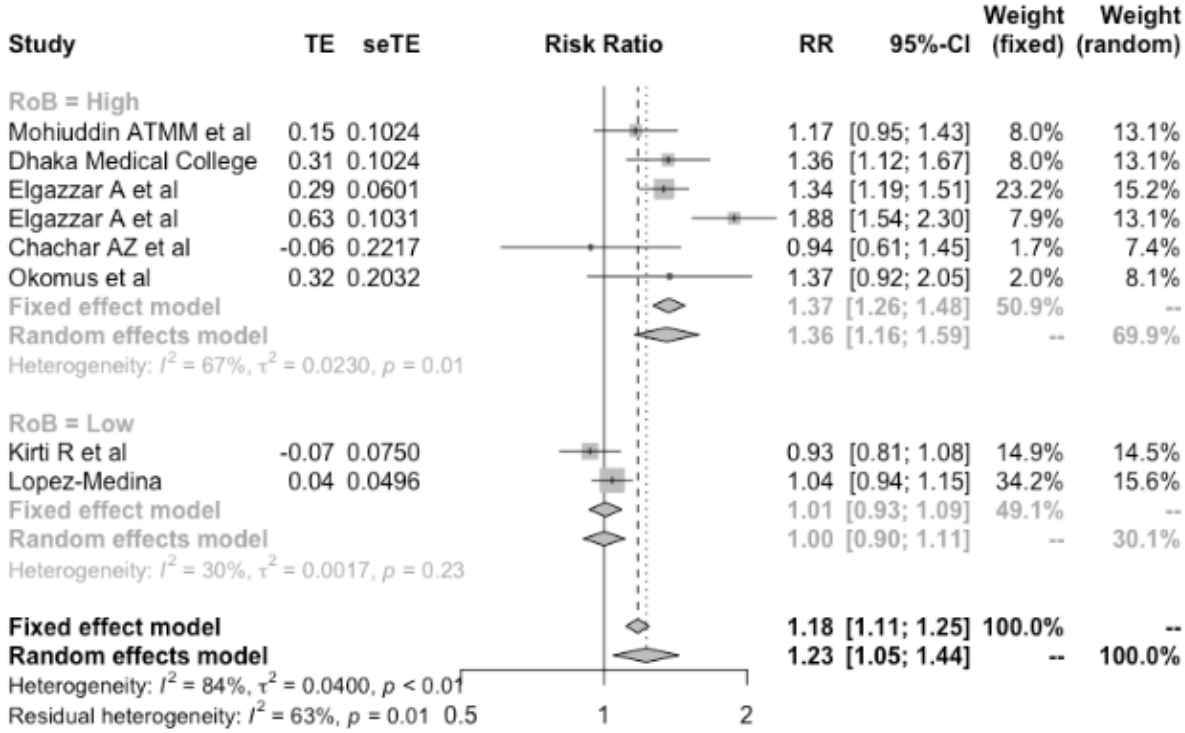


Figure 19: Symptom resolution or improvement in randomized studies comparing ivermectin with standard of care or other treatments in patients with COVID-19



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

Baricitinib

We identified one RCT including 1033 patients in which baricitinib in combination with remdesivir was compared against remdesivir combined with placebo. The study included moderate to severe patients. Our results showed:

- Baricitinib may reduce mortality, RR 0.65 (95%CI 0.39 to 1.07); RD -2.5% (95%CI -5.4% to 0.4%); Low certainty ⊕⊕◯◯
- Baricitinib may reduce mechanical ventilation, RR 0.65 (95%CI 0.46 to 0.93); RD -5.2% (95%CI -9.5% to -0.94%); Low certainty ⊕⊕◯◯

- Baricitinib may improve time to symptom resolution, RR 1.24 (95%CI 1.07 to 1.44); Low certainty ⊕⊕◯◯
- Baricitinib may not increase severe adverse events, RR 0.65 (95%CI 0.46 to 0.93); RD -4.9% (95%CI -9.6% to -0.2%); Low certainty ⊕⊕◯◯

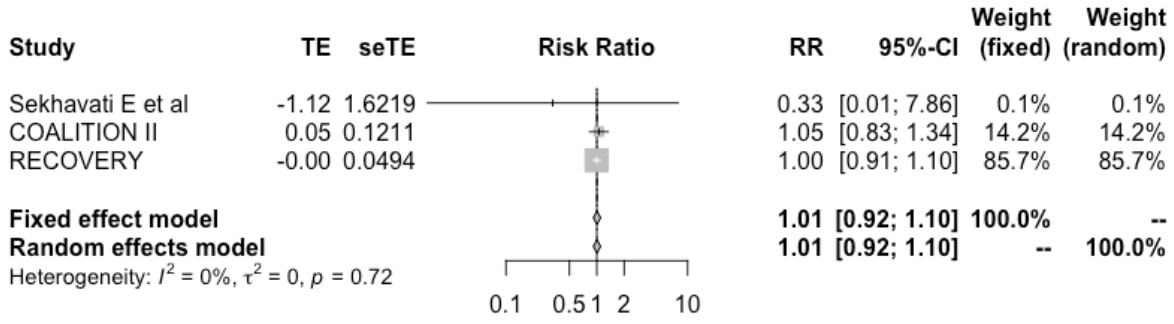
Azithromycin

See Summary of findings Table 12, Appendix 1

We identified seven RCT including 9716 patients in which azithromycin was compared against standard of care or other treatments. RECOVERY trial was the biggest study including 7762 patients with severe disease (mortality in the control arm 19%). Our results showed:

- Azithomycin probably does not reduce mortality, RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ (Figure 19.)
- Azithomycin probably does not reduce mechanical ventilation requirements, RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⊕⊕⊕◯
- Azithromycin does not improve time to symptom resolution, RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕
- It is uncertain if azithromycin increases severe adverse events, RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯

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

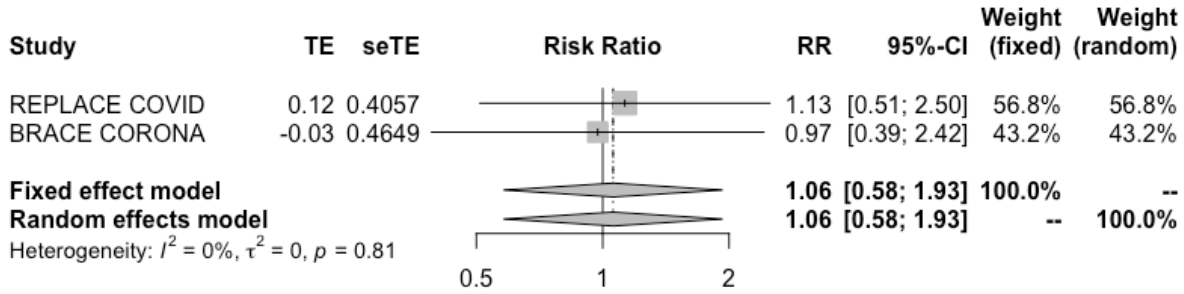


ACEI/ARB discontinuation

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

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

Figure 20. Mortality in randomized studies comparing discontinuation vs continuation of ACEI/ARB in patients with COVID-19



Colchicine

See Summary of findings Table 13, Appendix 1

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

- Colchicine may reduce mortality, RR 0.45 (95%CI 0.18 to 1.12); RD -8.8% (95%CI -13.1% to 1.9%); Low certainty ⊕⊕◯◯ (Figure 21.)
- Colchicine may reduce mechanical ventilation requirements, RR 0.48 (95%CI 0.24 to 0.96); RD -9% (95%CI -13.1% to -0.7%); Low certainty ⊕⊕⊕◯
- Colchicine does not significantly increase severe adverse events, RR 0.78 (95%CI 0.61 to 1); RD -2.2% (95%CI -4% to 0%); High certainty ⊕⊕⊕⊕
- Colchicine may not significantly increase pulmonary embolism, RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⊕◯◯◯

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

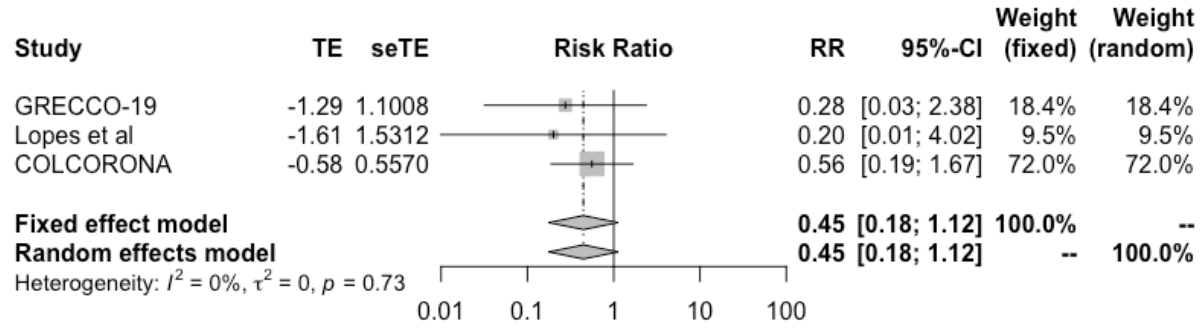
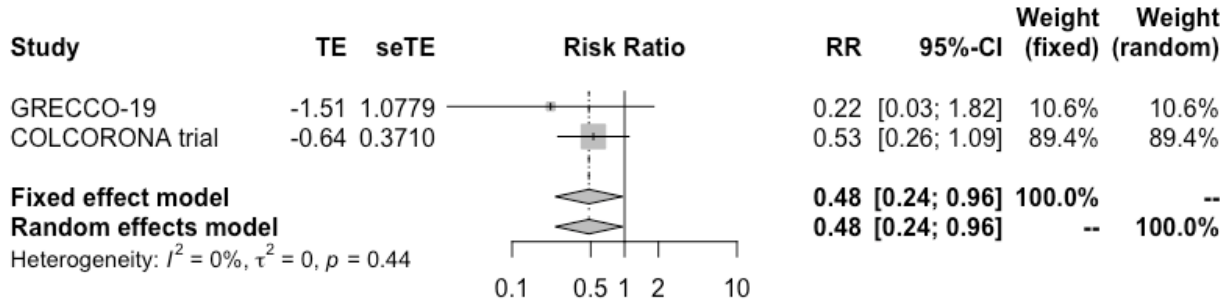


Figure 22. Mechanical ventilation in randomized studies comparing colchicine vs standard of care in patients with COVID-19



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

Full description of included studies

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

Table 5. Description of included studies and interventions effects

99mTc-MDP Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence**
RCT					
Yuan et al;[13] preprint; 2020	Patients with mild COVID-19 infection. 10 assigned to 99mTc-MDP 5/ml once a day for 7 days and 11 assigned to standard of care	Median age 61 ± 20, male 42.9%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) continuation Continuing ACEIs OR ARBs may not increase mortality or mechanical ventilation requirements. Further research is needed to confirm or discard these findings					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
REPLACE COVID trial;[14] Cohen et al; Peer reviewed; 2020	Patients with mild to severe COVID-19 previously treated with ACEI/ARB. 75 assigned to continuation of ACEI/ARB and 77 assigned to discontinuation of ACEI/ARB	Mean age 62 ± 12, male 55.5%, hypertension 100%, diabetes 37%, COPD 17%, asthma %, CHD 12%,	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1.06 (95%CI 0.58 to 1.93); RD 1% (95%CI -6.7% to 14.9%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.63 to 1.39); RD -1.04% (95%CI -6.4% to 6.7%); Moderate certainty ⨁⨁◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
BRACE CORONA trial;[15] Lopes et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 334 assigned to continuation of ACEI/ARB and 325 assigned to discontinuation of ACEI/ARB	Median age 55.5 ± 19, male 59.6%, hypertension 100%, diabetes 31.9%, COPD %, asthma 3.9%, CHD 4.6%, CKD 1.4%, , cancer 1.5%,	Steroids 49.5%, hydroxychloroquine 19.7%, tocilizumab 3.6%, azithromycin 90.6%, convalescent plasma %, antivirals 42%	Some Concerns for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Open label study with blinded outcome assessment. Significant number of patients excluded after randomization.	

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) treatment Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ATTRACT trial;[16] Tornling et al; Preprint; 2020	Patients with moderate to severe COVID-19. 51 assigned to C21 (ARB) 200mg a day for 7 days and 55 assigned to SOC	Mean age 52.6 ± 10.3, male 75.5%, hypertension 30.2%, diabetes 34%	Steroids 84.9%, remdesivir 67%, hydroxychloroquine 13.2%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Nouri-Vaskeh et al;[17] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection and non-treated hypertension. 41 assigned to losartan 50mg a day for 14 days and 39 assigned to Amlodipine 5mg a day for 14 days	Mean age 63.5 ± 16, male 51.2%, diabetes 23.7%, COPD 15%, asthma %, CHD 18.7%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Anakinra Anakinra may not improve time to symptom resolution. Further research is needed to confirm or discard these findings					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
CORIMUNO-ANA-1 trial;[18] Bureau et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 59 assigned to anakinra 400mg a day for 3 days followed by 200mg for 1 day followed by 100mg for 1 day and 55 assigned to SOC	Median age 66 ± 17, male 70%, diabetes 29.8%, COPD 7.9%, asthma 7%, CHD 31.6%, cancer 9.6%,	Steroids 46.5%, hydroxychloroquine 5.3%, lopinavir-ritonavir 3.5%, tocilizumab 0.8%, azithromycin 24.6%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 0.93 (95%CI 0.69 to 1.26); RD -4.2% (95%CI -18.8% to 15.8%) Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Anticoagulants There are specific recommendations on the use of antithrombotic agents.[8] Studies are ongoing to evaluate the preventive and therapeutic use of antithrombotic agents to mitigate the thrombotic and hemorrhagic events and assess the potential drug interactions with investigational drugs.					
Study; publication status	**Patients and 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;[19] Bertoldi Lemos et al; peer reviewed; 2020	Patients with critical COVID-19. Ten assigned to low molecular weight heparin therapeutic dose and ten assigned to prophylactic dose	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, coronary heart disease 10%, immuno-suppression 5%	Steroids 70%, hydroxy-chloroquine 25%, azithromycin 90%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Non-RCT					
Tang et al;[20] peer reviewed; 2020	Patients with severe COVID-19 infection. 99 received Anticoagulants (heparins mostly in prophylaxis dose) for 7 days or longer and 350 received alternative treatment	Mean age 65.1 ± 12, male 59.6%, comorbidities 60.6%	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression score was implemented to adjust for potential confounders (age, sex,	**Mortality:** Very low certainty ⊕◯◯◯

	schemes			comorbidities and coagulation parameters)	
Motta et al;[21] preprint; 2020	Patients with moderate to severe COVID-19 infection. 75 received anticoagulants (heparins in therapeutic dose) and 299 received heparins in prophylactic dose	Mean age 64.7 ± 18.1, male 58.8%, diabetes 31.6%, chronic lung disease 25.1%, coronary heart disease 56.7%, chronic kidney disease 10.7%, immuno-suppression 2.9%, cancer 12.3%	Hydroxychloroquine 58.6%, lopinavir-ritonavir 50.8%, tocilizumab 15%, ATB 58%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, race, ethnicity, body-mass index, smoking status, diabetes immunosuppression, heart disease, pulmonary disease, kidney disease, cancer, hyperlipidemia, need for intensive care unit admission, invasive mechanical ventilation, pharmacological treatments, laboratory measurements)	
Ayerbe et al;[22] peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 1734 received anticoagulants heparins in any dose and 285 received alternative treatment schemes	Mean age 67.6 ± 15.5, male 60.5%,	Steroids 46.2%, hydroxychloroquine 89.5%, lopinavir-ritonavir 59.3%, tocilizumab 20.3%, azithromycin 58.9%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, clinical parameters and concomitant interventions)	

Stabile et al;[23] preprint; 2020	Patients with severe to critical COVID-19 infection. 131 received heparins in therapeutic dosage (enoxaparin 40mg a day) and 126 received heparins in prophylactic dosage (enoxaparin 70/100 mg/kg every 12 hs)	Mean age 69.3 ± 10.7, male 67.7%, hypertension 63%, diabetes 17.9%, chronic lung disease 8.6%, asthma %, coronary heart disease 17.1%, chronic kidney disease 8.6%, cancer 7%, obesity 9.7%	Steroids 56.8%, hydroxychloroquine 92.2%, lopinavir-ritonavir 91.8%, tocilizumab 9.7%, azithromycin 90.3%,	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (other treatments)	
Jonmaker et al;[24] preprint; 2020	Patients with critical COVID-19 infection. 37 received heparins in therapeutic dosage (tinzaparin ≥175 IU/kg of body weight per daily), 48 received heparins in intermediate dosage (tinzaparin >4500 IU daily to <175 IU/kg of body weight daily) and 67 received heparins in prophylactic dosage (tinzaparin 2500-4500 IU daily)	Mean age 61 ± 17, male 82.2%, hypertension 45.4%, diabetes 16.5%, chronic lung disease 19.7%, coronary heart disease 7.9%, chronic kidney disease 5.9%, immuno-suppression 5.3%, cancer 5.9%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (sex, age, body-mass index, invasive mechanical ventilation, and Simplified Acute Physiology Score III)	
Patel et al;[25] preprint; 2020	Patients with moderate to severe COVID-19 infection. 78 received anticoagulants in therapeutic dosage and 1298 received anticoagulants in prophylactic dosage	Mean age NR, male 54.5%, hypertension 58.6%, diabetes 34.7%, chronic lung disease 10.7%, asthma 10.7%, coronary heart disease 15.4%, chronic kidney disease 19.3% immuno-suppression 1.3%, cancer 10.1%	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, race and ethnicity, body mass index (BMI), Charlson score, glucose	

				on admission, and use of antiplatelet agents)	
Schiavone et al;[26] peer reviewed; 2020	Patients with COVID-19 infection. 394 received heparins and 450 did not received heparins	Mean age 63.4 ± 16.1, male 61.7%, hypertension 45.1%, diabetes 16.6%, chronic lung disease 7.4%, coronary heart disease 9.2%, chronic kidney disease 7.5%, cerebrovascular disease 3.9%, obesity 9.4%	Steroids 11%, hydroxychloroquine 80.7%, tocilizumab 15%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Musoke et al;[27] peer-reviewed; 2020	Patients with COVID-19 infection. 101 received low molecular weight heparin 1 mg/kg q12 and 254 received alternative treatment schemes (prophylactic dosage or no anticoagulants)	Mean age 66.2 ± 14.2, male 51%, hypertension 77%, diabetes 47%, chronic lung disease 13%, asthma 8%, coronary heart disease 17%, chronic kidney disease 18%	Steroids 29%, hydroxychloroquine 61%, tocilizumab 12%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, gender, comorbidities, race, D-dimer test, venous thromboembolism, major bleeding)	
Hsu et al;[28] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 16 received intermediate dosage anticoagulants (low molecular weight heparin 40 mg twice daily or HSQ 7500 units three times daily) and 377 received prophylactic	Mean age 60 ± 24, male 55.2%, diabetes 35.1%, chronic lung disease 9.9%, coronary heart disease 12.2%	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, indicators of COVID-19 severity, baseline, comorbidities, and	

	dosage anticoagulants			baseline anticoagulant use)	
Paolisso et al;[29] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 89 received anticoagulants in intermediate dosage (low molecular weight heparin 40-60mg twice day) and 361 received anticoagulants in prophylactic dosage (low molecular weight heparin 40mg a day)	Median age 67 ± 24, male 63%, hypertension 50.7%, diabetes 14.4%, chronic lung disease 12.9%, coronary heart disease 8.2%, chronic kidney disease 6.7%, cancer 11.3%,	Hydroxychloroquine 80.7%, tocilizumab 16%,	High for mortality Notes: Non-randomized study with retrospective design. Propensity score and matching were implemented to adjust for potential confounders (age, hypertension, hemoglobin value, PaO2/FIO2 value, administration of hydroxychloroquine and Tocilizumab)	
Ferguson et al;[30] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 46 received anticoagulants in therapeutic dosage and 95 received anticoagulants in prophylactic dosage	Mean age 64 ± 19, male 55.3%, hypertension %, diabetes 24.1%	Remdesivir 14.2%, hydroxychloroquine 70.9%, azithromycin 62.4%, convalescent plasma 19.8%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Trinh et al;[31] preprint; 2020	Patients with severe to critical COVID-19 infection. 161 received anticoagulants in therapeutic dosage dosage and 83 received anticoagulants in prophylactic dosage	Mean age 59.6 ± 13.2, male 66%, hypertension 50%, diabetes 36.9%, chronic lung disease 4.1%, asthma 12.3%, chronic kidney disease 9.8%, cerebrovascular disease 6.2%, cancer 7.8%, obesity %	Steroids 83.2%, remdesivir 4.5%, hydroxychloroquine 88.4%, tocilizumab 14.3%,	High for mortality Notes: Non-randomized study with retrospective design. Regression and propensity score matching were implemented to adjust for potential confounders	

				(anticoagulation for 5 days, age, gender, history of chronic kidney disease, changes in creatinine over time, asthma, concurrent therapies, lactate, baseline sequential organ failure assessment (SOFA) score, and time from intubation day)	
Secco et al;[32] peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 48 received anticoagulants in therapeutic dosage and 64 received anticoagulants in prophylactic dosage	Median age 69 ± 23, male 67.8%, hypertension 40.9%, diabetes 14.8%,	Hydroxychloroquine 91.3%, tocilizumab 8.7%,	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Gonzalez-Porras et al;[33] preprint; 2020	Patients with COVID-19 infection. received Anticoagulants in intermediate dosage (low molecular weight heparin 1mg/kg once a day or equivalent) and received anticoagulants in prophylactic dosage (low molecular weight heparin 40 mg once daily or equivalent)	Mean age 72.5 ± 13.8, male 59.8%, comorbidities 48.9%	Steroids 49.4%, hydroxychloroquine 63.9%, lopinavir-ritonavir 56.2%, tocilizumab 30%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Nadkarni et al;[34] peer-reviewed;	Patients with moderate to critical	Median age 65 ± 24, male 66%,	NR	High for mortality	

2020	COVID-19 infection. 766 received anticoagulants in therapeutic dosage and 1860 received anticoagulants in prophylactic dosage	hypertension 34.8%, diabetes 22.6%, chronic lung disease 4.9%, asthma 6.3%, coronary heart disease 8.3%, chronic kidney disease 6.8%, cancer 7.8%		Notes: Non-randomized study with retrospective design. Inverse probability treatment weighted models were implemented to adjust for potential confounders (and age, sex, race and ethnicity, body mass index, history of hypertension, atrial fibrillation, heart failure, chronic kidney disease or renal failure, use of anticoagulants or antiplatelet agents prior to hospitalization, month of admission, intubation during hospitalization, time of implementation of institutional guidelines for AC at Mount Sinai, respiratory rate, oxygen saturation, and D-dimer at admission)	
Al-Samkari et al;[35] Peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 384 received anticoagulants in therapeutic dosage and 2425 received anticoagulants in prophylactic dosage	Median age 61 ± 18, male 64.5%, hypertension 61%, diabetes 40.5%, chronic lung disease 8.4%, asthma 10.6%, CHD 13.3%, CKD 12.6%, , immunosuppression 2.4%, cancer 5%	NR	High for mortality Notes: Non-randomized study. Retrospective design. Inverse probability treatment weighted models were implemented to adjust for potential confounders (age; sex; race; ethnicity; commorbodotoes;	

				duration of symptoms before ICU admission; severity-of-illness; and concurrent therapies received on ICU admission)	
Roomi et al;[36] Peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 34 received anticoagulants in therapeutic dosage and 142 received anticoagulants in prophylactic dosage	age NR , male NR, hypertension 74%, diabetes 41.4%, chronic lung disease 16%, asthma %, CHD 18.7%, CKD 22.1%	Steroids 28.4%, hydroxychloroquine 99.4%, tocilizumab 30%,	High for mortality Notes: Non-randomized study. Retrospective design. Logistic regression was implemented to adjust for potential confounders (baseline comorbidities and demographics)	

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

					studies): No information **Adverse events:** No information
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;[38] Tieu et al; Preprint; 2020	Patients with mild to moderate COVID-19. 39 assigned to Artemisinin 500mg for 5 days and 21 assigned to SOC	Mean age 43.3 ± 11.9, male 63.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯

Auxora Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Miller et al;[39] peer-reviewed; 2020	Patients with severe COVID-19 infection. 17 assigned to Auxora initial dose 2.0 mg/kg (max 250 mg), followed by 1.6 mg/kg (max 200 mg) at 24 and 48 h and nine assigned to standard of care	Mean age 60 ± 12, male 46.1%, hypertension 46.1%, diabetes 38.4%,	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. Analysis performed on a subgroup (patients that required high-flow nasal cannula (HFNC) were excluded from primary analysis).	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very Low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Azithomycin Azithrimycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Sekhavati et al;[40] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection.	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; High for	**Mortality:** RR 1.01 (95%CI 0.92 to 1.1); RD 0.2% (95%CI -

	56 assigned to azithromycin 500 mg twice-daily and 55 assigned to standard of care			symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	1.3% to 1.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.78 to 1.13); RD -1% (95%CI -3.8% to 2.2%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.02 (95%CI 0.99 to 1.04); RD 1.2% (95%CI -0.6% to 2.4%); High certainty ⊕⊕⊕⊕ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.23 (95%CI 0.51 to 2.96); RD 2.4% (95%CI -5% to 19.9%); Very low certainty ⊕◯◯◯
Guvenmez et al;[41] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600mg twice a day for 5 days and 12 assigned to Azithromycin 500mg on first day followed by 250mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COALITION II trial;[42] Furtado et al; peer-reviewed; 2020	Patients with severe COVID-19. 214 assigned to azithromycin 500mg once a day for 10 days and 183 assigned to standard of care	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, coronary heart disease 5.8%, chronic kidney disease 11%, cerebrovascular disease 3.8%, immunosuppression %, cancer 3.5%, obesity %	Steroids 18.1%, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir 1%, tocilizumab %, azithromycin %, convalescent plasma %, 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;[43] Horby et al; preprint; 2020	Patients with moderate to critical COVID-19. 2582 assigned to azithromycin 500mg a day for 10 days and	Mean age 65.3 ± 15.6, male 62%, diabetes 27.5%, COPD 24.5%, asthma %, coronary heart disease 26.5%, chronic kidney disease	Steroids 61%,	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection and adverse events	

	5182 assigned to standard of care	6%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Rashad et al;[44] preprint ; 2020	Patients with mild to moderate COVID-19. 107 assigned to AZT 500mg a day for 7 days, 99 assigned to Clarithromycin 1000mg a day for 7 days and 99 assigned to SOC	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PRINCIPLE trial;[45] Butler et al; peer reviewed; 2021	Patients with mild to severe COVID-19 infection. 500 assigned to azithromycin 500mg a day for 3 days and 629 assigned to SOC	Mean age 60.7 ± 7.8, male 43%, hypertension 42%, diabetes 18%, COPD 38%, asthma %, CHD 15%, cerebrovascular disease 6%,	NR	Some Concerns for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant loss to follow-up.	

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

Baricitinib Baricitinib may reduce mortality, mechanical ventilation requirements and may improve time to symptom resolution. However certainty of the evidence was low because of risk of bias and imprecision. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
ACTT-2 trial;[47] Kalil et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 515	Mean age 55.4 ± 15.7, male 63.1%, comorbidities 84.4%	Steroids 11.9%, convalescent plasma %	Some Concerns for mortality and mechanical ventilation;	**Mortality:** RR 0.65 (95%CI 0.39 to 1.07); RD -2.5% (95%CI -5.4% to

	assigned to baricitinib + remdesivir 4mg a day for 14 days + 200mg once followed by 100mg a day for 10 days and 518 assigned to remdesivir			some concerns for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	0.4%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.65 (95%CI 0.46 to 0.93); RD -5.2% (95%CI -9.5% to -0.94%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.24 (95%CI 1.07 to 1.44); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.65 (95%CI 0.46 to 0.93); RD -4.9% (95%CI -9.6% to -0.2%); Low certainty ⊕⊕◯◯

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;[48] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to Baloxavir 80mg a day on days	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease	Antivirals 100%, interferon 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	**Mortality:** No information **Invasive mechanical ventilation:** No information

	1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	13.8%		events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Bamlanivimab (monoclonal antibody) **Bamlanivimab may not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
BLAZE-1 trial;[49] Chen et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to bamlanivimab 700 mg, 2800 mg or 7000 mg once and 143 assigned to standard of care	Mean age 45 ± 68, male 55%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.04 (95%CI 0.99 to 1.09); RD 2.4% (95%CI -0.6% to 5.4%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis**
ACTIV-3/TICO trial;[50] Lundgren et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19. 163 assigned to bamlanivimab 7000mg once and 151 assigned to SOC	Median age 71 ± 22, male 66%, hypertension 49%, diabetes 29%, COPD %, asthma 9%, CHD 4%, CKD 11%, obesity 52%	Steroids 49%, remdesivir 95%,	Low for mortality and adverse events; high for symptom resolution. Notes: Significant lost to follow up for	

				symptom improvement/resolution outcome	**studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
Gottlieb et al;[51] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to Bamlanivimab 700-7000mg once, 112 assigned to Bamlanivimab + etesevimab and 156 assigned to SOC	Mean age 44.7 ± 15.7, male 45.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

Bamlanivimab + etesevimab (monoclonal antibodies)

Bamlanivimab + etesevid probably does not significantly improve time to symptom resolution. It is uncertain if it affects mortality, mechanical ventilation requirements or increases severe adverse events. Further research is needed.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Gottlieb et al;[51] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 309 assigned to Bamlanivimab 700-7000mg once, 112 assigned to Bamlanivimab + etesevimab and 156 assigned to SOC	Mean age 44.7 ± 15.7, male 45.4%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.04 (95%CI 0.98 to 1.1); RD 2.4% (95%CI -0.6% to 5.4%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No

					information **Adverse events:** Very Low certainty ⊕◯◯◯
BCG **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Padmanabhan et al;[52] preprint; 2020	Patients with severe COVID-19. 30 assigned to BCG 0.1ml once and 30 assigned to standard of care	Mean age 45.2 ± 36.5, male 60%, obesity 23%	Remdesivir 6.6%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Bromhexine hydrochloride Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Li T et al;[53] peer-reviewed; 2020	Patients with severe to critical COVID-19. 12 assigned to bromhexine hydrochloride 32mf three times a day for 14 days and 6 assigned to standard of care	Median age 52 ± 15.5, male 77.8%, hypertension 33.3%, diabetes 11.1%	Steroids 22.2%, interferon 77.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** Very low certainty ⨁◯◯◯
Ansarin et al;[54] peer-reviewed; 2020	Patients with mild to critical COVID-19. 39 assigned to bromhexine 8 mg three time a day for 14 days and 39 assigned to standard of care	Mean age 59.7 ± 14.9, male 55.1%, hypertension 50%, diabetes 33.3%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mikhaylov et al;[55] Preprint; 2021	Patients with exposed to COVID-19 infection. 25 assigned to bromhexine 12mg a day and 25 assigned to SOC	Mean age 40.6 ± 7.6, male 42%, comorbidity 6%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might	

				have introduced bias to symptoms and adverse events outcomes results.	
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;[56] Peer reviewed; 2020	Patients with mild COVID-19. 30 assigned to Chloroquine nasal drops 0.03% six times a day for 10 days and 30 assigned to SOC	Mean age 34.9 ± 10.35, male 78.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

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

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;[44] preprint ; 2020	Patients with mild to moderate COVID-19.	Mean age 44.4 ± 18, male 29.8%	NR	High for mortality and mechanical ventilation;	**Mortality:** No information

	107 assigned to AZT 500mg a day for 7 days, 99 assigned to Clarithromycin 1000mg a day for 7 days and 99 assigned to SOC			High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
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;[58] Altay et al; preprint; 2020	Patients with mild to moderate COVID-19. 71 assigned to Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine) and 22 assigned to standard of care	Mean age 35.6 ± 47, male 60%	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Outcome assessors not blinded. Possible reporting bias.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: Very low certainty ⨁◯◯◯
Colchicine **Colchicine may reduce mortality and mechanical ventilation requirements, however certainty of the evidence was low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
GRECCO-19 trial;[59] Deftereos et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 50 assigned to colchicine 1.5 mg once followed by 0.5 mg twice daily until hospital discharge or 21 days and 55 assigned to standard of care	Median age 64 ± 11, male 58.1%, hypertension 45%, diabetes 20%, chronic lung disease 4.8%, coronary heart disease 13.3%, immunosuppression 3.75%	Hydroxychloroquine 98%, lopinavir-ritonavir 31.4%, tocilizumab 3.8%, azithromycin 92%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.45 (95%CI 0.18 to 1.12); RD -8.8% (95%CI -13.1% to 1.9%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.48 (95%CI 0.24 to 0.96); RD -9% (95%CI -13.1% to -0.7%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.78 (95%CI 0.61 to 1); RD -2.2% (95%CI -4% to 0%); High certainty ⨁⨁⨁⨁
Lopes et al;[60] preprint; 2020	Patients with moderate to severe COVID-19 infection. 19 assigned to colchicine 0.5 mg three times a day, for 5 days followed by 0.5 mg twice daily for 5 days and 19 assigned to standard of care	Median age 50.75 ± 26.2, male 40%, diabetes 31.4%, chronic lung disease 14.2%, coronary heart disease 40%	Steroids 40%, hydroxychloroquine 100%, azithromycin 100%, heparin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Salehzadeh et al;[61] preprint; 2020	Patients with moderate to critical	Mean age 56, male 41%, hypertension	Hydroxychloroquine 100%	High for mortality and invasive mechanical	

	COVID-19. 50 assigned to colchicine 1 mg a day for 6 days and 50 assigned to standard of care	11%, diabetes 11%, chronic lung disease 4%, coronary heart disease 15%, chronic kidney disease 5%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Pulmonary embolism:** RR 5.55 (95%CI 1.23 to 25); RD 0.4% (95%CI 0.02% to 2.2%); Low certainty ⨁⨁◯◯
Tardif et al;[62] Preprint; 2020	Patients recently diagnosed mild COVID-19 and risk factors for severe disease. 2235 assigned to colchicine 1mg a day for 3 days followed by 0.5mg for a total of 27 days and 2253 assigned to SOC	Mean age 54.3 , male 46%, hypertension 36.3%, diabetes 19.9%, COPD 26.5%, CHD 5.4%, obesity 45.7%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

Convalescent plasma

Convalescent plasma probably does not reduce mortality nor significantly reduces mechanical ventilation requirements or improves time to symptom resolution.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Li et al;[63] 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	Steroids 39.2%, antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	**Mortality:** RR 0.99 (95%CI 0.92 to 1.06); RD -0.1% (95%CI -1.3% to 1%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.89 (95% CI 0.76 to 1.04); RD -1.9%

		10.7%		inappropriate.	(95%CI -4.2% to 0.7%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** RR 1 (95% CI 0.93 to 1.08); RD 0% (95%CI -4.2% to 4.8%); High certainty ⨁⨁⨁⨁ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 1.26 (95% CI 0.83 to 1.9); RD 2.7% (95%CI -1.7% to 9.4%); Very low certainty ⨁◯◯◯
CONCOVID trial; Gharbharan et al;[64] 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;[65] preprint; 2020	Patients with severe COVID-19. 38 assigned to convalescent plasma 250-300 ml once and 43 assigned to standard of care	Mean age 60.8 ± 15.5, male 54.3%, hypertension 39.5%, diabetes 20.9%, chronic lung disease 12.3%, asthma NR%, coronary heart disease 18.5%, chronic kidney disease 4.9%	Steroids 56.8%, remdesivir 4.94%, hydroxychloroquine 86.4%, lopinavir-ritonavir 41.9%, tocilizumab 28.4%, azithromycin 61.7%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
PLACID trial;[66] Agarwal et al; preprint; 2020	Patients with severe COVID-19. 235 assigned to convalescent plasma 200 ml twice in 24hs and 229 assigned to standard of care	Median age 52 ± 18, male 76.3%, hypertension 37.3%, diabetes 43.1%, chronic lung disease 3.2%, coronary heart disease 6.9%, chronic kidney disease 3.7%, cerebrovascular disease 0.9%, cancer 0.2%, obesity 7.1%	Steroids 64.4%, remdesivir 4.3%, hydroxychloroquine 67.7%, lopinavir-ritonavir 14.2%, tocilizumab 9%, azithromycin 63.8%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events	

				outcomes results.	
PLASM-AR trial;[67] Simonovich et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 228 assigned to convalescent plasma and 105 assigned to standard of care	Mean age 62 ± 20, male 67.6%, hypertension 47.7%, diabetes 18.3%, COPD 7.5%, asthma 4.2%, coronary heart disease 3.3%, chronic kidney disease 4.2%	Steroids 93.3%, hydroxychloroquine 0.3%, lopinavir-ritonavir 3%, tocilizumab 4.2%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
ILBS-COVID-02 trial;[68] 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;[69] preprint; 2020	Patients with severe to critical COVID-19. 20 assigned to convalescent plasma 200 ml twice and 20 assigned to standard of care	Mean age 51.6 ± 13.7, male 80%, hypertension 25%, diabetes 30%, COPD 7.5%, asthma %, coronary heart disease 10%, chronic kidney disease 5%	Steroids 12.5%, hydroxychloroquine 92.5%, lopinavir-ritonavir 85%, tocilizumab 30%, azithromycin 87.5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Fundacion INFANT-Plasma trial;[70] 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	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

		disease 2.5%, cancer 3.8%, obesity 7.5%			
PICP19 trial;[71] Ray et al; preprint; 2020	Patients with severe COVID-19. 40 assigned to convalescent plasma 200 ml and 40 assigned to standard of care	Mean age 61 ± 11.5, male 71.2%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
RECOVERY-Plasma trial;[72] Horby et al; Other; 2020	Patients with severe to critical COVID-19 infection. 5795 assigned to CP 275ml a day for two days and 5763 assigned to SOC	Median age 63.5 ± 14.7, male 64.2%, diabetes 26%, COPD 24%, CHD 22%	Steroids <1%, lopinavir-ritonavir <1%, azithromycin 10%, colchicine 14%	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Baklaushev et al;[73] peer reviewed; 2020	Patients with moderate to severe COVID-19. 46 assigned to CP 640ml divided in two infusions and 20 assigned to SOC	Age 56.3 ± 11 , male 60.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Balcells et al;[74] peer reviewed; 2020	Patients with moderate to severe COVID-19. 28	Mean age 65.8 ± 65, male 50%, hypertension 67.2%,	Steroids 51.7%, hydroxychloroquine 12%, lopinavir-	Low for mortality and invasive mechanical ventilation; high for	**Mortality:** Very Low certainty ⨁◯◯◯ **Invasive mechanical**

	assigned to convalescent plasma at enrolment, 200 mg twice and 30 assigned to convalescent plasma when clinical deterioration was observed (43.3% received CP in this arm)	diabetes 36.2%, chronic lung disease %, asthma 5.1%, coronary heart disease %, chronic kidney disease 8.6%, cerebrovascular disease 5.1%, immunosuppression 12%, cancer 7%, obesity 12%	ritonavir 1.7%, tocilizumab 3.4%	symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
Non-RCT					
Joyner et al;[75] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 20000 received CP	Median age 62.3 ± 79.3, male 60.8%	NR	Low for specific transfusion related adverse events	**Adverse events:** Transfusion related circulatory overload 0.18%; Transfusion related lung injury 0.10%; Severe allergic transfusion reaction 0.10%
Darunavir-Cobicistat **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
DC-COVID-19 trial;[76] Chen et al; peer-reviewed;	Patients with mild COVID-19 infection. 15 assigned to	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, coronary heart	NR	High for mortality and invasive mechanical ventilation; high for	**Mortality:** No information **Invasive mechanical**

2020	darunavir-Cobicistat 800mg/150 mg once a day for 5 days and 15 assigned to standard of care	disease 26.6%		symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
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;[77] 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
EAT-DUTA AndroCoV trial;[78] Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 43 assigned to Dutasteride 0.5mg a day for 30 days and 44 assigned to SOC	Mean age 41.9 ± 12.4, male 100%, hypertension 21.8%, diabetes 9.2%, COPD 0%, asthma 1.1%, CHD 1.1%, cancer 0%, obesity 10.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Significant lost to follow-up	

					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;[79] Delgado-Enciso et al; preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to electrolyzed saline nebulizations 4 times a day for 10 days and 39 assigned to standard of care	Mean age 47 ± 14.6, male 53.5%, hypertension 18.9%, diabetes 11.9%	Steroids 3.65%, remdesivir %, hydroxychloroquine 7.5%, ivermectin 9.4%, ATB 30.6%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** No information

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;[80] Preprint; 2020	Patients with moderate to severe COVID-19. assigned	NR	NR	High for mortality and mechanical ventilation; High for symptom	**Mortality:** No information

	to enisamium 500mg 4 times a day for 7 days or SOC. Number of patients in each arm not reported.			resolution, infection and adverse events Notes: 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
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					
Mather et al;[81] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 83 received famotidine and 689 received alternative treatment schemes	Mean age 67 ± 16, male 54.7%, hypertension 32.8%, diabetes 22.7%, chronic lung disease 6%, asthma 5%, coronary heart disease 6%, chronic kidney disease 28.2%	Steroids 48.8%, remdesivir 3.5%, hydroxychloroquine 51%, azithromycin 50.6%,	High for mortality Notes: Non-randomized study with retrospective design. Regression and propensity score matching were implemented to adjust for potential confounders (not specified)	**Mortality:** Very low certainty ⊕◯◯◯
Shoaibi et al;[82] preprint; 2020	Patients with moderate to severe COVID-19 infection.	age nr, male 59.6%, hypertension 43%, diabetes 41%, chronic	NR	High for mortality Notes: Non-	

	1623 received famotidine 20 to 40mg and 24404 received alternative treatment schemes	lung disease 17%, asthma %, coronary heart disease 47%, chronic kidney disease 41%, obesity 24%		randomized study with retrospective design. Regression was implemented to adjust for potential confounders (patient demographics and all observed conditions within 30 days prior to or on admission).	
Yeramaneni et al;[83] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 410 received famotidine median cumulative dose of 160mg and 746 received alternative treatment schemes	Mean age 62 ± 16.8, male 47%, hypertension 68.5%, diabetes 38.1%, chronic lung disease 22.4%, coronary heart disease 8.8%	Steroids 30%, remdesivir 0.75%, hydroxychloroquine 62.4%, tocilizumab 3.85%, azithromycin 77.4%	High for mortality Notes: Non-randomized study with retrospective design. Matching and regression was implemented to adjust for potential confounders (age, sex, race, ethnicity, body mass index, comorbidities, and in-hospital hydroxychloroquine).	

Favipiravir

favipiravir may improve time to symptom resolution. It is uncertain if favipiravir 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 and GRADE certainty of the evidence
RCT					
Chen et al; preprint;[84] 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg	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	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No

	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			events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Symptom resolution or improvement:** RR 1.3 (95%CI 1.09 to 1.55); RD 18.2% (95%CI 5.5% to 33.3%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Ivashchenko et al;[85] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 20 assigned to favipiravir 1600 mg once followed by 600 mg twice a day for 12 days, 20 assigned to favipiravir and 20 assigned to standard of care	Mean age not reported	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Lou et al;[48] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to baloxavir 80 mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%,	Antivirals 100%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Doi et al;[86] peer-reviewed; 2020	Patients with mild COVID-19. 44 assigned to favipiravir (early) 1800 mg on day 1 followed by 800 mg twice daily for 10 days and 45 assigned to favipiravir (late) 1800mg on day 6	Median age 50 ± 26.5, male 61.4%, comorbidities 39%	Steroids 2.3%, ATB 12.5%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	

	followed by 800 mg twice daily for 10 days			inappropriate.	
Dabbous et al;[87] preprint; 2020	Patients with mild to moderate COVID-19. 50 assigned to Favipiravir 3200 mg once followed by 1200 mg a day for 10 days and 50 assigned to hydroxychloroquine + oseltamivir 800 mg once followed by 400 mg a day for 10 days + 75 mg a day for 10 days	Mean age 36.3 ± 12, male 50%, any comorbidities 15%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zhao et al;[88] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 7 days, 7 assigned to TCZ 400 mg once or twice and 5 assigned to favipiravir + TCZ	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Khamis et al;[89] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 44 assigned to favipiravir + inhaled interferon beta-1B 1600 mg once followed by 600 mg twice a day for 10 days + 8million UI for 5 days and 45	Mean age 55 ± 14, male 58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart disease 15%, chronic kidney disease 20%	Steroids 67%, tocilizumab 35%, convalescent plasma 58%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	assigned to standard of care				
Ruzhentsova et al;[90] preprint; 2020	Patients with mild to moderate COVID-19. 112 assigned to favipiravir 1800 mg once followed by 800mg twice a day for 10 days and 56 assigned to standard of care	Mean age 42 ± 10.5, male 47%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Promomed; NCT04542694; Other; 2020	Patients with moderate COVID-19. 100 assigned to favipiravir 3200 mg once followed by 600 mg twice a day for 14 days and 100 assigned to standard of care	Mean age 49.68 ± 13.09, male 48.5%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Udwadia et al;[91] 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;[92] peer-reviewed;	Patients with moderate to severe	Mean age 49.7 ± 13, male 50%,	NR	High for mortality and mechanical ventilation;	

2020	COVID-19. 100 assigned to favipiravir 3200mf once followed by 1200mg a day for 14 days and 100 assigned to SOC	hypertension 28.5%, diabetes 9%, COPD 5%, asthma %, CHD 6%,		high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Febuxostat

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Davoodi et al;[93] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to febuxostat 80 mg per day and 30 assigned to HCQ	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Flevuxamine Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Lenze et al;[94] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 80 assigned to fluvoxamine incremental dose to 100 mg three times a day for 15 days and 72 assigned to standard of care	Median age 45.5 ± 20.5, male 28.2%, hypertension 19.7%, diabetes 11%, asthma 17.1%, obesity 56.6%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Helium (inhaled) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Shogenova et al;[95] peer reviewed; 2020	Patients with severe to critical COVID-19. 38 assigned to	Mean age 53.5 ± 16, male 51.4%	NR	High for mortality and mechanical ventilation; High for symptom	**Mortality:** No information **Invasive mechanical**

	Helium 50% to 79% mixed with oxygen and 32 assigned to SOC			resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Hydroxychloroquine and chloroquine

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
CloroCOVID19 trial;[96] Borba et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 41 assigned to chloroquine 600 mg twice a day for 10 days and 40 assigned to chloroquine 450 mg twice on day 1 followed by 450 mg once a day for 5 days	Mean age 51.1 ± 13.9, male 75.3%, hypertension 45.5%, diabetes 25.5%, chronic lung disease NR%, asthma 7.4%, coronary heart disease 17.9%, chronic kidney disease 7.4%, alcohol use disorder 27.5%, HIV 1.8%, tuberculosis 3.6%,	Azithromycin 100%, oseltamivir 89.7%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.1% (95%CI -0.3% to 2.7%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.05 (95%CI 0.9 to 1.22); RD 0.9% (95%CI -1.7% to 3.8%); Moderate certainty ⊕⊕⊕◯
Huang et al;[97] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection.	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for	**Symptom resolution or improvement:** RR

	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			symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	1.05 (95%CI 0.95 to 1.16); RD 3% (95%CI -3% to 9.7%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):** RR 0.9 (95%CI 0.73 to 1.1); RD -1.7% (95%CI -4.7% to 1.7%); Low certainty ⨁⨁◯◯ **Severe Adverse events:** RR 1.1 (95%CI 0.78 to 1.54); RD 1% (95%CI -2.2% to 5.5%); Low certainty ⨁⨁◯◯
RECOVERY - Hydroxychloroquine trial;[98] 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;[99] Mitja et al; preprint; 2020	Patients exposed to COVID-19. 1116 assigned to hydroxychloroquine 800 mg once followed by 400 mg x once a day for 6 days and 1198 assigned to standard of care	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, coronary heart disease 13.3%, Nervous system disease 4.1%	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant number of patients excluded from analysis.	
COVID-19 PEP	Patients exposed to	Median age 40 ± 6.5,	NR	High for mortality and	

trial;[100] Boulware et al; peer-reviewed; 2020	COVID-19. 414 assigned to hydroxychloroquine 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma 7.6%, comorbidities 27.4%		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;[101] Cavalcanti et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 159 assigned to hydroxychloroquine 400 mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to standard of care	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%, diabetes 19.1%, chronic lung disease 1.8%, asthma 16%, coronary heart disease 0.8%, chronic kidney disease 1.8%, cancer 2.9%, obesity 15.5%	Steroids 1.5%, ACE inhibitors 1.2%, ARBs 17.4%, NSAID 4.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Kamran SM et al trial;[102] Kamran et al; preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to hydroxychloroquine 400 mg twice a day once then 200 mg twice a day for 4 days and 151 assigned to standard of care	Mean age 36 ± 11.2, male 93.2%, diabetes 3%, comorbidities 7.6%	NR	High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-19 PET trial;[103] 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	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	

	and 211 assigned to standard of care				
BCN PEP CoV-2 trial;[104] 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;[105] 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%	Steroids 7%, lopinavir-ritonavir 17%, umifenovir 47%, oseltamivir 11%, entecavir 1%, ATB 39%, ribavirin 47%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcome results.	
Chen et al;[106] preprint; 2020	Patients with moderate COVID-19 infection. 31 assigned to hydroxychloroquine 200 mg twice a day for 5 days and 31 assigned to standard of care	Mean age 44 ± 15.3, male 46.8%,	ATB 100%, IVIG 100%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Chen et al;[107] preprint; 2020	Patients with moderate COVID-19	Mean age 47.4 ± 14.46, male 45.8%,	NR	High for mortality and invasive mechanical	

	infection. 18 assigned to hydroxychloroquine 200 mg twice a day for 10 days, 18 assigned to chloroquine and 12 assigned to standard of care	hypertension 16.7%, diabetes 18.7%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Chen et al;[108] preprint; 2020	Patients with mild to severe COVID-19 infection. 21 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg twice a day for 6 days and 12 assigned to standard of care	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
HC-nCoV trial;[109] 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 probably inappropriate.	
Abd-Elsalam et al;[110] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg tablets twice	Mean age 40.7 ± 19.3, male 58.8%, chronic kidney disease 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	

	daily for 15 days and 97 assigned to standard of care			study. Concealment of allocation probably inappropriate.	
COVID-19 PREP trial;[111] Rajasingham et al; peer-reviewed; 2020	Patients exposed to COVID-19. 989 assigned to hydroxychloroquine 400 mg twice in one day followed by 400 mg once weekly for 12 weeks or 400 mg twice weekly for 12 weeks and 494 assigned to standard of care	Median age 41 ± 15, male 49%, hypertension 14%, asthma 10%	NR	Low for infection and adverse events	
TEACH trial;[112] Ulrich et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 67 assigned to hydroxychloroquine 800 mg on day 1 followed by 200 mg twice a day for 2 to 5 days and 61 assigned to standard of care	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart disease 26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%	Steroids 10.2%, remdesivir 0.8%, lopinavir-ritonavir 0.8%, azithromycin 23.4%, convalescent plasma 13.3%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
PrEP_COVID trial;[113] Grau-Pujol et al; preprint; 2020	Patients exposed to COVID-19. 142 assigned to hydroxychloroquine 400 mg daily for four days followed by 400 mg weekly for 6 months and 127 assigned to standard of care	Median age 39 ± 20, male 26.8%, hypertension 1.8%, diabetes 0.4%, chronic lung disease 2.6%	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	
PATCH trial;[114] Abella et al; peer-	Patients exposed to COVID-19. 64	Median age 33 ± 46, male 31%,	NR	Low for mortality and invasive mechanical	

reviewed; 2020	assigned to hydroxychloroquine 600 mg a day for 8 weeks and 61 assigned to standard of care	hypertension 21%, diabetes 3%, asthma 17%		ventilation; low for symptom resolution, infection and adverse events	
WHO SOLIDARITY trial;[115] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 947 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 10 days and 906 assigned to standard of care	Age < 70 years 61%, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%, chronic kidney disease %	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Davoodi et al;[93] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to Febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%, chronic lung disease 1.9%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-19 PEP (University of Washington) trial; Barnabas et al;[116] Abstract; 2020	Patients exposed to COVID-19. 381 assigned to hydroxychloroquine 400mg 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;[117] Self et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 242 assigned to hydroxychloroquine 800 mg on day 1 followed for 200 mg twice a day for 5 days and 237 assigned to standard of care	Median age 58.5 ± 24.5, male 56%, hypertension 52.8%, diabetes 34.6%, COPD 8.1%, asthma %, coronary heart disease %, chronic kidney disease 8.8%,	Steroids 18.4%, remdesivir 21.7%, azithromycin 19%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
HAHPS trial;[118] Brown et al; peer-reviewed; 2020	Patients with moderate to critical COVID-19. 42 assigned to hydroxychloroquine 800 mg once followed by 200 mg twice a day for 5 days and 43 assigned to azithromycin	Median age 55 ± 23, male 61%, diabetes 26%, coronary heart disease 11%, chronic kidney disease 9%, cerebrovascular disease 8%, cancer 2%	Steroids 15%, remdesivir 11%, lopinavir-ritonavir 1%, tocilizumab 24%, convalescent plasma 24%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Co-interventions were not balanced between study arms	
HYCOVID trial;[119] Dubee et al; preprint; 2020	Patients with mild to moderate COVID-19. 124 assigned to hydroxychloroquine 800 mg once followed by 400 mg a day for 8 days and 123 assigned to standard of care	Median age 77 ± 28, male 48.4%, hypertension 53.4%, diabetes 17.3%, COPD 11.2%, cerebrovascular disease 17.3%, obesity 27.7%	Steroids 9.6%, lopinavir-ritonavir 1.2%, azithromycin 8.4%	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
Q-PROTECT trial;[120] 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;[121] peer reviewed; 2020	Patients with mild to moderate COVID-19. 44 assigned to favipiravir 3200mg once followed by 600 mg twice a day for 10 days and 48 assigned to CQ	Mean age 35.5 ± 16.8, male 48.9%, comorbidities 18.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
HYDRA trial;[122] Hernandez-Cardenas et al; Preprint; 2020	Patients with severe to critical COVID-19. 106 assigned to HCQ 400mg a day for 10 days and 108 assigned to SOC	Mean age 49.6 ± 12, male 75%, hypertension 16%, diabetes 47%, CHD 11%, CKD 0%, obesity 66%	Steroids 52.4%, lopinavir-ritonavir 30.4%, tocilizumab 2.5%, azithromycin 24.5%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
COVID-19 Early Treatment trial;[123] Johnston et al; peer-reviewed; 2020	Patients with mild COVID-19. 60 assigned to HCQ 800mg once followed by 400mg a day for 10 days, 65 assigned to HCQ + AZT 500mg once followed by 250mg a day for 5 days and 65 assigned to SOC	Median age 37 ± , male 43.3%, hypertension 20.9%, diabetes 11.6%, COPD 9.3%, asthma 1.6%, immunosuppressive therapy 0.8%, obesity 76%	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Purwati et al;[124] peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to Lopinavir-Ritonavir 500/100 a day, 123 assigned to HCQ 200mg a day and 119 to SOC	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Beltran et al;[125]	Patients with	Mean age 54 ± 23.5,	Steroids 9.6%,	High for mortality and	

Preprint; 2020	moderate to severe COVID-19. 33 assigned to HCQ 800mg once followed by 400mg a day for 5 days and 37 assigned to SOC	male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	lopinavir-ritonavir 44.7%	mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
PATCH 1 trial;[126] Amaravadi et al; Preprint; 2020	Patients with mild COVID-19 infection. 17 assigned to HCQ 400mg a day and 17 assigned to SOC	Median age 53 ± 37, male 26%, hypertension 18%, diabetes 9%, , asthma 12%,	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Bermejo Galan et al;[127] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to Ivermectin 42mg and 115 assigned to HCQ or CQ	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer 3%, obesity 37.5%	Steroids 98%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

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;[128] preprint; 2020	Patients with moderate to severe	Mean age 51.6 ± 11.5, male 53.3%,	NR	Low for mortality and invasive mechanical	**Mortality:** Very low certainty ⊕◯◯◯

	COVID-19 infection. 10 assigned to icatibant 30 mg every 8 hours for 4 days, and 10 assigned to iC1e/K	hypertension 50%, diabetes 46.7%,%, asthma 3.3%, obesity 43.3%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** 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;[129] 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 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 ⊕◯◯◯
INM005 (polyclonal fragments of equine 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					
Lopardo et al;[130] preprint; 2020	Patients with moderate to severe COVID-19. 118 assigned to INM005 4mg/kg in two doses on days 1 and 3 and 123 assigned to SOC	Mean age 53.8 ± 12.5, male 65.1%, comorbidities 80%	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:** RR 0.66 (95%CI 0.37 to 1.18); RD -3.5% (95%CI -6.4% to 1.8%); Low certainty ⊕⊕◯◯

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

Interferon beta-1a IFN beta-1a probably does not reduce mortality nor invasive mechanical ventilation requirements. Inhaled interferon beta-1a may improve time to symptom resolution.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Davoudi-Monfared et al;[132] preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%,	Steroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%,	High for mortality and invasive mechanical ventilation; high for symptom resolution,	**Mortality:** RR 1.04 (95%CI 0.88 to 1.23); RD 0.6% (95%CI -1.9% to

	µg subcutaneous, three times a week and 39 assigned to standard of care	chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	immunoglobulin 30.8%	infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	3.7%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.83 to 1.16); RD -0.3% (95%CI -2.9% to 2.8%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** HR 1.1 (95%CI 0.64 to 1.87); RD 6% (95%CI -21.8% to 52.7%); Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
WHO SOLIDARITY;[115] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2050 assigned to Interferon beta-1a three doses over six days of 44µg and 2050 assigned to standard of care	age < 70 years 61% , male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%,	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
COVIFERON trial;[133] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6, 20 assigned to interferon beta-1b 0.25mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Darazam et al;[134] 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 8.3%, cerebrovascular	Steroids 1.1%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded	

	interferon beta-1a 44 micrograms on days 1, 3 and 6	disease 5.4%, cancer 0.6%		study which might have introduced bias to symptoms and adverse events outcomes results.	
Monk P et al;[135] 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 ⨁◯◯◯

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;[136] peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to	Median age 60 ± 10.5, male 59%, hypertension 40.9%,	Steroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for	**Mortality:** Very low certainty ⨁◯◯◯

	Interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to standard of care	diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%		symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
COVIFERON trial;[133] Darazam et al; Preprint; 2020	Patients with severe to critical COVID-19 infection. 20 assigned to interferon beta-1a 44 micrograms on days 1, 3 and 6, 20 assigned to interferon beta-1b 0.25mg on days 1, 3 and 6 and 20 assigned to SOC	Mean age 69 ± 27, male 51.7%, hypertension 33.3%, diabetes 23.3%, CHD 16.3%, CKD 8.3%, cancer 1.7%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Interferon 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;[137] 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	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or**

				study. Concealment of allocation probably inappropriate.	**improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Itolizumab **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ITOLI-C19-02-I-00 trial;[138] Kumar et al; preprint; 2020	Patients with severe COVID-19. 20 assigned to itolizumab 1.6 mg/kg once followed by 0.8 mg/kg weekly and 10 assigned to standard of care	Mean age 49 ± 13, male 86.6%, hypertension 20%,	Nr	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

Ivermectin Ivermectin may not reduce mortality and probably does not improve time to symptom resolution. It is uncertain if it affects mechanical ventilation requirements, symptomatic infection as prophylaxis or severe adverse events.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Zagazig University trial;[139] Shouman et al; Other; 2020	Patients exposed to COVID-19. 203 assigned to ivermectin 15 to 24 mg and 101 assigned to standard of care	Mean age 38.72 ± 15.94, male 51.3%, hypertension 10.2%, diabetes 8.1%, CKD 1%, asthma 2.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 0.94 (95%CI 0.51 to 1.73); RD -0.96% (95%CI -7.8% to 11.7%); Low certainty ⨁⨁◯◯ **Invasive mechanical ventilation:** RR 0.89 (95%CI 0.38 to 2.07); RD -1.9% (95%CI -10.7% to 18.5%); Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** RR 1 (95%CI 0.9 to 1.11); RD 0% (95%CI -6% to 6.6%); Moderate certainty ⨁⨁⨁◯ **Symptomatic infection (prophylaxis studies):**RR 0.14 (95%CI 0.09 to 0.21); RD -15% (95%CI -13.7% to -15.8%); Very low certainty ⨁◯◯◯ **Adverse events:** RR 1.04 (95%CI 0.32 to 3.38); RD 0.4%
Chowdhury et al;[140] preprint; 2020	Patients with mild to moderate COVID-19. 60 assigned to ivermectin plus doxycycline 200 µgm/kg single dose + 100 mg BID for 10days and 56 assigned to hydroxychloroquine plus azithromycin	Mean age 33.9 ± 14.1, male 72.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Podder et al;[141] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 µgm/kg once and 30 assigned to standard of care	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded	

				study. Concealment of allocation probably inappropriate.	(95%CI -6.9% to 24.2%); Very low certainty ⨁◯◯◯
Hashim HA et a (Alkarkh Health Directorate-Baghdad) trial;[142] Hashim et al; preprint; 2020	Patients with mild to critical COVID-19. 70 assigned to Ivermectin plus doxycycline 200 µgm/kg two or three doses + 100 mg twice a day for 5 to 10 days and 70 assigned to standard of care	Mean age 48.7 ± 8.6, male %	Steroids 100%, azithromycin 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mahmud et al; NCT04523831; Other; 2020	Patients with mild to moderate COVID-19. 183 assigned to Ivermectin plus doxycycline 12 mg once + 100 mg twice a day for 5 days and 180 assigned to standard of care	Mean age 39.6 ± 13.2, male 58.8%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
Elgazzar et al (mild);[143] preprint; 2020	Patients with mild to moderate COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 55.2 ± 19.8, male 69.5%, hypertension 11.5%, diabetes 14.5%, COPD %, asthma 5.5%, coronary heart disease 4%, chronic kidney disease %	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Elgazzar et al (severe);[143] preprint; 2020	Patients with severe COVID-19. 100 assigned to ivermectin 400 µgm/kg once for 4 days and 100	Mean age 58.9 ± 19.5, male 71%, hypertension 16%, diabetes 20%, COPD %, asthma 13%, coronary heart disease	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	assigned to hydroxychloroquine	7.5%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Elgazzar et al (prophylaxis);[143] preprint; 2020	Patients exposed to COVID-19. 100 assigned to ivermectin 400 µgm/kg twice (second dose after one week) and 100 assigned to standard of care	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Krolewiecki et al;[144] preprint; 2020	Patients with moderate to severe COVID-19. 20 assigned to ivermectin 0.6 mg/kg for 5 days and 12 assigned to standard of care	Mean age 40.2 ± 12, male 55.5%, hypertension 13.3%, diabetes 15.5%, COPD 11.1%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Niaee et al;[145] preprint; 2020	Patients with mild to severe COVID-19. 120 assigned to Ivermectin 200-800 microg/kg and 60 assigned to standard of care	Median age 67 ± 22, male 50%	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation possibly inappropriate.	
Ahmed et al;[146]	Patients with mild	Mean age 42 , male	NR	High for mortality and	

peer-reviewed; 2020	COVID-19. 55 assigned to ivermectin 12 mg a day for 5 days +/- doxycycline and 23 assigned to standard of care	46%,		mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	
SAINT trial;[147] 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;[148] peer-reviewed; 2020	Patients with mild COVID-19. 25 assigned to ivermectin 36mg once and 25 assigned to SOC	Mean age 40.6 ± 17, male 62%, hypertension 26%, diabetes 40%, obesity 12%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Babalola et al;[149] Preprint; 2020	Patients with mild to severe COVID-19. 42 assigned to ivermectin 12 to 24mg a week for 2 weeks and 20 assigned to lopinavir-ritonavir	Mean age 44.1 ± 14.7, male 69.4%, hypertension 14.5%, diabetes 3.2%,	Steroids 3.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Kirti et al;[150] Preprint; 2020	Patients with mild to moderate COVID-19. 55 assigned to	Mean age 52.5 ± 14.7, male 72.3%, hypertension 34.8%,	Steroids 100%, remdesivir 20.5%, hydroxychloroquine	Low for mortality and mechanical ventilation; low for symptom	

	ivermectin 24mg divided in two doses and 57 assigned to SOC	diabetes 35.7%, COPD 0.9%, asthma 0.9%, CHD 8.9%, CKD 2.7%, cerebrovascular disease 0%, cancer 5.4%, obesity %	100%, tocilizumab 6.3%, convalescent plasma 13.4%	resolution, infection and adverse events	
IVERCAR-TUC trial; NCT04701710 Peral de Bruno et al; Other; 2020	Patients exposed to COVID-19. 117 assigned to ivermectin + iota-carrageenan 12mg a week + 6 sprays a day for 4 weeks and 117 assigned to SOC	Mean age 39 ± 8.4, male 46.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mohan et al;[151] Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to Ivermectin 0.2-0.4 mg/kg once or SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. RoB assessment from secondary sources as publication not available.	
Rezai et al;[151] Unpublished; 2020	Patients with moderate to severe COVID-19 assigned to Ivermectin 0.2 mg/kg once or SOC	NR	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes: RoB assessment from secondary sources as publication	

				not available.	
Spoorthi et al;[151] Unpublished; 2020	Patients with mild to moderate COVID-19 assigned to Ivermectin 0.2 mg/kg once or SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. RoB assessment from secondary sources as publication not available.	
Raad et al;[151] Unpublished; 2020	Patients with mild COVID-19. 100 assigned to Ivermectin 0.2 mg/kg once and assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. RoB assessment from secondary sources as publication not available.	
Bukhari et al;[152] Preprint; 2020	Patients with mild to moderate COVID-19. 45 assigned to Ivermectin 12 mg once and 41 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Okumus et al;[153] ; Preprint; 2021	Patients with severe COVID-19. 30 assigned to Ivermectin 0.2 mg/kg for 5 days and 30 assigned to SOC	Mean age 62 ± 12, male 66%, hypertension 21.6%, diabetes 45%, COPD 1.6%, CHD 1.6%, cancer 1.6%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Beltran et al;[125] Preprint; 2021	Patients with moderate to severe COVID-19. 36 assigned to Ivermectin 12-18 mg once and 37 assigned to SOC	Mean age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, COPD 1%, CHD 7.4%, cerebrovascular disease 5.3%	Steroids 9.6%, lopinavir-ritonavir 44.7%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Lopez-Medina et al;[154] Peer reviewed; 2021	Patients with mild to moderate COVID-19 infection. 200 assigned to Ivermectin 300 µg/kg a day for 5 days and 198 assigned to SOC	Median age 37 ± 19, male 42%, hypertension 13.4%, diabetes 5.5%, COPD 3%, CHD 1.7%, cancer %, obesity 18.9%	Steroids 4.5%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Bermejo Galan et al;[127] peer reviewed; 2021	Patients with severe to critical COVID-19 infection. 53 assigned to Ivermectin 42mg and 115 assigned to HCQ or CQ	Mean age 53.4 ± 15.6, male 58.2%, hypertension 43.4%, diabetes 28.1%, COPD 5.3%, CKD 2.5%, cancer 3%, obesity 37.5%	Steroids 98%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
Pott-Junior et al;[155] Peer reviewed; 2021	Patients with moderate to critical COVID-19 infection. 27 assigned to	Mean age 49.4 ± 14.6, male 45.2%	Steroids 32.3%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection	

	Ivermectin 100 to 400 mcg/kg and 4 assigned to SOC			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Intravenous immunoglobulin (IVIG)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Sakoulas et al;[156] preprint; 2020	Patients with severe COVID-19 infection. 16 assigned to IVIG 0.5 g/kg/day for 3 days and 17 assigned to standard of care	Mean age 54 ± NR, male 60.6%, hypertension 33.3%, diabetes 36.3%, chronic lung disease 12%, coronary heart disease 3%, chronic kidney disease 3%, immunosuppression 3%	Steroids 78.7%, remdesivir 51.5%, convalescent plasma 15.2%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
Gharebaghi et al;[157] preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to IVIG 5 gr a day for 3 days and 29 assigned to standard of care	Mean age 56 ± 16, male 69.5%, hypertension 22%, diabetes 27.1%, chronic lung disease 3.3%,	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	

Tabarsi et al;[158] peer-reviewed; 2020	Patients with severe COVID-19. 52 assigned to IVIG 400 mg/Kg daily for three doses and 32 assigned to standard of care	Mean age 53 ± 13, male 77.4%, hypertension 20.2%, diabetes 21.4%, COPD 1.2%, asthma %, coronary heart disease %, chronic kidney disease 4.7%, cancer 1.2%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Raman et al;[159] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to IVIG 0.4/gr/kg for 5 days and 50 assigned to SOC	Mean age 48.7 ± 12, male 33%, hypertension 31%, obesity 16%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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;[160] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50mg every 12hs (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 probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

Wang et al;[161] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day followed by 20 mg a day for 8 days and 24 assigned to standard of care	Median age 55.7 ± 21.5, male 50%, hypertension 27.2%, diabetes 4.5%, chronic lung disease 4.5%, coronary heart disease 2.3%, cancer 2.3%	Steroids 34.1%, hydroxychloroquine 56.8%, lopinavir-ritonavir 11.4%, umifenovir 75%, IVIG 20.4%, ATB 63.6%, IFN 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** 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;[162] Preprint; 2020	Patients with mild to moderate COVID-19. 25 assigned to levamisole 150mg a day for 3 days and 25 assigned to SOC	Mean age 36.6 ± 13.7, male 60%,	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement: Mortality:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Lincomycin

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Guvenmez et al;[41] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

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;[163] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Steroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution,	**Mortality:** RR 1.02 (95%CI 0.92 to 1.22); RD 0.3% (95%CI -1.3% to

	Lopinavir-Ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care			infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	1.9%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to 1.17); RD 1.2% (95%CI -0.3% to 2.9%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.92 to 1.15); RD 1.8% (95%CI -4.8% to 9%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.6 (95%CI 0.37 to 0.98); RD -4.1% (95%CI -6.5% to -0.2%); Low certainty ⊕⊕◯◯
ELACOI trial;[164] Li et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to Lopinavir-Ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to Umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Steroids 12.5%, intravenous immunoglobulin 6.3%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY - Lopinavir-ritonavir trial;[165] 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;[97] 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10 days			infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zheng et al; preprint;[166] 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-Ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-Ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Chen et al; preprint;[167] 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to ribavirin 2gr IV loading dose followed by orally 400-600 mg every 8 hours for 14 days, 36 assigned to lopinavir-ritonavir and 32 assigned to Ribavirin plus Lopinavir-Ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
WHO SOLIDARITY - trial;[115] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 1399 assigned to lopinavir-ritonavir 200/50 mg twice a day for 14	Age 61% < 70 years, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events	

	days and 1372 assigned to standard of care			Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Sali et al;[168] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to Sofosbuvir 400mg a day and 32 assigned to Lopinavir-Ritonavir 400/100mg every 12 hours	Mean age 56.5 ± 14, male 53.7%, diabetes 33%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Purwati et al;[169] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 128 assigned to Lopinavir-Ritonavir 500/100 a day, 123 assigned to HCQ 200mg a day and 119 to SOC	Median age 36.5 ± NR, male 95.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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;[170] Preprint; 2020	Patients with mild to moderate COVID-19. 24 assigned to	Mean age 51.85 ± 14.25, male 59.1%, hypertension 25%,	NR	High for mortality and mechanical ventilation; High for symptom	**Mortality:** Very low certainty ⊕◯◯◯

	melatonin 9mg a day for 14 days and 20 assigned to SOC	diabetes 22.7%, CHD 6.8%, cancer 6.8%,		resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate. Significant loss to follow-up.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Mesenchymal stem cell transplantation **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Shu et al;[171] 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%	Steroids 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 probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information
Shi et al;[172] preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem	Mean age 60.3 ± 8.4, male 56%, hypertension 27%, diabetes 17%, COPD	Steroids 22%	Low for mortality and mechanical ventilation	

	cell three infusions with 4.0×107 cells each and 35 assigned to standard of care	2%			**Adverse events:** No information
Lanzoni et al;[173] preprint; 2020	Patients with severe to critical COVID-19. 12 assigned to mesenchymal stem cell 100±20 x106 UC-MSC twice and 12 assigned to standard of care	Mean age 58.7 ± 17.5, male 54.1%, hypertension 66.7%, diabetes 45.8%, coronary heart disease 12.5%, , cancer 4.2%, obesity 66.6%	Steroids 90.4%, remdesivir 66.7%, hydroxychloroquine 12.5%, tocilizumab 20.8%, convalescent plasma 29.1%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	

Metisoprinol

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Borges et al;[174] peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to metisoprinol 1500 mg/kg/day for 14 days and 30 assigned to SOC	Mean age 33.2 ± 16, male 53.3%, COPD 10%, CKD 16.6%, cancer 3.3%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably 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

Molnupiravir Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Painter et al;[175] Preprint; 2020	Patients with mild to moderate COVID-19. 64 assigned to Molnupiravir 80 to 1600mg twice a day for 5.5 days	Mean age 39.6 ± 39, male 82.8%,	NR	Low for adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Mouthwash (hydrogen peroxide) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and 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;[176] preprint ; 2020	Patients with mild to critical COVID-19. 46 assigned to mouthwash with	Mean age 49, male 78.2%, hypertension 37%, diabetes 41.3%, coronary heart disease	Steroids 53.2%, remdesivir 26%, hydroxychloroquine 21.7%, lopinavir-	High for mortality and mechanical ventilation; high for symptom resolution, infection	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very

	hydrogen peroxide 2% and chlorhexidine gluconate mixed solution three times a day and 46 assigned to standard of care	6.5%, chronic kidney disease 12%, c obesity 31.5%	ritonavir 54.3%, azithromycin 57.6%, convalescent plasma 13%	and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Mouthwash (povidone iodine or essential oils) **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
GARGLES trial;[177] Mohamed et al; preprint; 2020	Patients with COVID-19. 10 assigned to mouthwash with povidone iodine or essential oils 3 times a day and 10 assigned to mouthwash with water or no mouthwash	Median age 28.9 ± nr, male 80%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No
KILLER trial;[178] Guenezan et al; Peer reviewed; 2020	Patients with mild COVID-19. 12 assigned to Mouthwash with 25ml of 1% povidone iodine and 12	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	

	assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	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;[179] peer-reviewed; 2020	Patients with severe COVID-19. 68 assigned to NAC 21 gr once and 67 assigned to standard of care	Mean age 58.5 ± 22.5, male 59.2%, hypertension 46.6%, diabetes 37.7%, cancer 12.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯

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;[180] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 14 assigned to nasal hypertonic saline 250 cc twice daily, 14 assigned to nasal hypertonic saline plus surfactant and 17 assigned to standard of care	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%, diabetes 6.6%, chronic lung disease 15.5%, coronary heart disease 4.4%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
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;[181] Rocco et al; preprint; 2020	Patients with mild COVID-19. 194 assigned to nitazoxanide 500 mg	Age range 18 - 77 , male 47%, comorbidities 13.2%	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical**

	three times a day for 5 days and 198 assigned to standard of care			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant lost to follow up.	**ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Fontanesi et al;[182] preprint ; 2020	Patients with mild to critical COVID-19. 25 assigned to nitazoxanide 1200mg a day for 7 days and 25 assigned to SOC	age > 65 46% , male 30%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	
Silva et al;[183] preprint; 2021	Patients with mild to moderate COVID-19 infection. 23 assigned to nitazoxanide 2-3 gr a day for 14 days and 13 assigned to SOC	Male 72.2%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

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;[166] preprint; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to novaferon 40 microg twice a day (inh), 30 assigned to novaferon plus lopinavir-Ritonavir 40 microg twice a day (inh) + 400/100 mg a day and 29 assigned to lopinavir-Ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Non-steroidal anti-inflammatory drugs (NSAID) Current best evidence suggests no association between NSAID consumption and COVID-19 related mortality. However certainty of the evidence is very low because of risk of bias. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
Non-RCT					
Eilidh et al;[184] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 54 received NSAID	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%, coronary heart disease	NR	High for mortality Notes: Non-randomized study with	**Mortality:** OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⊕◯◯◯

	and 1168 received alternative treatment schemes	22.3%, chronic kidney disease 38.7%,		retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function)	
Jeong et al;[185] 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;[186] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 224	Median age 54 ± 23, male 41.5%, chronic lung disease 3.9%,	Steroids 7.1%	High for mortality and invasive mechanical ventilation	

	received NSAID and 896 received alternative treatment schemes	asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%		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;[187] 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;[188] preprint; 2020	Patients exposed to COVID-19 infection. 535519 received NSAID and 1924095 received alternative treatment schemes	Median age 51 ± 23, male 42.7%, hypertension 19.6%, diabetes 9.6%, chronic lung disease 2.4%, asthma %, coronary heart disease 0.5%, chronic kidney disease 2.8%, cancer 5.2%,	Steroids 2.2%, hydroxychloroquine 0.6%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, vaccination and deprivation)	
Imam et al;[189] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection.	Mean age 61 ± 16.3, male 53.8%, hypertension 56.2%,	NR	High for mortality Notes: Non-	

	466 received NSAID and 839 received alternative treatment schemes	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%,		randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Esba et al;[190] preprint; 2020	Patients with mild to severe COVID-19 infection. 146 received NSAID and 357 received alternative treatment schemes	Median age 41.7 ± 30, male 57.2%, hypertension 20.4%, diabetes 22.5%, chronic lung disease 5.2%, chronic kidney disease 3.2%, cancer 1.4%	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age; sex; comorbidities: hypertension, diabetes mellitus (DM), dyslipidemia, asthma or chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), renal or liver impairment, and malignancy).	

Omega-3 fatty acids

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Sedighiyan et al;[191] Preprint; 2020	Patients with mild to moderate COVID-19. 15 assigned to omega-3 670mg	Mean age 66.7 ± 2.5, male 60%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; High for symptom resolution, infection	**Mortality:** No information **Invasive mechanical**

	three times a day for 2 weeks and 15 assigned to SOC			and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
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;[192] 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 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:**
SEOT trial;[193] Shah et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19. 30 assigned to Ozone 150ml rectal insufflation plus 5ml with venous blood once a day for 10	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	

	days and 30 assigned to SOC			study. Concealment of allocation probably inappropriate.	Very low certainty ⊕◯◯◯
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;[194] Feld et al; preprint; 2020	Patients with mild to severe COVID-19. 30 assigned to Peg-IFN lambda 180 µg subcutaneous injection once and 30 assigned to standard of care	Median age 46 ± 22, male 58%, comorbidities 15%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
COVID-Lambda trial;[195] Jagannathan et al; preprint; 2020	Patients with mild COVID-19. 60 assigned to Peg-IFN lambda 180 mcg subcutaneous injection once and 60 assigned to standard of care	Median age 36 ± 53, male 68.3%,	NR	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

Pentoxifylline Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Maldonado et al;[196] peer-reviewed; 2020	Patients with severe to critical COVID-19. 26 assigned to pentoxifylline 400 mg three times a day while hospitalized and 12 assigned to standard of care	Mean age 57.5 ± 11.7, male 55.2%, hypertension 39.4%, diabetes 50%, obesity 55.2%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Progesterone Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Ghandehari et al;[197] preprint; 2020	Patients with severe COVID-19. 18 assigned to progesterone 100 mg	Mean age 55.3 ± 16.4, male 100%, hypertension 48%, diabetes 25%, obesity	Steroids 60%, remdesivir 60%, hydroxychloroquine 2.5%, tocilizumab	High for mortality and mechanical ventilation; high for symptom resolution, infection	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very

	twice a day for 5 days and 22 assigned to standard of care	45%	12.5%, azithromycin 50%, convalescent plasma 5%	and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
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;[198] Sigamani et al; preprint; 2020	Patients with mild COVID-19. 5 assigned to prolectin-M 40 gr a day and 5 assigned to standard of care	Mean age 28.5 ± 3.85, male 20%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information
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;[199] Duarte Silveira et al; Preprint; 2020	Patients with moderate to critical COVID-19. 82 assigned to propolis 400-800mg a day for 7 days and 42 assigned to SOC	Mean age 50 ± 12.8, male 69.4%, hypertension 45.2%, diabetes 21%, COPD 7.3%, asthma %, obesity 51.6%	Steroids 80.6%, hydroxychloroquine 3.2%, azithromycin 95.2%,	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:**Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Proxalutide Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and 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;[200] Preprint; 2020	Patients with mild COVID-19. 114 assigned to proxalutinde 200mg a day for 15 days and 100 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Randomization and concealment methods probably not appropriate	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 3.34 (95%CI 2.17 to 5.15); RD 57.1% (95%CI -28.5% to 76%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
AB-DRUG-SARS-004 trial;[201] Cadegiani et al; Peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 171 assigned to Proxalutide 200mg a day for 15 days and 65 assigned to SOC	Mean age 45.3 ± 13, male 54.2%, hypertension 22.5%, diabetes 8.9%, COPD 0%, asthma 5%, CKD 0.4%, cancer 17%, obesity 15.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Concealment of allocation and blinding probably inappropriate.	

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;[202] Preprint; 2020	Patients with moderate to severe COVID-19. 52 assigned to Quercetin 1000mg and 395 assigned to SOC	Age > 50 65.7% , male 56.6%, hypertension 38.7%, diabetes 28.2%, COPD 6%, asthma 13.9%, CHD 22.6%, CKD 0.2%, cancer 3.6%, obesity 0.9%	Hydroxychloroquine 97.5%, favipiravir 13.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Randomization and concealment process probably inappropriate. Non-blinded study	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
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;[203] Amat-Santos et al; preprint; 2020	Patients exposed to COVID-19. 50 assigned to Ramipril 2.5 mg a day	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%, diabetes 20.65%,	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution,	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No

	progressively increased to 10 mg a day and 52 assigned to standard of care	chronic lung disease 7.35%, coronary heart disease 22.45%, chronic kidney disease 34.15%, cerebrovascular disease 11.15%		infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very low certainty ⨁◯◯◯ **Adverse events:** 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;[204] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 46 assigned to Recombinant Super-Compound interferon 12 million IU twice daily (nebulization) and 48 assigned to Interferon alfa	Median age 54 ± 23.5, male 46.8%, hypertension 19.1%, diabetes 9.6%, chronic lung disease 1.1%, coronary heart disease 7.4%, cerebrovascular disease 5.3%, liver disease 6.4%	Steroids 9.6%, ATB 22.3%, intravenous immunoglobulin 3.2%, Lopinavir-ritonavir 44.7%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

REGN-COV2 (Regeneron) Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Weinreich et al;[205] Peer reviewed; 2020	Patients with mild COVID-19. 143 assigned to REGN-COV2 (Regeneron) 2.4 to 8gr single infusion and 78 assigned to SOC	Median age 44 ± 17, male 49%, obesity 42%, comorbidities 64%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events Notes:	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

Remdesivir Remdesivir may slightly reduce mortality and improve time to symptom resolution without significantly increasing the risk of severe adverse events. However, the certainty is low because of risk of bias and imprecision.					
Study; publication status	**Patients and 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;[206] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 541	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%,	NR	Low for mortality and invasive mechanical ventilation; low for	**Mortality:** RR 0.94 (95%CI 0.82 to 1.08); RD -1%

	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	diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,		symptom resolution, infection and adverse events	(95%CI -2.9% to 1.3%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.65 (95%CI 0.39 to 1.11); RD -6% (95%CI -10.6% to 1.9%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.17 (95%CI 1.03 to 1.33); RD 10.3% (95%CI 1.8% to 20%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.8 (95%CI 0.48 to 1.33); RD -2% (95%CI -5.3% to 3.4%); Low certainty ⊕⊕◯◯
SIMPLE trial; Goldman et al;[207] peer-reviewed; 2020	Patients with severe COVID-19 infection. 200 assigned to remdesivir (5 days) 200 mg once followed 100mg for 5 days and 197 assigned to remdesivir (10 days)	Median age 61.5 ± 20, male 63.7%, hypertension 49.8%, diabetes 22.6%, asthma 12.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
CAP-China remdesivir 2 trial;[208] Wang et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 158 assigned to remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions and 79 assigned to standard of care	Median age 65 ± 7.5, male 60.5%, hypertension 43%, diabetes 23.7%, coronary heart disease 7.2%	Steroids 65.6%, lopinavir-ritonavir 28.4%, IFN 32.2%, ATB 91.1%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	
SIMPLE 2 trial; Spinner et al;[209]	Patients with moderate COVID-19	Median age 57 ± 9, male 61.3%,	Steroids 17%, hydroxychloroquine	Some Concerns for mortality and invasive	

peer-reviewed; 2020	infection. 384 assigned to remdesivir 200 mg on day 1 followed by 100 mg a day for 5 to 10 days and 200 assigned to standard of care	hypertension 42%, diabetes 40%, asthma 14%, coronary heart disease 56%	21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY;[115] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2743 assigned to remdesivir 200 mg once followed by 100 mg a day for 10 days and 2708 assigned to standard of care	age < 70 years 61%, male 62%, hypertension %, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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;[210] peer-reviewed; 2020	Patients with moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100	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	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information

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

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

Ruxolitinib

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Cao et al;[212] peer-reviewed; 2020	Patients with severe COVID-19 infection. 22 assigned to ruxolitinib 5mg twice a day and 21	Mean age 63 ± 10, male 58.5%, hypertension 39%, diabetes 19.5%, coronary heart disease	Steroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse	**Mortality:** No information **Invasive mechanical ventilation:** No information

	assigned to standard of care	7.3%,		events	**Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Sarilumab **Sarilumab may reduce mortality and mechanical ventilation requirements. However certainty of the evidence is low. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
REMAP-CAP - tocilizumab trial;[213] Gordon et al; preprint; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8mg/kg once or twice, 48 assigned to sarilumab 400mg once and 402 assigned to SOC	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%, cancer %, obesity %	Steroids 75.6%, remdesivir 32.8%	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 0.75 (95%CI 0.48 to 1.16); RD -4% (95%CI -8.3% to 2.5%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.67 (95%CI 0.42 to 1.05); RD -5.6% (95%CI -10% to 0.8%); Low certainty ⊕⊕◯◯
Lescure et al;[214] peer-reviewed; 2020	Patients with severe to critical COVID-19. 332 assigned to sarilumab 200-400mg once and 84 assigned to SOC	Mean age 59 ± 18, male 62.7%, hypertension 42.5%, diabetes 26.4%, COPD 4.3%, asthma 4.1%, CHD 5.3%, CKD 4.3%,	Steroids 46.4%, hydroxychloroquine 34.5%, azithromycin 46.4%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Symptom resolution or improvement:** RR 0.95 (95%CI 0.85 to 1.06); RD -3% (95%CI -9% to 3.7%);

		cancer 10.1%, obesity 20.7%			Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 1.17 (95%CI 0.77 to 1.79); RD 1.8% (95%CI -2.3% to 8.1%); Low certainty ⊕⊕◯◯
Sofosbuvir +/- daclatasvir **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and 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;[215] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60 mg twice daily and 24 assigned to hydroxychloroquine plus lopinavir-ritonavir	Median age 52.5 ± NR, male 37.5%, hypertension 35.4%, diabetes 37.5%, chronic lung disease 2%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information
Sadeghi et al;[216] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60 mg once a	Median age 58 ± 13, male 20.21%, hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%,	Steroids 30.2%, lopinavir-ritonavir 48.4%, antibiotics 89.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events	

	day for 14 days and 33 assigned to standard of care	coronary heart disease 15.1%, cancer 4.5%, obesity 25.7%		Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation probably inappropriate.	**Adverse events:** No information
Yakoot et al;[217] preprint; 2020	Patients with mild to severe COVID-19. 44 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 10 days and 45 assigned to standard of care	Median age 49 ± 27, male 42.7%, hypertension 26%, diabetes 19%, COPD %, asthma 1%, coronary heart disease 8%	Hydroxychloroquine 100% azithromycin 100%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Roozbeh et al;[218] Peer reviewed; 2020	Patients with moderate COVID-19. 27 assigned to sofosbuvir/daclatasvir 400/60mg once a day for 7 days and 28 assigned to SOC	Median age 53 ± 16, male 47%, comorbidities 38%	Azithromycin 100%, Hydroxychloroquine 100%	High for symptom resolution, infection and adverse events Notes: Blinding method possibly inappropriate which might have introduced bias to symptoms and adverse events outcomes results.	
Sali et al;[168] Peer reviewed; 2020	Patients with moderate to severe COVID-19. 22 assigned to Sofosbuvir 400mg a day and 32 assigned to Lopinavir-Ritonavir 400/100mg every 12 hours	Mean age 56.5 ± 14, male 53.7%, diabetes 33%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Sofosbuvir/ledipasvir Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Khalili et al;[219] Peer reviewed; 2020	Patients with mild to moderate COVID-19. 42 assigned to sofosbuvir/ledipasvir 400/90 mg a day for 10 days and 40 assigned to SOC	Median age 62.2 ± 23.1, hypertension 45.1%, diabetes 45.1%, COPD 4.9%, CHD 31.7%, cancer 3.6%,	Steroids 8.5%, hydroxychloroquine 10.9%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**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
Steroids Steroids reduce mortality and probably reduce invasive mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Steroids may not significantly increase the risk of severe adverse events					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
GLUCOCOVID trial;[220] Corral-	Patients with moderate to severe	Mean age 69.5 ± 11.5, male 61.9%,	Hydroxychloroquine 96.8%, lopinavir-	High for mortality and invasive mechanical	**Mortality:** RR 0.90 (95%CI 0.80 to

Gudino et al; preprint; 2020	COVID-19 infection. 56 assigned to methylprednisolone 40mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%, cerebrovascular disease 12.7%	ritonavir 84.1%, azithromycin 92%	ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	1.02); RD -1.6% (95%CI -3.2% to 0.3%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.87 (95%CI 0.72 to 1.05); RD -2.2% (95%CI -4.8% to 0.8%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR 1.27 (95%CI 0.98 to 1.65); RD 16.4% (95%CI -1.2% to 39.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 0.89 (95%CI 0.68 to 1.17); RD -1.1% (95%CI -3.3% to 1.7%); Low certainty ⊕⊕◯◯
Metcovid trial;[221] Prado Jeronimo et al; peer-reviewed; 2020	Patients with severe COVID-19 infection. 194 assigned to methylprednisolone 0.5mg/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;[222] Horby et al; peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 2104 assigned to Dexa 6mg once daily for 10 days and 4321 assigned to standard of care	Mean age 66.1 ± 15.7, male 64%, diabetes 24%, chronic lung disease 21%, asthma NR%, coronary heart disease 27%, chronic kidney disease 8%, liver disease 2%, any comorbidities 56%	Steroids NA%, remdesivir 0.08%, hydroxychloroquine 1%, lopinavir-ritonavir 0.5%, tocilizumab 3%, azithromycin 25%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
DEXA-COVID19 trial;[223] 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	NR	NR	Low for mortality and invasive mechanical ventilation Notes: RoB judgment from published SR	

	assigned to standard of care				
CoDEX trial;[224] 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;[225] 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;[223] Petersen et al; Unpublished; 2020	Patients with severe to critical COVID-19. 15 assigned to hydrocortisone 200 mg a day for 7 days and 14 assigned to standard of care	NR	NR	Low for mortality and invasive mechanical ventilation Notes: Risk of bias judgment from published SR	
CAPE COVID trial;[226] Dequin et al; peer-reviewed;	Patients with severe to critical COVID-19. 76 assigned to	Median age 64.7 ± 19.3, male 69.8%, hypertension %,	Remdesivir 3.4%, hydroxychloroquine 46.9%, lopinavir-	Low for mortality and invasive mechanical ventilation; Low for	

2020	Hydrocortisone 200mg a day progressively reduced to 50mg a day for 7 to 14 days and 73 assigned to standard of care	diabetes 18.1%, chronic lung disease 7.4%, immunosuppression 6%	ritonavir 14.1%, tocilizumab 2%, azithromycin 34.2%	symptom resolution, infection and adverse events	
Steroids-SARI trial;[213] 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;[227] preprint; 2020	Patients with severe to critical COVID-19. 14 assigned to methylprednisolone 1000 mg/day for three days followed by prednisolone 1 mg/kg for 10 days, and 15 assigned to standard of care	Mean age 64 ± 13.5	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Edalatifard et al;[228] peer-reviewed; 2020	Patients with severe COVID-19. 34 assigned to methylprednisolone 250 mg/day for 3 days and 28 assigned to standard of care	Mean age 58.5 ± 16.6, male 62.9%, hypertension 32.3%, diabetes 35.5%, chronic lung disease 9.7%, coronary heart disease 17.7%, chronic kidney disease 11.3%, cancer 4.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Tang et al;[229] Peer	Patients with	Median age 56 ± 27,	NR	Low for mortality and	

reviewed; 2020	moderate to severe COVID-19. 43 assigned to Methylprednisolone 1 mg/kg for 7 days and 43 assigned to SOC	male 47.7%, hypertension 36%, diabetes 9.3%, COPD 3.5%, asthma 2.4%, CHD 7%, CKD 1.2%		mechanical ventilation; Low for symptom resolution, infection and adverse events	
Jamaati et al;[230] Peer-reviewed ; 2020	Patients with moderate to severe COVID-19. 25 assigned to Dexamethasone 20mg a day for 5 days followed by 10mg a day until day 10 and 25 assigned to SOC	Median age 62 ± 16.5, male 72%, hypertension 50%, diabetes 54%, COPD 20%, CHD 14%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ranjbar et al;[231] Preprint; 2020	Patients with severe to critical COVID-19 infection. 44 assigned to Methylprednisolone 2mg/kg daily for 5 days followed by tapering using same scheme at half dose every 5 days, 42 assigned to dexamethasone 6mg a day for 10 days	Mean age 58.7 ± 17.4, male 56.9%, hypertension 45.3%, diabetes 32.5%, CHD 30.2%, CKD 2.3%,	NR	Some concerns for mortality and mechanical ventilation; Some concerns for symptom resolution, infection and adverse events Notes: Unbalanced prognostic factors (age and gender)	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Steroids (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					
STOIC trial;[232] Ramakrishnan et al; preprint ; 2020	Patients with mild to moderate COVID-19. 71 assigned to budesonide (inh) 800µg twice a day and 69 assigned to SOC	Mean age 45 ± 56, male 42.4%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Sulodexide Uncertainty in potential benefits and harms. Further research is needed.					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
ERSul trial;[233] Gonzalez Ochoa et al; preprint; 2020	Patients with mild (early within 3 days of onset) COVID-19. 124 assigned to	Median age 52 ± 10.6, male 47.4%, hypertension 34.2%, diabetes 22.2%, COPD	Steroids 62.5%, hydroxychloroquine 33.7%, ivermectin 43%	Some Concerns for mortality and mechanical ventilation; some concerns for	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very

	sulodexide 500 RLU twice a day for 3 weeks and 119 assigned to standard of care	23%, coronary heart disease 21%,		symptom resolution, infection and adverse events Notes: Significant loss to follow up.	low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯
Telmisartan **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Duarte et al;[234] preprint; 2020	Patients with mild to severe COVID-19 infection. 38 assigned to Telmisartan 80 mg twice daily and 40 assigned to standard of care	Mean age 61.9 ± 18.2, male 61.5%, hypertension 30.7%, diabetes 11.5%, chronic lung disease 11.5%, asthma 1.3%, chronic kidney disease 2.6%, cerebrovascular disease 7.7%, obesity 12.8%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information
Tocilizumab **Tocilizumab probably reduces mortality and mechanical ventilation requirements without increasing severe adverse events.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COVACTA trial; Rosas et al;[235] peer-reviewed; 2020	Patients with severe COVID-19. 294 assigned to tocilizumab 8 mg/kg once and 144 assigned to standard of care	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, coronary heart disease 28%, obesity 20.5%	Steroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 0.90 (95%CI 0.78 to 1.03); RD -1.6% (95%CI -3.5% to 0.5%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.80 (95%CI 0.71 to 0.9); RD -3.5% (95%CI -5% to -1.7%); High certainty ⨁⨁⨁⨁ **Symptom resolution or improvement:** RR 1.10 (95%CI 0.99 to 1.22); RD 6% (95%CI -0.6% to 13.3%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.89 (95%CI 0.75 to 1.07); RD -1.1% (95%CI -2.6% to
Wang et al;[236] preprint; 2020	Patients with moderate to severe COVID-19. 34 assigned to tocilizumab 400 mg once or twice and 31 assigned to standard of care	Median age 63 ± 16, male 50.8%, hypertension 30.8%, diabetes 15.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zhao et al;[88] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to favipiravir 3200 mg once followed by 600mg twice a day for 7 days, 7 assigned to tocilizumab 400	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	

	mg once or twice and 5 assigned to favipiravir plus tocilizumab			allocation probably inappropriate.	0.7%); Moderate certainty ⊕⊕⊕◯
RCT-TCZ-COVID-19 trial;[237] 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;[238] Stone et al; peer-reviewed; 2020	Patients with severe COVID-19. 161 assigned to tocilizumab 8 mg/kg once and 81 assigned to standard of care	Median age 59.8 ± 15.1, male 58%, hypertension 49%, diabetes 31%, COPD 9%, asthma 9%, coronary heart disease 10%, chronic kidney disease 17%, cancer 12%,	Steroids 9.5%, remdesivir 33.9%, hydroxychloroquine 3.7%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
CORIMUNO-TOCI 1 trial;[239] Hermine et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 63 assigned to tocilizumab 8 mg/kg once followed by an optional 400 mg dose on day 3 and 67 assigned to standard of care	Median age 63.6 ± 16.2, male 67.7%, diabetes 33.6%, COPD 4.7%, asthma 6.3%, coronary heart disease 31.2%, chronic kidney disease 14%, cancer 7%,	Steroids 43%, remdesivir 0.7%, hydroxychloroquine 6.2%, lopinavir-ritonavir 3%, azithromycin 15.4%,	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
EMPACTA trial;[240]	Patients with	Mean age 55.9 ± 14.4,	Steroids 59.4%,	Low for mortality and	

Salama et al; preprint; 2020	moderate to severe COVID-19. 249 assigned to tocilizumab 8 mg/kg once and 128 assigned to standard of care	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%	remdesivir 54.6%,	mechanical ventilation; low for symptom resolution, infection and adverse events	
REMAP-CAP - tocilizumab trial;[213] Gordon et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 353 assigned to TCZ 8mg/kg once or twice, 48 assigned to sarilumab 400mg once and 402 assigned to SOC	Mean age 61.4 ± 12.7, male 72.7%, diabetes 35.4%, COPD 24%, CHD 10.2%, immunosuppressive therapy 1.4%, cancer %, obesity %	Steroids 75.6%, remdesivir 32.8%, hydroxychloroquine %, lopinavir-ritonavir %, tocilizumab %, azithromycin %, convalescent plasma %	Low for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Veiga et al;[241] peer reviewed; 2020	Patients with severe to critical COVID-19. 65 assigned to TCZ 8mg/kg once and 64 assigned to SOC	Mean age 57.4 ± 14.6, male 68%, hypertension 49.6%, diabetes 32.6%, COPD 3%, CHD 5.5%, cancer 7%,	Steroids 71.3%	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
RECOVERY-TCZ trial;[242] Horby et al; preprint; 2020	Patients with severe to critical COVID-19. 2022 assigned to TCZ 400-800mg once or twice and 2094 assigned to SOC	Mean age 63.6 ± 13.6, male 67.3%, diabetes 28.5%, COPD 23%, asthma %, CHD 23%, CKD 5.5%	Steroids 82%, hydroxychloroquine 2%, lopinavir-ritonavir 3%, tocilizumab %, azithromycin 9%,	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events	

				Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Triazavirin **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
Wu et al;[243] peer-reviewed; 2020	Patients with mild to critical COVID-19. 26 assigned to triazavirin 250 mg orally three or four times a day for 7 days and 26 assigned to standard of care	Median age 58 ± 17, male 50%, hypertension 28.8%, diabetes 15.4%, chronic lung disease 5.8%, coronary heart disease 15.4%, cerebrovascular disease 7.7%	Steroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, antibiotics 69.2%, interferon 48.1%, umifenovir 61.5%, ribavirin 28.9%,	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯

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;[84] preprint; 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to Umifenovir 200 mg three times daily for 7 days	Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation 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
ELACOI trial; Li et al;[164] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to Lopinavir-Ritonavir 200/50 mg twice daily for 7-14 days, 35 assigned to Umifenovir and 17 assigned to standard of care	Mean age 49.4 ± 14.7, male 41.7%	Steroids 12.5%, IVIG 6.3%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Nojomi et al;[244] preprint; 2020	Patients with severe COVID-19. 50 assigned to umifenovir 100 mg two twice a day for 7 to 14 days and 50	Mean age 56.4 ± 16.3, male 60%, hypertension 39%, diabetes 28%, asthma 2%, coronary heart disease 9%, chronic	Hydroxychloroquine 100%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events	

	assigned to Lopinavir-ritonavir 400 mg a day for 7 to 14 days	kidney disease 2%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Yethindra et al;[245] peer-reviewed; 2020	Patients with mild COVID-19. 15 assigned to umifenovir 200 mg three times a day for 1 to 5 days and 15 assigned to standard of care	Mean age 35.5 ± 12.1, male 60%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ghaderkhani S et al (Tehran University of Medical Sciences) trial;[246] Ghaderkhani et al; preprint; 2020	Patients with mild to moderate COVID-19. 28 assigned to Umifenovir 200 mg three times a day for 10 days and 25 assigned to standard of care	Mean age 44.2 ± 19, male 39.6%,	Hydroxychloroquine 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Vitamin C

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Zhang et al;[247] preprint; 2020	Patients with severe COVID-19 infection.	Mean age 67.4 ± 12.4, male 66.7%,	NR	High for mortality and invasive mechanical	**Mortality:** Very low certainty ⨁◯◯◯

	26 assigned to vitamin C 12 gr twice a day for 7 days and 28 assigned to standard of care	hypertension 44.4%, diabetes 29.6%, chronic lung disease 5.6%, coronary heart disease 22.2%, chronic kidney disease 1.85%, cancer 5.6%, nervous system disease 20.4%		ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Kumari et al;[248] Peer reviewed; 2020	Patients with severe COVID-19. 75 assigned to Vit C 50mg/kg a day and 75 assigned to SOC	Mean age 52.5 ± 11.5	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Jamali Moghadam Siahkali et al;[249] Preprint; 2020	Patients with severe to critical COVID-19. 30 assigned to Vit C 5gr a day for 5 days and 30 assigned to SOC	Mean age 59.2 ± 17, male 50%, hypertension 41.6%, diabetes 38.3%, COPD 10%,	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVIDAtoZ - Vit C trial;[250] Thomas et al; peer reviewed; 2020	Patients with mild COVID-19. 48 assigned to Vit C 8000mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Steroids 8.4%,	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias	

				to symptoms and adverse events outcomes results.	
Vitamin D **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
COVIDIOL trial; Entrenas Castillo et al;[251] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 50 assigned to vitamin D 0.532 once followed by 0.266 twice and 26 assigned to standard of care	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, coronary heart disease 3.9%, immunosuppression 9.2%, cancer %, obesity %	Hydroxychloroquine 100%, azithromycin 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯
SHADE trial;[252] 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 probably inappropriate.	
Murai et al;[253] peer-reviewed; 2020	Patients with severe COVID-19. 117 assigned to vitamin D 200,000 IU once and 120 assigned to standard of care	Mean age 56.3 ± 14.6, male 56.3%, hypertension 52.5%, diabetes 35%, COPD %, asthma 6.3%, coronary heart disease	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

		13.3%, chronic kidney disease 1%,			
Lakkireddy et al;[254] preprint; 2021	Patients with mild to moderate with low plasmatic vitamin D COVID-19 infection. 44 assigned to Vit D 60000 IU a day for 8 to 10 days and 43 assigned to SOC	Mean age 45.5 ± 13.3, male 75%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Zinc

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Hassan et al;[255] preprint; 2020	Patients with mild to critical COVID-19. 49 assigned to zinc 220 mg twice a day and 56 assigned to standard of care	Mean age 45.9 ± 17.5, male 58.2%, hypertension 10.4%, diabetes 11.2%, coronary heart disease 3%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No
Abd-Elsalam et al;[256] peer-reviewed; 2020	Patients with mild to critical COVID-19. 96 assigned to zinc 220 mg twice a day for 15 days and 95 assigned to standard of care	Mean age 43 ± 14, male 57.7%, hypertension 18.4%, diabetes 12.9%	Hydroxychloroquine 100%,	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	

				inappropriate.	information
Abdelmaksoud et al;[257] Peer reviewed; 2020	Patients with mild to critical COVID-19. 49 assigned to Zinc 220mg twice a day and 56 assigned to SOC	NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVIDAtoZ -Zinc trial;[250] Thomas et al; ; 2020	Patients with mild COVID-19. 58 assigned to Zinc 50mg a day and 50 assigned to SOC	Mean age 45.2 ± 14.6, male 38.3%, hypertension 32.7%, diabetes 13.6%, COPD %, asthma 15.4%	Steroids 8.4%,	Low for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
ZINC COVID trial;[258] Patel et al; Peer reviewed; 2020	Patients with severe to critical COVID-19. 15 assigned to Zinc 0.24 mg/kg a day for 7 days and 18 assigned to SOC	Mean age 61.8 ± 16.9, male 63.6%, hypertension 48.4%, diabetes 18.2%, COPD 6%, CHD 21.2%,	Steroids 75.8%, remdesivir 30.3%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

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;[259] 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

Appendix 1. Summary of findings tables

Summary of findings table 1.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.9 (CI 95% 0.8 - 1.02) Based on data from 8000 patients in 12 studies	**160** per 1000	**144** per 1000 Difference: **16 fewer per 1000** (CI 95% 32 fewer - 3 more)	**Moderate** Due to serious imprecision[1]	Steroids probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 5942 patients in 6 studies Follow up 28	**172** per 1000	**150** per 1000 Difference: **22 fewer per 1000** (CI 95% 48 fewer - 9 more)	**Moderate** Due to serious imprecision[2]	Steroids probably decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.27 (CI 95% 0.98 - 1.65) Based on data from 646 patients in 5 studies	**606** per 1000	**770** per 1000 Difference: **164 more per 1000** (CI 95% 12 fewer - 394 more)	**Moderate** Due to serious risk of bias[3]	Steroids probably increases symptom resolution or improvement
Severe adverse events 28 days	Relative risk: 0.89 (CI 95% 0.68 - 1.17) Based on data from 833 patients in 6 studies	**102** per 1000	**91** per 1000 Difference: **11 fewer per 1000** (CI 95% 33 fewer - 17 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Steroids may have little or no difference on severe adverse events

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

Summary of findings table 2.

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

Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.94 (CI 95% 0.82 - 1.08) Based on data from 7331 patients in 4 studies Follow up Median 28 days	**160** per 1000	**150** per 1000 Difference: **10 fewer per 1000** (CI 95% 29 fewer - 13 more)	**Low** Due to serious imprecision, Due to serious risk of bias[1]	Remdesivir may decrease mortality slightly
Mechanical ventilation 28 days	Relative risk: 0.65 (CI 95% 0.39 - 1.11) Based on data from 6551 patients in 4 studies Follow up Median 28 days	**173** per 1000	**112** per 1000 Difference: **61 fewer per 1000** (CI 95% 106 fewer - 19 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Remdesivir may decrease mechanical ventilation requirements
Symptom resolution or improvement 28 days	Relative risk: 1.17 (CI 95% 1.03 - 1.33) Based on data from 1873 patients in 3 studies Follow up 28 days	**606** per 1000	**709** per 1000 Difference: **103 more per 1000** (CI 95% 18 more - 200 more)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Remdesivir may improve symptom resolution or improvement
Severe adverse events	Relative risk: 0.8 (CI 95% 0.48 - 1.33) Based on data from 1869 patients in 3 studies	**102** per 1000	**82** per 1000 Difference: **20 fewer per 1000** (CI 95% 53 fewer - 34 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Remdesivir may have little or no difference on severe adverse events

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

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

Summary of findings table 3.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 15 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 8838 patients in 10 studies Follow up Median 15 days	**160** per 1000	**171** per 1000 Difference: **11 more per 1000** (CI 95% 3 fewer - 27 more)	**Moderate** Due to serious risk of bias[1]	HCQ probably increases mortality
Mechanical ventilation 15 days	Relative risk: 1.05 (CI 95% 0.9 - 1.22) Based on data from 7168 patients in 7 studies Follow up Median 15 days	**173** per 1000	**182** per 1000 Difference: **9 more per 1000** (CI 95% 17 fewer - 38 more)	**Moderate** Due to serious risk of bias[2]	Hcq probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.05 (CI 95% 0.95 - 1.16) Based on data from 6305 patients in 7 studies Follow up 28 days	**606** per 1000	**636** per 1000 Difference: **30 more per 1000** (CI 95% 30 fewer - 97 more)	**Moderate** Due to serious inconsistency[3]	Hcq probably has little or no difference on symptom resolution or improvement
COVID-19 infection (in exposed individuals)	Relative risk: 0.9 (CI 95% 0.73 - 1.1) Based on data from 5707 patients in 6 studies	**174** per 1000	**157** per 1000 Difference: **17 fewer per 1000** (CI 95% 47 fewer - 17 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Hcq may have little or no difference on covid-19 infection (in exposed individuals)
Severe adverse events	Relative risk: 1.1 (CI 95% 0.78 - 1.54) Based on data from 5042 patients in 10 studies	**102** per 1000	**112** per 1000 Difference: **10 more per 1000** (CI 95% 22 fewer - 55 more)	**Low** Due to serious risk of bias, Due to serious imprecision[5]	Hcq may have little or no difference on severe adverse events

1. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;

2. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
3. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** I2 82%; **Imprecision: No serious.** Secondary to inconsistency;
4. **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 no infection reduction;
5. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Low number of patients;

Summary of findings table 4.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	LPV	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 1.02 (CI 95% 0.92 - 1.12) Based on data from 8010 patients in 3 studies Follow up Median 28 days	**160** per 1000	**163** per 1000 Difference: **3 more per 1000** (CI 95% 13 fewer - 19 more)	**Moderate** Due to serious imprecision[1]	Lpv probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 1.07 (CI 95% 0.98 - 1.17) Based on data from 7580 patients in 3 studies Follow up Median 28 days	**173** per 1000	**185** per 1000 Difference: **12 more per 1000** (CI 95% 3 fewer - 29 more)	**High**	Lpv does not reduce mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.03 (CI 95% 0.92 - 1.15) Based on data from 5239 patients in 2 studies Follow up 28 days	**606** per 1000	**624** per 1000 Difference: **18 more per 1000** (CI 95% 48 fewer - 91 more)	**Moderate** Due to serious risk of bias[2]	Lpv probably has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.6 (CI 95% 0.37 - 0.98) Based on data from 199 patients in 1 study	**102** per 1000	**61** per 1000 Difference: **41 fewer per 1000** (CI 95% 64 fewer - 2 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[3]	Lpv may have little or no difference on severe adverse events

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

Summary of findings table 5.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	CP	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.99 (CI 95% 0.92 - 1.06) Based on data from 13000 patients in 11 studies Follow up Median 28 days	**160** per 1000	**158** per 1000 Difference: **2 fewer per 1000** (CI 95% 13 fewer - 10 more)	**Moderate** Due to serious imprecision[1]	Convalescent plasma probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.89 (CI 95% 0.76 - 1.04) Based on data from 8149 patients in 7 studies Follow up Median 28 days	**173** per 1000	**154** per 1000 Difference: **19 fewer per 1000** (CI 95% 42 fewer - 7 more)	**Moderate** Due to serious imprecision[2]	Convalescent plasma probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.0 (CI 95% 0.93 - 1.08) Based on data from 12554 patients in 5 studies Follow up 28 days	**606** per 1000	**606** per 1000 Difference: **0 fewer per 1000** (CI 95% 42 fewer - 48 more)	**High**	Convalescent plasma has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.26 (CI 95% 0.83 - 1.9) Based on data from 81 patients in 1 study	**102** per 1000	**129** per 1000 Difference: **27 more per 1000** (CI 95% 17 fewer - 92 more)	**Very Low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[3]	We are uncertain whether convalescent plasma increases or decreases severe adverse events
Specific severe adverse events	Based on data from 20000 patients in 1 study	Observed risk of severe adverse events were: TRALI 0.1%, TACO 0.1%, severe allergic reactions 0.1%		-	Convalescent plasma infusion related adverse events are probably exceptional

1. **Imprecision: Serious.** 95%CI includes significant mortality reduction and increase;
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: Very Serious.** Low number of patients, Wide confidence intervals;

Summary of findings table 6.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	 TCZ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.9 (CI 95% 0.78 - 1.03) Based on data from 6350 patients in 8 studies Follow up Median 28 days	**160** per 1000	**144** per 1000 Difference: **16 fewer per 1000** (CI 95% 35 fewer - 5 more)	**Moderate** Due to serious imprecision[1]	TCZ probably decreases mortality
Mechanical ventilation 28 days	Relative risk: 0.79 (CI 95% 0.71 - 0.88) Based on data from 5352 patients in 8 studies Follow up Median 28 days	**173** per 1000	**137** per 1000 Difference: **36 fewer per 1000** (CI 95% 50 fewer - 21 fewer)	**High** [2]	TCZ decreases mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.1 (CI 95% 0.99 - 1.22) Based on data from 4549 patients in 4 studies Follow up 28 days	**606** per 1000	**667** per 1000 Difference: **61 more per 1000** (CI 95% 6 fewer - 133 more)	**Low** Due to serious imprecision, Due to serious risk of bias[3]	TCZ may increase symptom resolution or improvement
Severe adverse events	Relative risk: 0.89 (CI 95% 0.75 - 1.07) Based on data from 2312 patients in 8 studies	**102** per 1000	**91** per 1000 Difference: **11 fewer per 1000** (CI 95% 25 fewer - 7 more)	**Moderate** Due to serious risk of bias[4]	Tcz probably has little or no difference on severe adverse events

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

Summary of findings table 7.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	ACO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality: Therapeutic dose (i.e enoxaparin 1mg/kg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40mg a day)[1] 28 days	Relative risk: 2.02 (CI 95% 0.7 - 5.8) Based on data from 2409 patients 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[2]	We are uncertain whether ACO in therapeutic dose increases or decreases mortality in comparison to ACO in prophylactic dose
Mortality: Intermediate dose (i.e enoxaparin 40mg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40mg a day)[3] 28 days	Relative risk: 0.29 (CI 95% 0.13 - 0.64) Based on data from 843 patients 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[4]	We are uncertain whether ACO intermediate dose increases or decreases mortality in comparison to ACO prophylactic dose

1. Therapeutic dose (i.e enoxaparin 1mg/kg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40mg a day)
2. **Risk of bias: Very Serious. Imprecision: Very Serious.** 95%CI includes significant mortality reduction and increase
3. Therapeutic dose (i.e enoxaparin 40mg every 12 hs) vs. prophylactic dose (i.e enoxaparin 40mg a day)
4. **Risk of bias: Very Serious.**

Summary of findings table 8.

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

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

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

Summary of findings table 9.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	IFN	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 1.04 (CI 95% 0.88 - 1.23) Based on data from 4242 patients in 3 studies Follow up Median 28 days	**160** per 1000	**166** per 1000 Difference: **6 more per 1000** (CI 95% 19 fewer - 37 more)	**Moderate** Due to serious imprecision[1]	IFN probably has little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.98 (CI 95% 0.83 - 1.16) Based on data from 3981 patients in 3 studies Follow up 28 days	**173** per 1000	**170** per 1000 Difference: **3 fewer per 1000** (CI 95% 29 fewer - 28 more)	**Moderate** Due to serious imprecision[2]	IFN probably has little or no difference on mechanical ventilation
Symptom resolution or improvement 28 days	Hazard Ratio: 1.1 (CI 95% 0.64 - 1.87) Based on data from 121 patients in 2 studies Follow up 28 days	**606** per 1000	**641** per 1000 Difference: **35 more per 1000** (CI 95% 157 fewer - 219 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[3]	We are uncertain whether IFN increases or decreases symptom resolution or improvement
Symptom resolution or improvement (inhaled)[4] 30 days	Hazard Ratio: 2.19 (CI 95% 1.03 - 4.69) Based on data from 81 patients in 1 study Follow up 28 days	**606** per 1000	**870** per 1000 Difference: **264 more per 1000** (CI 95% 11 more - 381 more)	**Low** Due to very serious imprecision[5]	IFN (inhaled) may increase symptom resolution or improvement

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

Summary of findings table 10.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	favipiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.34 (CI 95% 0.01 - 8.38) Based on data from patients in 1 study Follow up Median 28 days	**160** per 1000	**54** per 1000 Difference: **106 fewer per 1000** (CI 95% 158 fewer - 1181 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[1]	We are uncertain whether favipiravir increases or decreases mortality
Symptom resolution or improvement 28 days	Relative risk: 1.3 (CI 95% 1.09 - 1.55) Based on data from 759 patients in 6 studies Follow up 28 days	**606** per 1000	**788** per 1000 Difference: **182 more per 1000** (CI 95% 55 more - 333 more)	**Low** Due to very serious imprecision, Due to serious imprecision[2]	favipiravir may increase symptom resolution or improvement
Severe adverse events[3] 30 days	Relative risk: 1.02 (CI 95% 0.32 - 3.23) Based on data from 163 patients in 1 study Follow up 28 days	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 412 fewer - 1351 more)	**Very Low** Due to very serious imprecision[4]	IFN (inhaled) may increase symptom resolution or improvement

1. **Risk of bias: Serious. Imprecision: Very 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, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Serious.** 95%CI includes significant benefits and absence of benefits ;
3. Nebulizations
4. **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits;

Summary of findings table 11.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality[1]	Relative risk: 0.94 (CI 95% 0.51 - 1.73) Based on data from 747 patients in 4 studies	**160** per 1000	**150** per 1000 Difference: **10 fewer per 1000** (CI 95% 78 fewer - 117 more)	**Low** Due to very serious imprecision[2]	Ivermectin may have little or no difference on mortality
Mechanical ventilation	Relative risk: 0.89 (CI 95% 0.38 - 2.07) Based on data from 312 patients in 3 studies	**173** per 1000	**154** per 1000 Difference: **19 fewer per 1000** (CI 95% 107 fewer - 185 more)	**Very Low** Due to serious indirectness, Due to serious publication bias, Due to very serious imprecision[3]	We are uncertain whether ivermectin increases or decreases mortality
Symptom resolution or improvement[1]	Relative risk: 1.0 (CI 95% 0.9 - 1.11) Based on data from 508 patients in 2 studies	**606** per 1000	**606** per 1000 Difference: **0 fewer per 1000** (CI 95% 61 fewer - 67 more)	**Moderate** Due to serious imprecision[4]	Ivermectin probably has little or no difference on symptom resolution or improvement
Symptomatic infection[5]	Relative risk: 0.14 (CI 95% 0.09 - 0.21) Based on data from 738 patients in 3 studies	**174** per 1000	**24** per 1000 Difference: **150 fewer per 1000** (CI 95% 158 fewer - 137 fewer)	**Very Low** Due to very serious risk of bias, Due to serious imprecision[6]	We are uncertain whether ivermectin increases or decreases symptomatic infection
Severe adverse events	Relative risk: 1.04 (CI 95% 0.32 - 3.38) Based on data from 824 patients in 4 studies Follow up 28 days	**102** per 1000	**106** per 1000 Difference: **4 more per 1000** (CI 95% 69 fewer - 243 more)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias, Due to serious publication bias[7]	We are uncertain whether ivermectin increases or decreases severe adverse events

1. Based on low risk of bias studies
2. **Imprecision: Very Serious.** 95%CI includes significant benefits and harms;

3. **Indirectness: Serious.** Most events from studies that compared ivermectin against hydroxychloroquine; **Imprecision: Very Serious.** Wide confidence intervals; **Publication bias: Serious.**
4. **Imprecision: Serious.** Wide confidence intervals;
5. Symptomatic infection in persons at risk or exposed to SARS-COV2
6. **Risk of bias: Very Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Serious.** Few events, optimal information size not met (n=86);
7. **Risk of bias: Very Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits; **Publication bias: Serious.**

Summary of findings table 12.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 1.01 (CI 95% 0.92 - 1.1) Based on data from 8272 patients in 3 studies	**160** per 1000	**162** per 1000 Difference: **2 more per 1000** (CI 95% 13 fewer - 16 more)	**Moderate** Due to serious imprecision[1]	Azithromycin probably has little or no difference on mortality
Invasive mechanical ventilation	Relative risk: 0.94 (CI 95% 0.78 - 1.13) Based on data from 8544 patients in 3 studies	**173** per 1000	**163** per 1000 Difference: **10 fewer per 1000** (CI 95% 38 fewer - 22 more)	**Moderate** Due to serious imprecision[2]	Azithromycin probably has little or no difference on invasive mechanical ventilation
Symptom resolution or improvement[3]	Relative risk: 1.02 (CI 95% 0.99 - 1.04) Based on data from 9086 patients in 3 studies	**606** per 1000	**618** per 1000 Difference: **12 more per 1000** (CI 95% 6 fewer - 24 more)	**High**	Azithromycin has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 1.23 (CI 95% 0.51 - 2.96) Based on data from 439 patients in 1 study Follow up 28 days	**102** per 1000	**125** per 1000 Difference: **23 more per 1000** (CI 95% 50 fewer - 200 more)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias[4]	We are uncertain whether azithromycin increases or decreases severe adverse events

1. **Imprecision: Serious.** 95%CI includes significant benefits and harms;
2. **Imprecision: Serious.** 95%CI includes significant benefits and harms;
3. Symptomatic infection in persons at risk or exposed to SARS-COV2
4. **Risk of bias: Serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits ;

Summary of findings table 13.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** SOC	Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Relative risk: 0.45 (CI 95% 0.18 - 1.12) Based on data from 4665 patients in 3 studies	**160** per 1000	**72** per 1000 Difference: **88 fewer per 1000** (CI 95% 131 fewer - 19 more)	**Low** Due to very serious imprecision[1]	Colchicine may decrease mortality
Invasive mechanical ventilation	Relative risk: 0.48 (CI 95% 0.24 - 0.96) Based on data from 4593 patients in 2 studies Follow up 30 days	**173** per 1000	**83** per 1000 Difference: **90 fewer per 1000** (CI 95% 131 fewer - 7 fewer)	**Low** Due to very serious imprecision[2]	Colchicine probably decreases invasive mechanical ventilation
Severe adverse events	Relative risk: 0.78 (CI 95% 0.61 - 1.0) Based on data from 4488 patients in 1 study Follow up 30 days	**102** per 1000	**80** per 1000 Difference: **22 fewer per 1000** (CI 95% 40 fewer - 0 fewer)	**High** [3]	Colchicine has little or no difference on severe adverse events
Pulmonary embolism	Relative risk: 5.55 (CI 95% 1.23 - 25.0) Based on data from 4399 patients in 1 study Follow up 30 days	**0.9** per 1000	**5.0** per 1000 Difference: **4.1 more per 1000** (CI 95% 0.21 more - 21.6 more)	**Low** Due to very serious imprecision[4]	Colchicine may have little or no difference on pulmonary embolism

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

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