COVID-19

Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence

RAPID REVIEW, 18 December 2020

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

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Disclaimer

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

Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence. Rapid Review, 18 December 2020

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Summary of the evidence

In this section we present a summary of the evidence on therapeutics for the prevention and treatment of patients with COVID-19, by intervention. Table 1 summarizes the evidence provided by randomized controlled trials (RCT) and table 2, the evidence from non-randomized controlled trials (non-RCT).

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Table 1. Interventions effects and certainty in RCT

Intervention	Overall number of studies including the intervention, n=158	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	31	8	7	5	6	8
Glucocorticoids	11	10	4	3		6
Ivermectin	11	5		4		2
Convalecent plasma	10	9	5	4		3
Favipiravir	9			5		1
Lopinavir-Ritonavir	7	3	3	2		1
Tocilizumab	7	5	5	3		6
Remdesivir	6	4 (*)	4	3		3
Umifenovir	5					
Azithromycin	3	3	2	2		1
Colchicine	3	1	1			
Interferon beta-1a	3	2	3	2		
IVIG	3	3	2			1
Mesenchimal cell tranplantation	3	1		1		1
Sofosbuvir/Daclatasvir	3	1	1	1		
Vitamin D	3	1	1			1
Bromhexine Hydrochloride	2	1	1	1		1
Leflunomide	2					
Zinc	2	1	1	1		
99mTc-MDP	1					
Anticoagulants	1	1				
Aprepitant	1					
Auxora	1	1	1			
Azvudine	1					
Baloxavir	1			1		
Bamlanivimab	1	1		1		1
Baricitinib	1	1	1	1		1
BCG	1	1				
Cofactors	1			1		1
CIGB-325	1			1		1
Darunavir-Cobicistat	1					
Dutasteride	1					
Electrolyzed saline	1	1		1		
Febuxostat	1					
Flebuxamine	1	1	1			1
Icatibant	1	1				
iC1e/K	1	1				
IFN-alpha2b + IFN-gamma	1					
IFX-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
Lincomicin	1					
Mouthwash (hydrogen peroxide)	1	1	1	1		
Mouthwash (povidone iodine or essenti	1					
N-acetylcysteine	1	1	1			1
Nasal hypertonic saline	1			1		
Nitazoxanide	1			1		
Novaferon	1					
Ozone	1	1				1
Peg-IFN lambda	1					1
Progesterone	1	1	1			1
Prolectin-M						
Ramipril	1	1			1	
Recombinant Super-Compound IFN	1	1		1		
Ribavirin	1					
Ribavirin + Interferon beta-1b	1					
Ruxolitinib	1			1		
rhG-CSF	1	1		1		1
Sulodexide	1	1	1			1
Telmisartan	1	1	1			
Triazavirin	1	1		1		1
Vitamin C	1	1	1	1		
α-Lipoic acid	1	1				

(*) 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 beneficial effect nor harmfull effect		
Harmfull effect		
Uncertain effect		
No evidence or no estimable effect		

Table 2. Interventions effects and certainty in non-RCT

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	14	12				
NSAID	7	7				
Famotidine	3	3				
Colchicine	2	2				

* Only specific transfusion related adverse events

	GRADE High- Moderate certainty	GRADE Low certainty
Beneficial effect		
No beneficial effect nor harmfull effect		
Harmfull effect		
Uncertain effect		
No evidence or no estimable effect		

Take home message thus far

• More than 200 therapeutic options or their combinations are being investigated in more than 1,700 clinical trials. In this review we examined 66 therapeutic options (Tables 1,2,3).

• The body of evidence on steroids including ten RCT shows that low/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 ARDS secondary to alternative etiologies (not COVID-19 related) were randomized to steroids or placebo/no steroids.

• 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 other five RCT, remdesivir may slightly reduce mortality, 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 or discard these findings.

• The body of evidence on hydroxychloroquine, Lopinavir-Ritonavir and interferon beta-1a, including anticipated RECOVERY trial and SOLIDARITY trial findings 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 or discard these findings.

• The results of nine RCT assessing convalescent plasma in COVID-19 patients showed a non-statistically significant trend towards reduction in mortality and invasive mechanical ventilation requirements. Overall certainty of the evidence is very low and further research is needed to confirm or discard these findings.

• The results of seven RCT shows that in patients with severe disease, tocilizumab probably reduces mechanical ventilation requirements but may not affect mortality. Further research is needed to confirm or discard these findings.

• Currently, as to ivermectin, pooled estimates suggest significant benefits. However, included studies methodological limitations and a small overall number of events results in very low certainty of the evidence. Further research is needed to confirm or discard those findings.

• Currently as to colchicine and famotidine, there is very low certainty of its effects on clinical important outcomes.

• 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.

• Currently, as to NSAID exposure, no association with increased mortality was observed. However, certainty of the evidence is very low and further research is needed to confirm or discard these findings.

• The use of medications such as ivermectin, antivirals, and immunomodulators, among others, should be done in the context of patient consented, ethically approved, randomized clinical trials that evaluate their safety and efficacy.

• 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, and particularly as it applies to any special sub-group populations such as children, expectant mothers, those with immune conditions etc.

• 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 to minority sub-groups. These groups are plagued by social and structural inequities that bring to bear a disproportionate burden of COVID illness onto them.

• 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 includes patients with COVID-19 before most therapeutic options can be administered with any confidence. The importance of an adequately designed and reported clinical trial is paramount in evidence-based medicine. Most of the research to date on COVID has very poor methodology that is hidden and very difficult to validate. The depth of transparency that is required is very lacking.

Mensajes clave hasta el momento

• Más de 200 intervenciones terapéuticas o sus combinaciones están siendo investigadas en más de 1700 estudios clínicos. En esta revisión se incluyen 66 posibles intervenciones para el manejo de pacientes con COVID-19 (cuadro 3).

• El conjunto de evidencia sobre los esteroides incluye diez estudios aleatorizados y controlados (ECA) y muestra que la administración de dosis bajas a moderadas (la dosis utilizada en el estudio RECOVERY fue dexametasona 6 mg por vía oral o endovenosa al día durante 10 días) probablemente reducen la mortalidad en pacientes con infección grave por COVID-19. Estos resultados fueron uniformes luego de agregar al análisis estudios en los que pacientes con SDRA de otras etiologías fueron aleatorizados a recibir corticosteroides o manejo estándar.

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

• 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, requerimientos de ventilación mecánica invasiva o en 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 no estadísticamente significativa hacia una reducción en el riesgo de infección. Más información de estudios con un diseño adecuado es necesaria para confirmar o descartar estos hallazgos.

• Los resultados de nueve ECA que evaluaron el uso de plasma de convaleciente en pacientes con COVID-19 mostraron una tendencia no significativa desde el punto de vista estadístico hacia una reducción en la mortalidad y la necesidad de ventilación mecánica invasiva. La certeza en la evidencia es muy baja y se necesita más información de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• Los resultados de siete ECA muestran que tocilizumab probablemente reduce los requerimientos de ventilación invasiva pero podría no afectar la mortalidad. Se necesita más información de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• Hasta el momento, en relación con la ivermectina, los resultados combinados de los estudios incluidos sugieren beneficios con dicha intervención. Sin embargo, las limitaciones metodológicas de los estudios incluidos y pequeña cantidad de eventos resultan en una certeza en la evidencia muy baja. Se necesita más información de estudios con un diseño adecuado para confirmar o descartar estos hallazgos.

• Hasta el momento, en relación con colchicina y famotidina hay evidencia de muy baja certeza, por lo que sus efectos son inciertos. Se necesita más información de estudios con un diseño adecuado para evaluar la utilidad de ivermectina en este supuesto.

• 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.

• Hasta el momento, en relación con el uso de AINES no se observa una asociación con un incremento en la mortalidad. Sin embargo, la certeza en la evidencia es muy baja, por lo que se necesita más información de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• La administración de medicamentos como ivermectina, antivirales e inmunomoduladores, entre otros, debería realizarse solo en el ámbito de estudios clínicos diseñados para evaluar su eficacia y seguridad, éticamente aprobados y con previo consentimiento de los pacientes.

• 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 o los pacientes inmunocomprometidos, entre otros.

• La OPS también tiene en cuenta las diferencias en los efectos de la COVID-19 en función de la identidad étnica de las personas y sobre las minorías. En consecuencia, recopila de manera continua 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 desproporcionada relacionada con la COVID.

• La seguridad de los pacientes afectados por la COVID-19 es una prioridad para mejorar 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 ECA 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.

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

Table 1, below, summarizes the status of evidence for the 58 potential therapeutic options for COVID-19 for which studies were identified through our systematic review. Tables 2 and 3, which divide the total group of identified studies into randomized (Table 2) and non-randomized (Table 3) designs, indicate the primary outcome measures used for each investigation and the level of certainty.

Table 1. Summary of evidence for potential therapeutic options for COVID-19 (n=66), as of 18 December 2020

	Intervention	Summary of evidence
1	**99mTc-MDP**	Uncertainty in potential benefits and harms. Further research is needed.
2	**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.
3	**Aprepitant**	Uncertainty in potential benefits and harms. Further research is needed.
4	**Auxora**	Uncertainty in potential benefits and harms. Further research is needed.
5	**Azithromycin**	Azithrimycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.
6	**Azvudine**	Uncertainty in potential benefits and harms. Further research is needed.
7	**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.
8	**Baloxavir**	Uncertainty in potential benefits and harms. Further research is needed.
9	**Bamlanivimab (monoclonal antibody)**	Uncertainty in potential benefits and harms. Further research is needed.
10	**BCG**	Uncertainty in potential benefits and harms. Further research is needed.

11	**Bromhexine hydrochloride**	Uncertainty in potential benefits and harms. Further research is needed.
12	**CIGB-325**	Uncertainty in potential benefits and harms. Further research is needed.
13	**Cofactors (L-carnitine, N-acetylcysteine, nicotinamide, serine)**	Uncertainty in potential benefits and harms. Further research is needed.
14	**Colchicine**	Uncertainty in potential benefits and harms. Further research is needed.
15	**Convalescent plasma**	Uncertainty in potential benefits and harms. Although pooled estimates suggest small benefits with convalescent plasma, included studies methodological limitations and a small overall number of events results in very low certainty of the evidence. Further research is needed to confirm or discard those findings.
16	**Darunavir-cobicistat**	Uncertainty in potential benefits and harms. Further research is needed.
17	**Dutasteride**	Uncertainty in potential benefits and harms. Further research is needed**.**
18	**Electrolyzed saline**	Uncertainty in potential benefits and harms. Further research is needed.
19	**Famotidine**	Uncertainty in potential benefits and harms. Further research is needed.
20	**Favipiravir**	Favipravir may improve time to symptom resolution. It is uncertain if favipravir affects mortality or mechanical ventilation requirements. Further research is needed.
21	**Febuxostat**	Uncertainty in potential benefits and harms. Further research is needed.
22	**Flevuxamine**	Uncertainty in potential benefits and harms. Further research is needed.

23	**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.
24	**Icatibant/iC1e/K**	Uncertainty in potential benefits and harms. Further research is needed.
25	**IFX-1**	Uncertainty in potential benefits and harms. Further research is needed.
26	**Interferon alpha-2b and Interferon gamma**	Uncertainty in potential benefits and harms. Further research is needed.
27	**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.
28	**Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
29	**Interferon kappa and TFF2**	Uncertainty in potential benefits and harms. Further research is needed.
30	**Itolizumab**	Uncertainty in potential benefits and harms. Further research is needed.
31	**Ivermectin**	Uncertainty in potential benefits and harms. 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. Further research is needed to confirm or discard those findings.
32	**Intravenous immunoglobulin**	Uncertainty in potential benefits and harms. Further research is needed.
33	**Leflunomide**	Uncertainty in potential benefits and harms. Further research is needed.
34	**Lincomycin**	Uncertainty in potential benefits and harms. Further research is needed.

35	**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.
36	**Mesenchymal stem-cell transplantation**	Uncertainty in potential benefits and harms. Further research is needed.
37	**Mouthwash (hydrogen peroxide)**	Uncertainty in potential benefits and harms. Further research is needed.
38	**Mouthwash (povidone iodine or essential oils)**	Uncertainty in potential benefits and harms. Further research is needed.
39	**N-acetylcysteine**	Uncertainty in potential benefits and harms. Further research is needed.
40	**Nasal hypertonic saline**	Uncertainty in potential benefits and harms. Further research is needed.
41	**Nitazoxanide**	Uncertainty in potential benefits and harms. Further research is needed.
42	**Novaferon**	Uncertainty in potential benefits and harms. Further research is needed.
43	**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.
44	**Ozone**	Uncertainty in potential benefits and harms. Further research is needed.
45	**Peg-interferon lamda**	Uncertainty in potential benefits and harms. Further research is needed.
46	**Pentoxifylline**	Uncertainty in potential benefits and harms. Further research is needed.
47	**Progesterone**	Uncertainty in potential benefits and harms. Further research is needed

48	**Prolectin-M**	Uncertainty in potential benefits and harms. Further research is needed
49	**Ramipril**	Uncertainty in potential benefits and harms. Further research is needed.
50	**Recombinant super-Compound Interferon**	Uncertainty in potential benefits and harms. Further research is needed.
51	**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.
52	**rhG-CSF (in patients with lymphopenia)**	Uncertainty in potential benefits and harms. Further research is needed.
53	**Ribavirin**	Uncertainty in potential benefits and harms. Further research is needed.
54	**Ribavirin + Interferon beta-1b**	Uncertainty in potential benefits and harms. Further research is needed.
55	**Ruxolitinib**	Uncertainty in potential benefits and harms. Further research is needed.
56	**Sofosbuvir/daclatasvir**	Uncertainty in potential benefits and harms. Further research is needed.
57	**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.
58	**Sulodexide**	Uncertainty in potential benefits and harms. Further research is needed.
59	**Telmisartan**	Uncertainty in potential benefits and harms. Further research is needed.

60	**Tocilizumab**	Tocilizumab may not affect mortality but may reduce invasive mechanical ventilation requirements and improve time to symptom resolution. However, certainty of the evidence is low because of imprecision. Further research is needed.
61	**Triazavirin**	Uncertainty in potential benefits and harms. Further research is needed.
62	**Umifenovir**	Uncertainty in potential benefits and harms. Further research is needed.
63	**Vitamin C**	Uncertainty in potential benefits and harms. Further research is needed.
64	**Vitamin D**	Uncertainty in potential benefits and harms. Further research is needed.
65	**Zinc**	Uncertainty in potential benefits and harms. Further research is needed.
66	**α-Lipoic acid**	Uncertainty in potential benefits and harms. Further research is needed.

Table 2. List of RCTs of interventions for COVID-19 with primary outcome measures and certainty (n=158)

Intervention	Overall number of studies including the intervention, n=158	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	31	8	7	5	6	8
Glucocorticoids	11	10	4	3		6
Ivermectin	11	5		4		2
Convalecent plasma	10	9	5	4		3
Favipiravir	9			5		1
Lopinavir-Ritonavir	7	3	3	2		1
Tocilizumab	7	5	5	3		6
Remdesivir	6	4 (*)	4	3		3
Umifenovir	5					
Azithromycin	3	3	2	2		1
Colchicine	3	1	1			
Interferon beta-1a	3	2	3	2		
IVIG	3	3	2			1
Mesenchimal cell tranplantation	3	1		1		1
Sofosbuvir/Daclatasvir	3	1	1	1		
Vitamin D	3	1	1			1
Bromhexine Hydrochloride	2	1	1	1		1
Leflunomide	2					
Zinc	2	1	1	1		
99mTc-MDP	1					
Anticoagulants	1	1				
Aprepitant	1					
Auxora	1	1	1			
Azvudine	1					
Baloxavir	1			1		
Bamlanivimab	1	1		1		1
Baricitinib	1	1	1	1		1
BCG	1	1				
Cofactors	1			1		1
CIGB-325	1			1		1
Darunavir-Cobicistat	1					
Dutasteride	1					
Electrolyzed saline	1	1		1		
Febuxostat	1					
Flebuxamine	1	1	1			1
Icatibant	1	1				
iC1e/K	1	1				
IFN-alpha2b + IFN-gamma	1					
IFX-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
Lincomicin	1					
Mouthwash (hydrogen peroxide)	1	1	1	1		
Mouthwash (povidone iodine or essenti	1					
N-acetylcysteine	1	1	1			1
Nasal hypertonic saline	1			1		
Nitazoxanide	1			1		
Novaferon	1					
Ozone	1	1				1
Peg-IFN lambda	1					1
Progesterone	1	1	1			1
Prolectin-M						
Ramipril	1	1			1	
Recombinant Super-Compound IFN	1	1		1		
Ribavirin	1					
Ribavirin + Interferon beta-1b	1					
Ruxolitinib	1			1		
rhG-CSF	1	1		1		1
Sulodexide	1	1	1			1
Telmisartan	1	1	1			
Triazavirin	1	1		1		1
Vitamin C	1	1	1	1		
α-Lipoic acid	1	1				

(*) 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 3. 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	15	12				
NSAID	7	7				
Famotidine	3	3				
Colchicine	2	2				

* Only specific transfusion related adverse events

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

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 66 therapeutic options.

• **Steroids:** The body of evidence on steroids, which includes ten 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 ten RCTs assessing convalescent plasma in COVID-19 patients showed a non-statistically significant trend towards reduction in mortality and invasive mechanical ventilation requirements. Overall certainty of the evidence is very low and further research is needed to confirm these findings.

• **Tocilizumab:** The results of seven RCTs using tocilizumab show that, in patients with severe disease, tocilizumab possibly reduces mechanical ventilation requirements but may not affect mortality. Further research is needed to confirm these findings.

• **Ivermectin:** Although the results of four RCT suggest mortality reduction with ivermectin the certainty of the evidence was very low because of methodological limitations and small number of events. Further research is needed to confirm these findings.

• **Colchicine and famotidine:** Currently, there is very low certainty about the effects of colchicine and 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.

• **Cautionary note:** The use of medications such as ivermectin, antivirals, n-acetylcysteine, monoclonal antibodies and immunomodulators, among others, should be done in the context of patient consented, ethically approved, randomized clinical trials that evaluate their safety and efficacy.

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 58 intervenciones para el manejo de pacientes con COVID-19.

• **Esteroides:** El conjunto de evidencia sobre los esteroides incluye diez 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 diez ECCA que evaluaron el uso de plasma de convalecientes en pacientes con COVID-19 mostraron una tendencia no significativa desde el punto de vista estadístico hacia una reducción en la mortalidad y la necesidad de ventilación

mecánica invasiva. La certeza en la evidencia es muy baja y se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• **Tocilizumab:** Los resultados de siete ECCA muestran que el tocilizumab posiblemente reduce la necesidad de ventilación invasiva pero podría no afectar a la mortalidad. Se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• **Ivermectina:** A pesar que los resultado de cuatro estudios sugieren una reducción en la mortalidad con ivermectina, la certeza en la evidencia resultó muy baja por limitaciones metodológicas y un número pequeño de eventos. Se necesita más información procedente de estudios con un diseño adecuado para confirmar o descartar estas conclusiones.

• **Colchicina y famotidina:** Hasta el momento, la evidencia sobre los efectos de la ivermectina, colchicina y famotidina es de muy baja certeza. Se necesita más información procedente de estudios con un diseño adecuado para evaluar la utilidad de la ivermectina en este supuesto.

• **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.

• **Nota de advertencia:** La administración de medicamentos como ivermectina, antivirales e inmunomoduladores, entre otros, debería realizarse solo en el ámbito de ensayos clínicos diseñados para evaluar su eficacia y seguridad, éticamente aprobados y con el consentimiento de los pacientes.

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 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 ECCA 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 December 18, 2020. 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). For some of these interventions (anticoagulants and non-steroidal anti-inflammatory drugs [NSAIDs]), 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 (https://isaric.tghn.org/). For baseline infection risk in exposed to COVID-19 we used estimates from a SR on physical distancing and mask utilization,[5] and for adverse events and symptom resolution/improvement we used the mean risk in the control groups from included RCTs. 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.[6] 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 4).

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

A total of 185 studies were selected for inclusion, 158 RCT and 27 non-RCT.

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 3. 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

Main findings

Corticosteroids

See Summary of findings Table 1, Appendix 1

We identified 11 RCTs including 7,914 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 0.89 (95%CI 0.78 to 1.02); RD -3.6% (95%CI -7.3% to 0.6%); Moderate certainty ⊕⊕⊕◯ (Figure 1.)
- Steroids probably reduce invasive mechanical ventilation requirement, RR 0.84 (95%CI 0.67 to 1.04); RD -1.8% (95%CI -3.8% to 0.4%); Moderate certainty ⊕⊕⊕◯
- Steroids probably improve time-to-symptom resolution, RR 1.49 (95%CI 1.22 to 1.84); RD 27.1% (95%CI 12.2% to 46.5%); Moderate certainty ⊕⊕⊕◯
- Steroids may not significantly increase the risk of severe adverse events, RR 0.89 (95%CI 0.68 to 1.17); RD -0.6% (95%CI -1.7% to 0.9%); 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

Study	TE	seTE	RR	95%-CI	Weight (fixed)	Weight (random)
RECOVERY - Dexamethasone	-0.11	0.0476	0.89	[0.81; 0.98]	65.4%	34.1%
GLUCOCOVID	0.22	0.4806	1.24	[0.48; 3.19]	0.6%	2.0%
Metcovid	-0.03	0.1299	0.97	[0.75; 1.25]	8.8%	16.9%
DEXA-COVID19	0.54	0.8797	1.71	[0.31; 9.61]	0.2%	0.6%
REMAP-CAP	-0.17	0.1715	0.84	[0.60; 1.18]	5.0%	11.8%
Steroids-SARI	-0.04	0.2621	0.96	[0.57; 1.60]	2.2%	6.1%
COVID STEROID	1.03	0.7270	2.80	[0.67; 11.64]	0.3%	0.9%
CoDEX	-0.09	0.0968	0.92	[0.76; 1.11]	15.8%	22.8%
CAPE COVID	-0.64	0.3377	0.53	[0.27; 1.02]	1.3%	3.9%
Edalatifard M et al (Tehran University of Medical Sciences)	-1.99	0.7199	0.14	[0.03; 0.56]	0.3%	0.9%
Fixed effect model			**0.90**	**[0.83; 0.97]**	**100.0%**	--
Random effects model			**0.89**	**[0.78; 1.02]**	--	**100.0%**

Heterogeneity: I^2 = 33%, τ^2 = 0.0121, p = 0.15

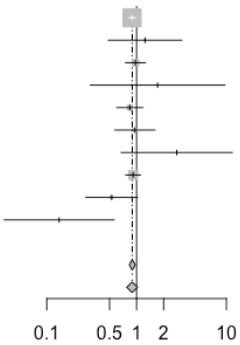


Figure 2. All-cause mortality in RCTs comparing corticosteroids with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19

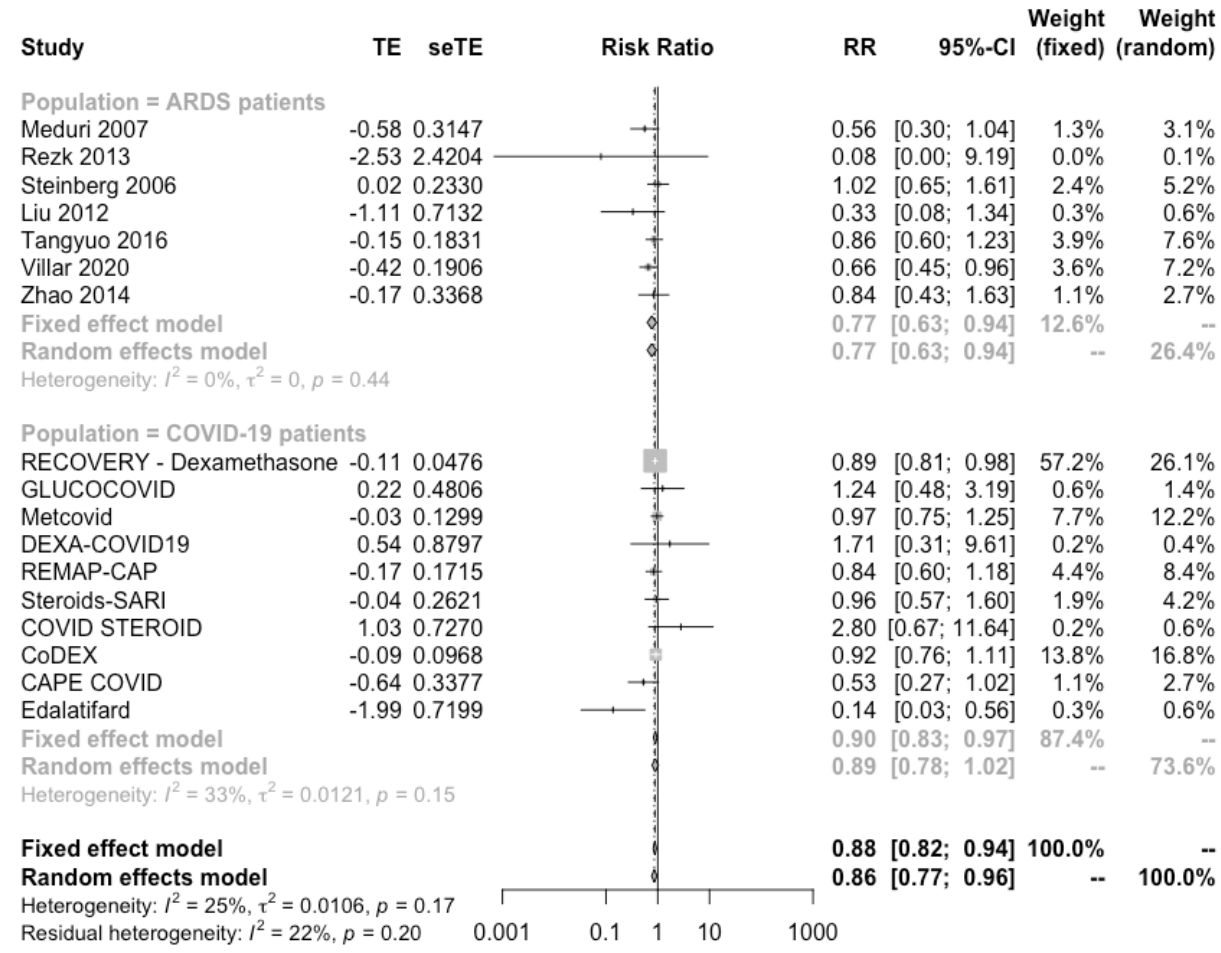
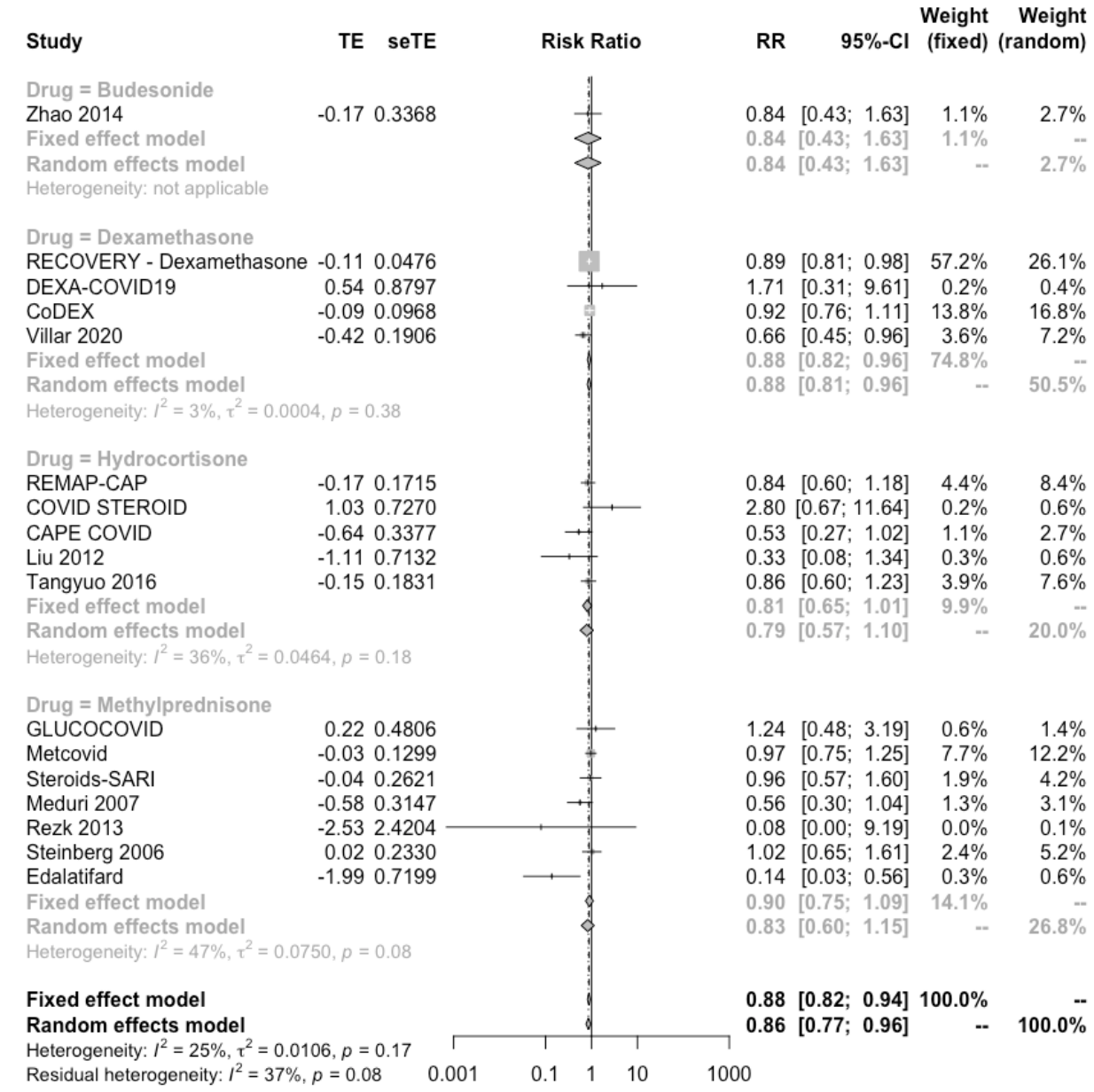


Figure 3. All-cause mortality by type of corticosteroids in RCTs using comparison with standard of care for treatment of patients with COVID-19 or ARDS without COVID-19



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 -2% (95%CI -5.9% to 2.6%); Low certainty ⊕⊕◯◯ (figure 4.)
- Remdesivir may reduce invasive mechanical ventilation requirement RR 0.65 (95%CI 0.39 to 1.11); RD -4.1% (95%CI -7.1% to -1.3%); Low certainty ⊕⊕◯◯ (Figure 5.)
- Remdesivir may improve time to symptom resolution, RR 1.17 (95%CI 1.03 to 1.33); RD 9.4% (95%CI 1.7% to 18.3%); 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 -1% (95%CI -2.8% to 1.8%); Low certainty ⊕⊕◯◯

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

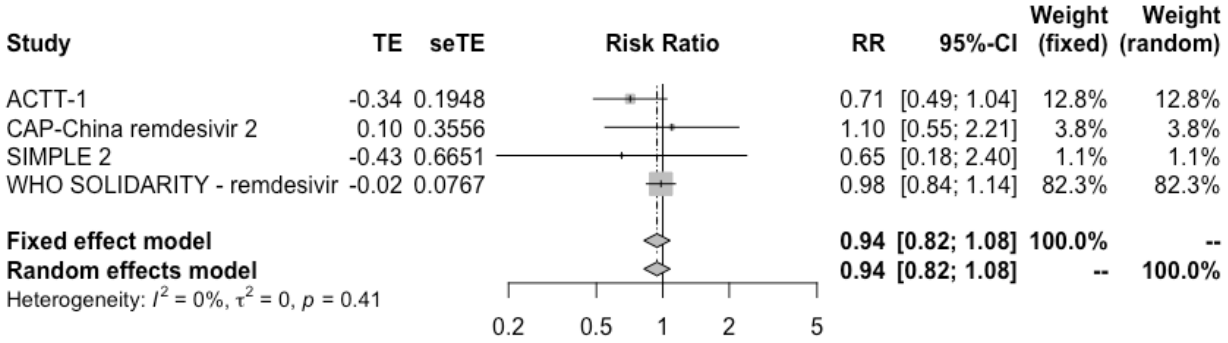


Figure 5. Invasive mechanical ventilation requirements in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19

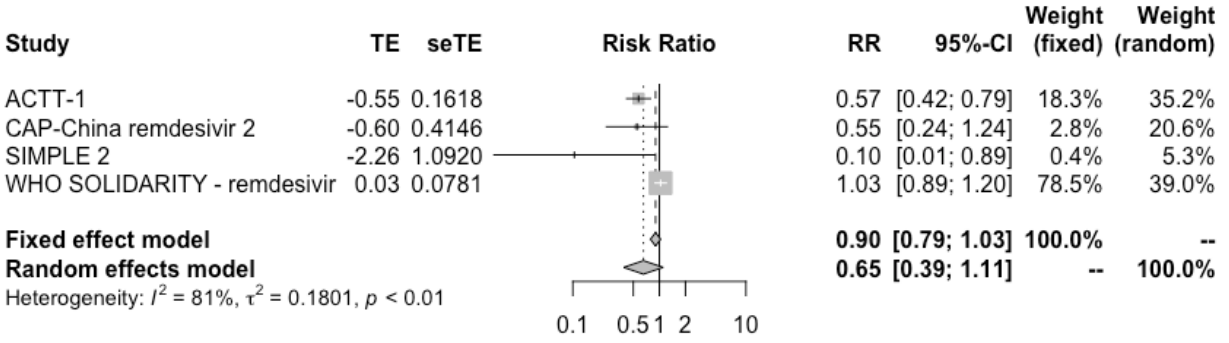
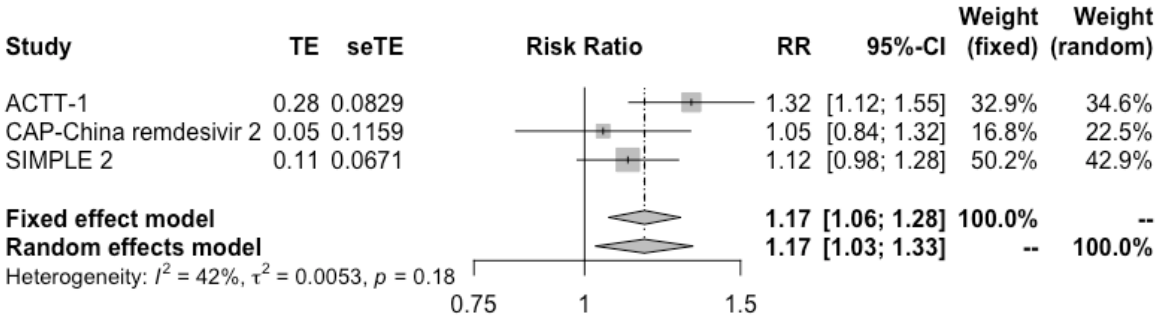


Figure 6. Symptom resolution or improvement in RCTs comparing remdesivir with standard of care for treatment of patients with COVID-19



Hydroxychloroquine and Chloroquine

See Summary of findings Table 3, Appendix 1

We identified 31 RCTs including 16,536 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 1.08 (95%CI 0.99 to 1.19); RD 2.6% (95%CI -0.3% to 6.6%); 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 0.6% (95%CI -1.1% to 2.6%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or chloroquine may not improve time to symptom resolution, RR 1.05 (95%CI 0.94 to 1.18); RD 2.8% (95%CI -3.3% to 10%); 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.)
- It is uncertain if hydroxychloroquine or chloroquine increase the risk of severe adverse events, RR 1.1 (95%CI 0.77 to 1.57); RD 0.5% (95%CI -1.2% to 3.1%); Low certainty ⊕⊕◯◯

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

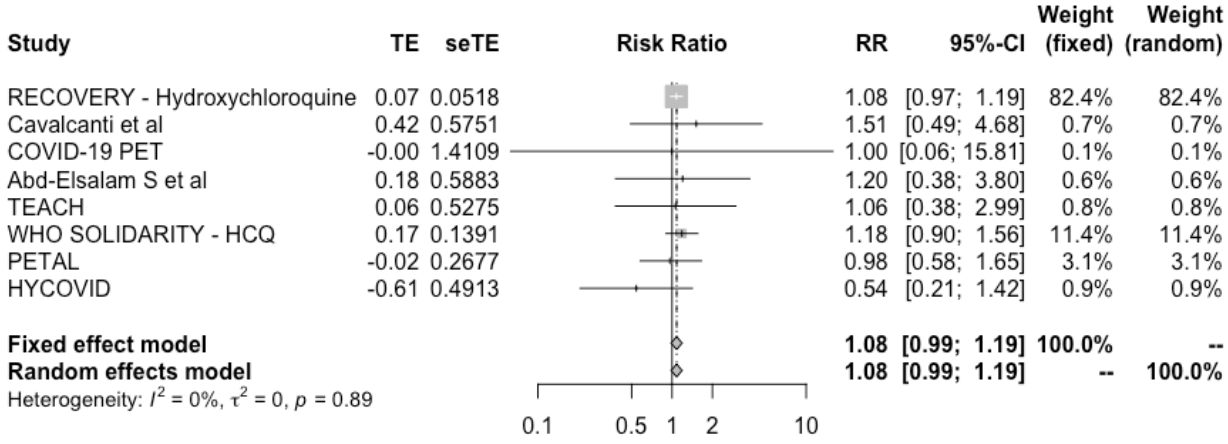
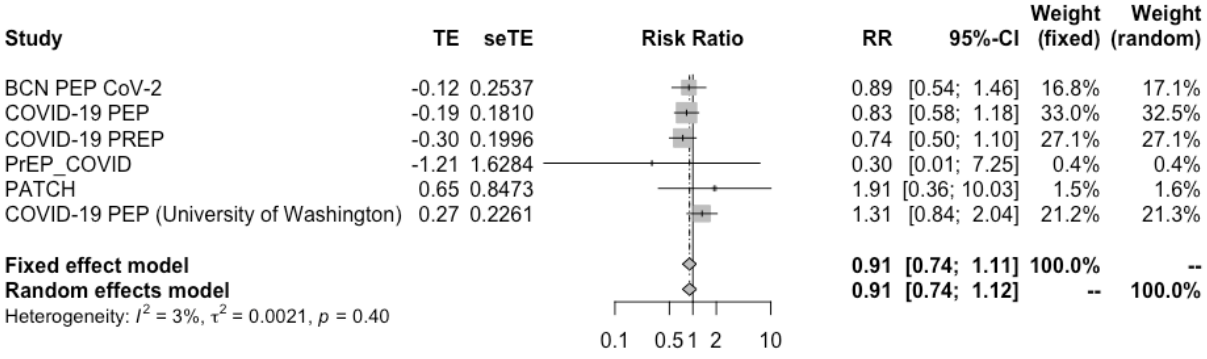


Figure 8. Symptomatic infection in RCTs comparing hydroxychloroquine or chloroquine with no prophylaxis among individuals exposed to COVID-19



In addition, we identified a systematic review[7] 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).

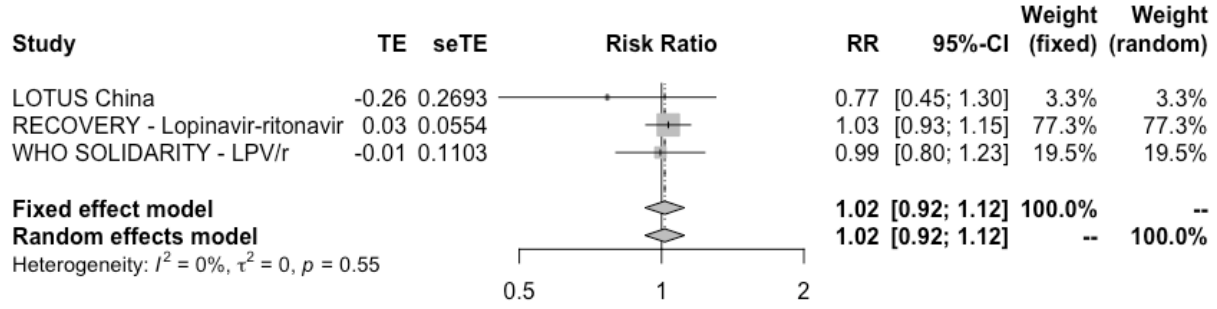
Lopinavir-Ritonavir

See Summary of findings Table 4, Appendix 1

We identified seven RCTs including 5,459 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 0.7% (95%CI -2.6% to 4%); Moderate certainty ⊕⊕⊕◯ (Figure 9.)
- Lopinavir-Ritonavir does not reduce invasive mechanical ventilation requirement; RR 1.07 (95%CI 0.98 to 1.17); RD 0.8% (95%CI -0.2% to 2%); High certainty ⊕⊕⊕⊕
- Lopinavir-Ritonavir probably does not improve symptom resolution or improvement; RR 1.03 (95%CI 0.92 to 1.15); RD 1.7% (95%CI -4.4% to 8.3%); Moderate certainty ⊕⊕⊕◯
- Lopinavir-ritonavir may not increase the risk of severe adverse events, RR 0.6 (95%CI 0.37 to 0.98); RD -2.2% (95%CI -3.4% to -0.09%); 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

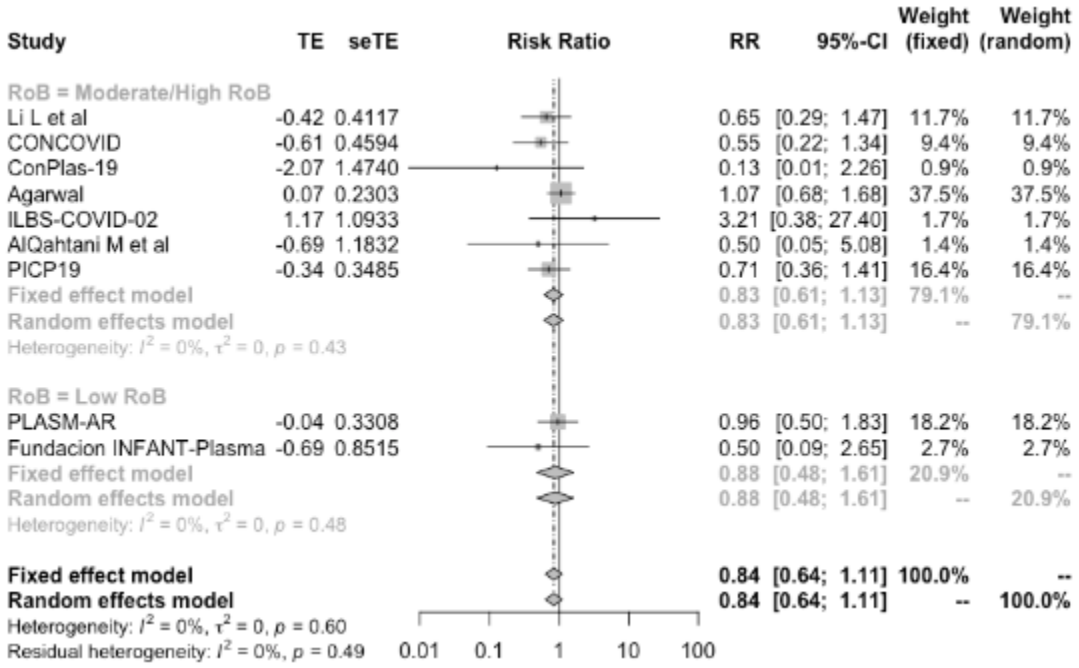
See summary of findings table 5 in appendix 1

We identified ten RCT including 1434 patients in which convalescent plasma was compared against standard of care or other treatments. Agarwal et al performed the biggest study to date

including 235 patients in the intervention arm and 229 in control. Most studies (8/9) included severely ill patients, as shown by the mortality rate in the control arms, ranging from 10% to 25.6%. The remaining study included patients with recent onset symptoms and reported a control-arm mortality rate of 5%. Convalescent plasma was administered in one or two infusions to symptomatic patients in all cases. Our results showed:

- It is uncertain if convalescent plasma affects mortality, RR 0.84 (95%CI 0.64 to 1.11); RD -5.3% (95%CI -11.9% to 3.6%); Very low certainty ⊕◯◯◯ (figure 10.).
- It is uncertain if convalescent plasma reduces invasive mechanical ventilation requirements, RR 0.78 (95% CI 0.51 to 1.17); RD -2.7% (95%CI -5.7% to 2%); Very Low certainty ⊕◯◯◯.
- It is uncertain if convalescent plasma affects symptom resolution or improvement, RR 1.03 (95% CI 0.89 to 1.2); RD 1.7% (95%CI -6.1% to 11.1%); Very low certainty ⊕◯◯◯
- It is uncertain if convalescent plasma increases severe adverse events, RR 1.26 (95% CI 0.83 to 1.9); RD 1.4% (95%CI -0.9% to 5%); 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 addition, we identified one study in which 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.

Tocilizumab

See Summary of findings Table 6 in Appendix 1

We identified seven RCTs including 1398 patients in which tocilizumab was compared against standard of care or other interventions. Five studies reported on mortality outcome and most included patients with severe disease as shown by the mortality rates in the control arms, which ranged from 8 to 19%. Our results showed:

- Tocilizumab may not reduce mortality, RR 1.08 (95%CI 0.79 to 1.48); RD 2.6% (95%CI -6.9% to 15.8%; Low certainty ⊕⊕◯◯ (Figure 11.)
- Tocilizumab may reduce invasive mechanical ventilation requirements, RR 0.73 (95%CI 0.57 to 0.94); RD -3.1% (95%CI -0.7% to -5%); Low certainty ⊕⊕◯◯
- Tocilizumab may not improve time to symptom resolution, RR 1.04 (95%CI 0.96 to 1.12); RD 2.2% (95%CI -2.2% to 6.6%); Moderate certainty ⊕⊕◯◯
- Tocilizumab probably does not significantly increase severe adverse events, RR 0.87 (95%CI 0.72 to 1.05); RD -0.7% (95%CI -1.5% to 2.7%); Moderate certainty ⊕⊕⊕◯

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

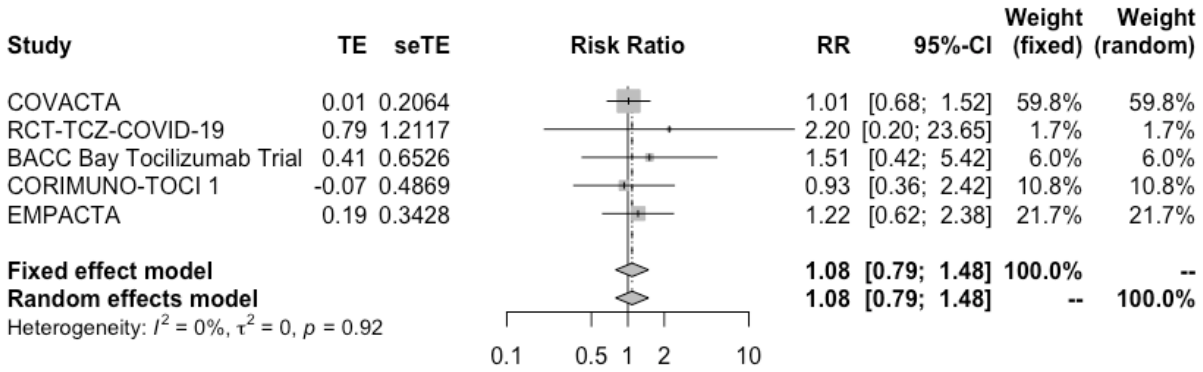
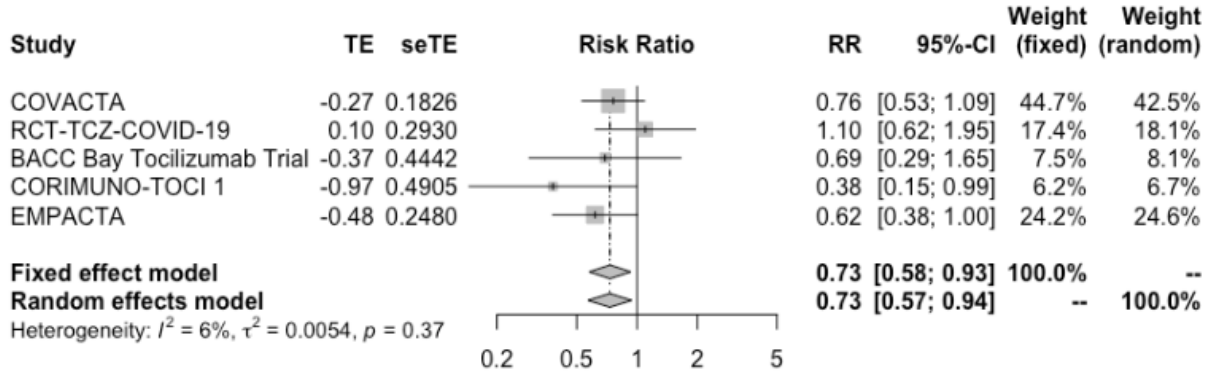


Figure 12: Mechanical ventilation requirement in RCTs comparing tocilizumab with standard of care for treatment of patients with COVID-19

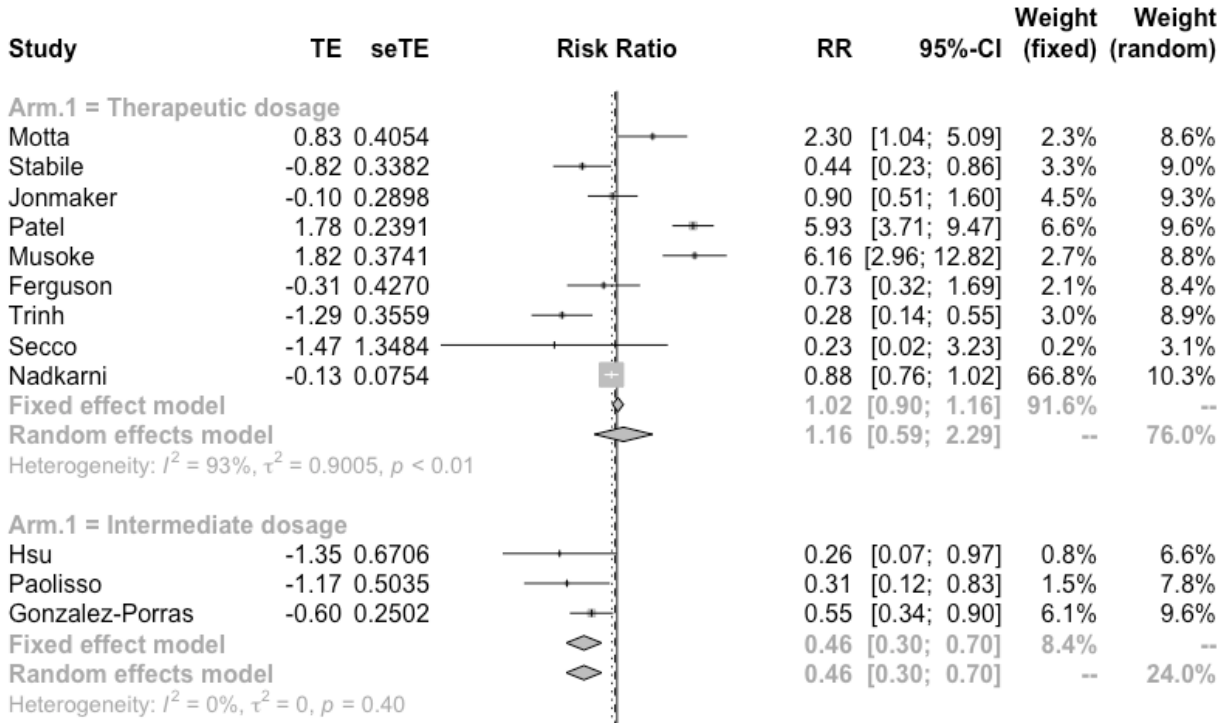


Anticoagulants

See Summary of findings Table 7, Appendix 1

Thromboembolic complications in patients infected with COVID-19 are relatively frequent.[8] As for hospitalized patients with severe medical conditions, current guidelines recommend thromboprophylaxis measures should be used for inpatients with COVID-19 infection.[9] To date, no 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



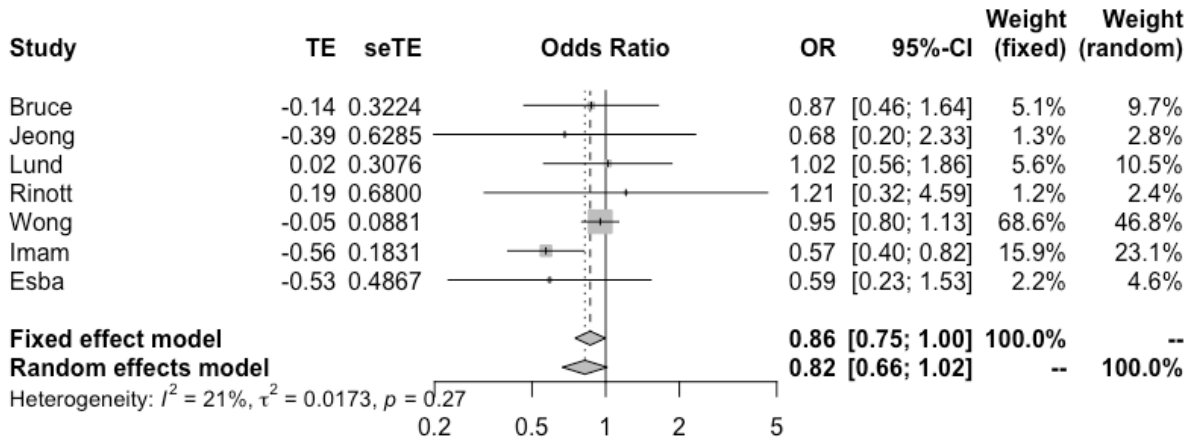
NSAIDs

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

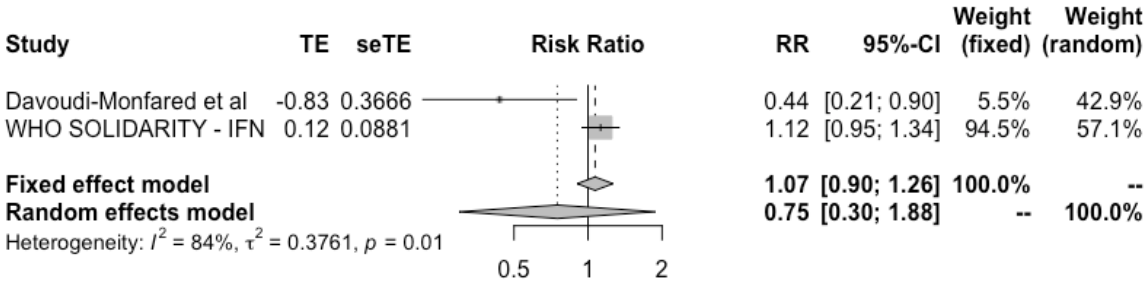
See Summary of findings Table 9, Appendix 1

We identified three RCT including 4279 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 19.4%. Our results showed:

- Interferon beta-1a (subcutaneous) probably does not reduce mortality, RR 1.07 (95%CI 0.90 to 1.26); RD 2.3% (95%CI -3.3% to 8.6%); Moderate certainty ⊕⊕⊕◯ (Figure 15.)
- Interferon beta-1a (subcutaneous) probably does not reduce invasive mechanical ventilation requirements, RR 0.98 (95%CI 0.83 to 1.17); RD -0.2% (95%CI -2% to 2%); Moderate certainty ⊕⊕⊕◯

- It is uncertain if interferon beta-1a (subcutaneous) affects symptom resolution or improvement; RR 1.1 (95%CI 0.64 to 1.87); RD 5.5% (95%CI -19.9% to 48.1%); Very low certainty ⊕◯◯◯
- Interferon beta-1a (inhaled) may increase symptom resolution or improvement, HR 2.19 (95%CI 1.03 to 4.69); RD 27.5% (95%CI 1.1% to 42.3%); 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 one RCT including 452 patients in which bamlanivimab was compared against standard of care. The study included mild to moderate patients as none died. Our results showed:

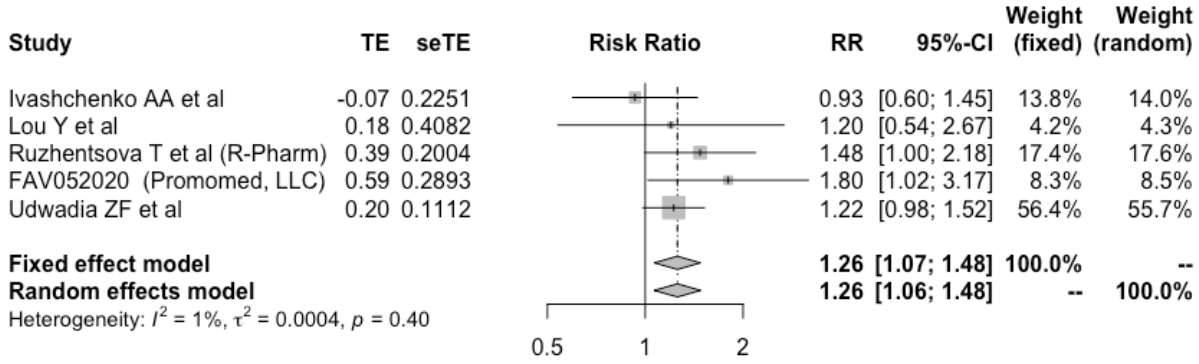
- It is uncertain if bamlanivimab reduces mortality or mechanical ventilation requirements; Very low certainty ⊕◯◯◯
- It is uncertain if bamlanivimab improves time to symptom resolution; Very low certainty ⊕◯◯◯
- It is uncertain if bamlanivimab increases the risk of severe adverse events; Very low certainty ⊕◯◯◯

Favipravir

We identified nine RCTs including 1054 patients in which favipravir was compared against standard of care or other treatments. Five studies including 559 patients reported on favipravir versus standard of care. All studies included patients with mild to moderate disease. Our results showed:

- It is uncertain if favipravir affects mortality or mechanical ventilation requirements; Very low certainty ⊕◯◯◯
- Favipravir may increase symptom resolution or improvement, RR 1.26 (95%CI 1.06 to 1.48); RD 14% (95%CI 3.3% to 26.6%); Low certainty ⊕⊕◯◯ (Figure 16.)
- It is uncertain if favipravir increases the risk of severe adverse events; Very low certainty ⊕◯◯◯

Figure 16. Symptom resolution at 7-15 days in randomized studies comparing favipravir with standard of care in patient with COVID-19

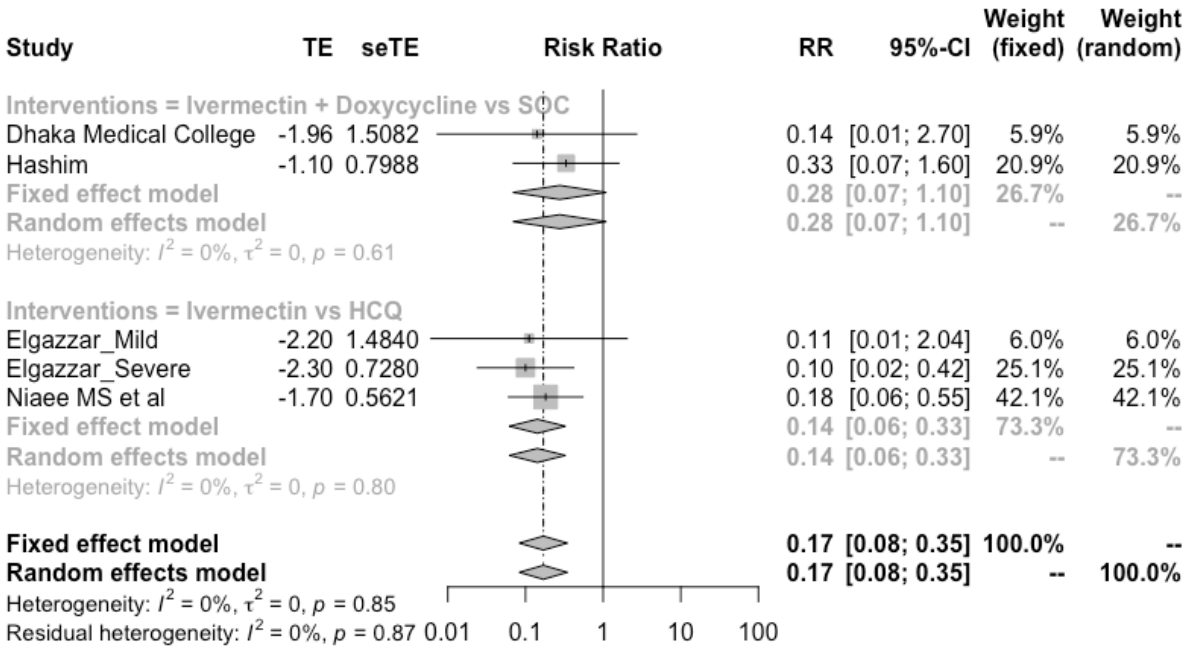


Ivermectin

We identified eleven RCT including 1842 patients in which ivermectin was compared against standard of care or other treatments. All studies patients with mild to severe disease, as shown by the mortality rates in the control arms, which ranged from 0% to 18%. Our results showed:

- It is uncertain if ivermectin affects mortality, RR 0.17 (95%CI 0.08 to 0.35); RD -27.3% (95%CI -21.4% to -30.3%); Very low certainty ⊕◯◯◯ (Figure 17)
- It is uncertain if ivermectin affects symptom resolution or improvement, RR 1.41 (95%CI 1.18 to 1.68); RD 22.7% (95%CI 9.9% to 37.6%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects symptomatic infection, RR 0.2 (95%CI 0.04 to 0.89); RD -13.9% (95%CI -19.2% to -16.6%); Very low certainty ⊕◯◯◯
- It is uncertain if ivermectin affects severe adverse events, RR 3.02 (95%CI 0.34 to 26.5); RD 10.9% (95%CI -3.6% to 95.6%); Very low certainty ⊕◯◯◯

Figure 17: Mortality in randomized studies comparing ivermectin with standard of care in patients with COVID-19



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. 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:

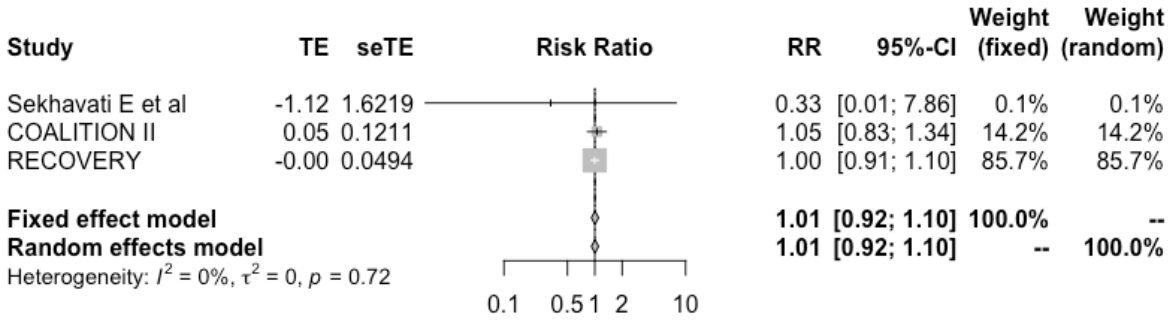
- Baricitinib may reduce mortality, RR 0.65 (95%CI 0.39 to 1.07); RD -2.5% (95%CI -5.4% to 0.4%); Low certainty ⊕⊕◯◯
- Baricitinib may reduce mechanical ventilation, RR 0.65 (95%CI 0.46 to 0.93); RD -5.2% (95%CI -9.5% to -0.94%); Low certainty ⊕⊕◯◯
- Baricitinib may improve time to symptom resolution,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

We identified three RCT including 8272 patients in which azithromicin was compared against standard of care without azithromicin. RECOVERY trial was the biggest study including 7762 patients with severe disease (mortality in the control arm 19%). Our results showed:

- Azythromicin probably does not reduce mortality, RR 1.01 (95%CI 0.92 to 1.1); RD 0.3% (95%CI -2.6% to 3.3%); Moderate certainty ⊕⊕⊕◯ (Figure 18.)
- Azythromicin probably does not reduce mechanical ventilation requirements, RR 0.94 (95%CI 0.79 to 1.14); RD -0.7% (95%CI -2.4% to 1.6%); Moderate certainty ⊕⊕⊕◯
- Azythromicin does not improve time to symptom resolution, RR 1.01 (95%CI 0.98 to 1.05); RD 0.5% (95%CI -1.1% to 2.8%); High certainty ⊕⊕⊕⊕
- It is uncertain if azythromicin increases severe adverse events; Very low certainty ⊕◯◯◯

Figure 18. Mortality in randomized studies comparing azythromicin with standard of care in patients with COVID-19



Full description of included studies

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

Table 5. Description of included studies and interventions effects

99mTc-MDP **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence**
RCT					
Yuan et al;[10] 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
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;[11] 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;[12] 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 schemes	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, comorbidities and coagulation parameters)	**Mortality:** Very low certainty ⨁◯◯◯

Motta et al;[13] 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;[14] 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;[15] preprint; 2020	Patients with severe to critical COVID-19 infection. 131 received heparins in therapeutic dosage	Mean age 69.3 ± 10.7, male 67.7%, hypertension 63%, diabetes 17.9%, chronic lung disease	Steroids 56.8%, hydroxychloroquine 92.2%, lopinavir-ritonavir 91.8%, tocilizumab 9.7%,	High for mortality Notes: Non-randomized study with retrospective design.	

	(enoxaparin 40mg a day) and 126 received heparins in prophylactic dosage (enoxaparin 70/100 mg/kg every 12 hs)	8.6%, asthma %, coronary heart disease 17.1%, chronic kidney disease 8.6%, cancer 7%, obesity 9.7%	azithromycin 90.3%,	Regression was implemented to adjust for potential confounders (other treatments)	
Jonmaker et al;[16] 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;[17] 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;[18] peer reviewed;	Patients with COVID-19 infection. 394	Mean age 63.4 ± 16.1, male 61.7%,	Steroids 11%, hydroxychloroquine	High for mortality	

2020	received heparins and 450 did not received heparins	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%	80.7%, tocilizumab 15%	Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Musoke et al;[19] 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;[20] 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 dosage anticoagulants	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 baseline anticoagulant use)	
Paolisso et al;[21] peer-reviewed;	Patients with moderate to severe	Median age 67 ± 24, male 63%,	Hydroxychloroquine 80.7%, tocilizumab	High for mortality	

2020	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)	hypertension 50.7%, diabetes 14.4%, chronic lung disease 12.9%, coronary heart disease 8.2%, chronic kidney disease 6.7%, cancer 11.3%,	16%,	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;[22] 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;[23] 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;[24] peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 48 received anticoagulants in therapeutic dosage and 64 received 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;[25] 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;[26] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 766 received anticoagulants in therapeutic dosage and 1860 received	Median age 65 ± 24, male 66%, hypertension 34.8%, diabetes 22.6%, chronic lung disease 4.9%, asthma 6.3%, coronary heart disease	NR	High for mortality Notes: Non-randomized study with retrospective design. Inverse probability treatment weighted	

	anticoagulants in prophylactic dosage	8.3%, chronic kidney disease 6.8%, cancer 7.8%		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)	

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;[27] 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	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No

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

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;[28] 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

Azithromycin

Azithrimycin probably does not reduce mortality or mechanical ventilation and does not improve time to symptom resolution.

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
Sekhavati et al;[29] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to azithromycin 500 mg twice-daily and 55 assigned to standard of care	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 1.01 (95%CI 0.92 to 1.1); RD 0.3% (95%CI -2.6% to 3.3%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.94 (95%CI 0.79 to 1.14); RD -0.7% (95%CI -2.4% to 1.6%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** RR 1.01 (95%CI 0.98 to 1.05); RD 0.5% (95%CI -1.1% to 2.8%); High certainty ⨁⨁⨁⨁ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯
Guvenmez et al;[30] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomicin 600mg twice a day for 5 days and 12 assigned to Azithromycin 500mg on first day followed by 250mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COALITION II trial;[31] Furtado et al; peer-reviewed; 2020	Patients with severe COVID-19. 214 assigned to azithromycin 500mg once a day for 10 days and 183 assigned to standard of care	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, coronary heart disease 5.8%, chronic kidney disease 11%, cerebrovascular disease 3.8%,	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	

		immunosuppression %, cancer 3.5%, obesity %		outcomes results.	
RECOVERY trial;[32] Horby et al; preprint; 2020	Patients with moderate to critical COVID-19. 2582 assigned to azitromicin 500mg a day for 10 days and 5182 assigned to standard of care	Mean age 65.3 ± 15.6, male 62%, diabetes 27.5%, COPD 24.5%, asthma %, coronary heart disease 26.5%, chronic kidney disease 6%	Steroids 61%,	Low for mortality and mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	

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;[33] 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;[34] Kalil et al; peer-reviewed; 2020	Patients with moderate to severe COVID-19. 515 assigned to baricitinib + remdesivir 4mg a day for 14 days + 200mg once followed by 100mg a day for 10 days and 518 assigned to remdesivir	Mean age 55.4 ± 15.7, male 63.1%, comorbidities 84.4%	Steroids 11.9%, convalescent plasma %	Some Concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	**Mortality:** RR 0.65 (95%CI 0.39 to 1.07); RD -2.5% (95%CI -5.4% to 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;[35] preprint; 2020	Patients with mild to severe COVID-19 infection. 10 assigned to Baloxavir 80mg a day on days 1, 4 and 7, 9 assigned to favipiravir and 10 assigned to standard of care	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, coronary heart disease 13.8%	Antivirals 100%, interferon 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Bamlanivimab (monoclonal antibody)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care (standard of care) and GRADE certainty of the evidence
RCT					
BLAZE-1 trial;[36]	Patients with mild to	Mean age 45 ± 68,	NR	High for mortality and	**Mortality:** No

Chen et al; peer-reviewed; 2020	moderate COVID-19. 309 assigned to bamlanivimab 700 mg, 2800 mg or 7000 mg once and 143 assigned to standard of care	male 55%		mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inappropriate.	information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **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;[37] 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;[38] 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):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Ansarin et al;[39] 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.	

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;[40] 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 ⊕◯◯◯

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;[41] 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 **Uncertainty in potential benefits and harms. Further research 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;[42] 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:** 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
Lopes et al;[43] 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	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	

	assigned to standard of care			allocation probably inappropriate.	
Salehzadeh et al;[44] preprint; 2020	Patients moderate to critical COVID-19. 50 assigned to colchicine 1 mg a day for 6 days and 50 assigned to standard of care	Mean age 56, male 41%, hypertension 11%, diabetes 11%, chronic lung disease 4%, coronary heart disease 15%, chronic kidney disease 5%	Hydroxychloroquine 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Non-RCT					
Scarsi et al;[45] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 122 received colchicine and 140 received alternative treatment schemes	Mean age 70 ± 9.6, male 63.7%, chronic lung disease 18.8%, coronary heart disease 69.4%, cancer 15%	Steroids 43%, hydroxychloroquine 51.6%, lopinavir-ritonavir 25.7%	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders. (demographical (gender and age), clinical and laboratory parameters (PaO2/FiO2 ratio, ferritin and C reactive protein), comorbidities (history of malignancies, cardiovascular disease or chronic obstructive pulmonary disease) and other treatments (HCQ, antivirals and dexamethasone)	**Mortality:** Very low certainty ⨁◯◯◯

Brunetti et al;[46] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 33 received colchicine and 33 received alternative treatment schemes	Mean age 62.9 ± 13.3, male 66.2%, hypertension 48.5%, diabetes 21.2%, chronic lung disease 13.6%, coronary heart disease 9.1%, cerebrovascular disease 10.6%, obesity 45.4%	Remdesivir 12.1%, hydroxychloroquine 72.7%, tocilizumab 34.8%, azithromycin 56%,	High for mortality Notes: Non-randomized study with retrospective design. Propensity score and matching was implemented to adjust for potential confounders (age, sex, body mass index (BMI), baseline laboratory values, baseline oxygen saturation on room air, receipt of tocilizumab, receipt of remdesivir, and comorbidity score)	

Convalescent plasma

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

Study; publication status	Patients and 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;[47] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 52 assigned to convalescent plasma 4 to 13 mL/kg of recipient body weight and 51 assigned to standard of care	Median age 70 ± 8, male 58.3%, hypertension 54.3%, diabetes 10.6%, coronary heart disease 25%, chronic kidney disease 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%	Steroids 39.2%, antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection**
CONCOVID trial; Gharbharan et al;[48] preprint;	Patients with moderate to critical COVID-19 infection.	Median age 62 ± 18, male 72%, hypertension 26%,	NR	Low for mortality and invasive mechanical ventilation; High for	

2020	43 assigned to convalescent plasma 300 ml once or twice and 43 assigned to standard of care	diabetes 24.4%, chronic lung disease 26.7%, coronary heart disease 23.2%, chronic kidney disease 8.1%, immunosuppression 12.8%, cancer 9.3%		symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**(prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Avendaño-Solá et al;[49] 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;[50] 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;[51] Simonovich et al; peer-reviewed;	Patients with severe to critical COVID-19. 228 assigned to	Mean age 62 ± 20, male 67.6%, hypertension 47.7%,	Steroids 93.3%, hydroxychloroquine 0.3%, lopinavir-	Low for mortality and mechanical ventilation; low for symptom	

2020	convalescent plasma and 105 assigned to standard of care	diabetes 18.3%, COPD 7.5%, asthma 4.2%, coronary heart disease 3.3%, chronic kidney disease 4.2%	ritonavir 3%, tocilizumab 4.2%	resolution, infection and adverse events	
ILBS-COVID-02 trial;[52] 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;[53] 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;[54] Libster et al; preprint; 2020	Patients with mild to moderate COVID-19. 80 assigned to convalescent plasma 250 ml and 80 assigned to standard of care	Mean age 77.1 ± 8.6, male 47.5%, hypertension 71.2%, diabetes 22.5%, COPD 4.4%, asthma 3.8%, coronary heart disease 13.1%, chronic kidney disease 2.5%, cancer 3.8%, obesity 7.5%	NR	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	
PICP19 trial;[55] Ray et al; preprint; 2020	Patients with severe COVID-19. 40 assigned to	Mean age 61 ± 11.5, male 71.2%,	NR	High for mortality and mechanical ventilation; high for symptom	

	convalescent plasma 200 ml and 40 assigned to standard of care			resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Balcells et al;[56] preprint; 2020	Patients with moderate to severe COVID-19. 28 assigned to convalescent plasma at enrolment, 200 mg twice and 30 assigned to convalescent plasma when clinical deterioration was observed (43.3% received CP in this arm)	Mean age 65.8 ± 65, male 50%, hypertension 67.2%, diabetes 36.2%, chronic lung disease %, asthma 5.1%, coronary heart disease %, chronic kidney disease 8.6%, cerebrovascular disease 5.1%, immunosuppression 12%, cancer 7%, obesity 12%	Steroids 51.7%, hydroxychloroquine 12%, lopinavir-ritonavir 1.7%, tocilizumab 3.4%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very Low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
Non-RCT					
Joyner et al;[57] 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;[58] Chen et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 15 assigned to darunavir-Cobicistat 800mg/150 mg once a day for 5 days and 15 assigned to standard of care	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, coronary heart disease 26.6%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

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;[59] Cadegiani et al; preprint; 2020	Patients with mild COVID-19. 64 assigned to dutasteride (dosage not reported) and 66 assigned to standard	Mean age 42 ± 12, male 100 %, diabetes 11%, COPD 0%, asthma 1%, coronary heart disease 1%, cancer 0%, obesity	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information

	of care	15.4%		Notes: Concealment of allocation probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Electrolyzed saline **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and interventions analyzed**	**Comorbidities**	**Additional interventions**	**Risk of bias and study limitations**	**Interventions effects vs standard of care and GRADE certainty of the evidence**
RCT					
TX-COVID19 trial;[60] 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
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;[61] 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)	
Shoaibi et al;[62] preprint; 2020	Patients with moderate to severe COVID-19 infection. 1623 received famotidine 20 to 40mg and 24404 received alternative treatment schemes	age nr, male 59.6%, hypertension 43%, diabetes 41%, chronic lung disease 17%, asthma %, coronary heart disease 47%, chronic kidney disease 41%, obesity 24%	NR	High for mortality Notes: Non-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).	**Mortality:** Very low certainty ⨁◯◯◯
Yeramaneni et al;[63] 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

Favipravir may improve time to symptom resolution. It is uncertain if favipravir 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;[64] 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to favipiravir 1600 mg twice the first day followed by 600 mg twice daily for 7 days and 120 assigned to umifenovir 200 mg three times daily for 7 days	Mean age not reported male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** RR 1.26 (95%CI 1.06 to 1.48); RD 14% (95%CI -3.3% to 26.6.9%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Ivashchenko et al;[65] 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;[35] 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;[66] peer-reviewed; 2020	Patients with mild COVID-19. 44 assigned to favipiravir (early) 1800 mg on day 1 followed by 800 mg twice daily for 10 days and 45 assigned to favipiravir (late) 1800mg on day 6 followed by 800 mg twice daily for 10 days	Median age 50 ± 26.5, male 61.4%, comorbidities 39%	Steroids 2.3%, ATB 12.5%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Dabbous et al;[67] 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;[68] peer-	Patients with	Mean age 72 ± 40,	NR	High for mortality and	

reviewed; 2020	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	male 54%, hypertension 42.3%, diabetes 11.5%, coronary heart disease 23.1%		invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Khamis et al;[69] peer-reviewed; 2020	Patients with moderate to severe COVID-19. 44 assigned to favipiravir +inhaled interferon beta-1B 1600 mg once followed by 600 mg twice a day for 10 days + 8million UI for 5 days and 45 assigned to standard of care	Mean age 55 ± 14, male 58%, hypertension 54%, diabetes 45%, COPD 5.6%, coronary heart disease 15%, chronic kidney disease 20%	Steroids 67%, tocilizumab 35%, convalescent plasma 58%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Ruzhentsova et al;[70] 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 favipravir 3200 mg	Mean age 49.68 ± 13.09, male 48.5%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection	

	once followed by 600 mg twice a day for 14 days and 100 assigned to standard of care			and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Udwadia et al;[71] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 72 assigned to favipravir 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.	

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;[72] 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;[73] 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 ⨁◯◯◯

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;[74] 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 1.08 (95%CI 0.99 to 1.19); RD 2.6% (95%CI -0.3% to 6.6%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 1.05 (95%CI 0.9 to 1.22); RD 0.6% (95%CI -1.1% to 2.6%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** RR 1.05 (95%CI 0.94 to 1.18); RD 2.8% (95%CI -3.3% to 10%); 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 0.77 to 1.57); RD 0.5% (95%CI -1.2% to 3.1%); Low certainty ⨁⨁◯◯
Huang et al;[75] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to chloroquine 500 mg twice a day for 10 days and 12 assigned to lopinavir-Ritonavir 400/100 mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
RECOVERY - Hydroxychloroquine trial;[76] 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;[77] Mitja et al; preprint; 2020	Patients exposed to COVID-19. 1116 assigned to hydroxychloroquine 800 mg once followed by 400 mg x once a day for 6 days and 1198 assigned to standard of care	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, coronary heart disease 13.3%, Nervous system disease 4.1%	NR	Some concerns for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant number of patients excluded from analysis.	
COVID-19 PEP trial;[78] Boulware et al; peer-reviewed; 2020	Patients exposed to COVID-19. 414 assigned to hydroxychloroquine 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to standard of care	Median age 40 ± 6.5, male 48.4%, hypertension 12.1%, diabetes 3.4%, asthma 7.6%, comorbidities 27.4%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Significant loss of information that might have affected the study's results.	
Cavalcanti et al trial;[79] 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;[80] 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;[81] Skipper et al; peer-reviewed; 2020	Patients with mild COVID-19 infection. 212 assigned to hydroxychloroquine 1400 mg once followed by 600 mg once a day for 5 days and 211 assigned to standard of care	Median age 40 ± 9, male 44%, hypertension 11%, diabetes 4%, chronic lung disease %, asthma 11%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	
BCN PEP CoV-2 trial;[82] 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;[83] 2020	Patients with mild to moderate COVID-19 infection. 75 assigned to hydroxychloroquine 1200 mg daily for three days followed by 800 mg daily to complete 7 days and	Mean age 46.1 ± 14.7, male 54.7%, hypertension 6%, diabetes 14%, other comorbidities 31%	Steroids 7%, lopinavir-ritonavir 17%, umifenovir 47%, oseltamivir 11%, entecavir 1%, ATB 39%, ribavirin 47%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might	

	75 assigned to standard of care			have introduced bias to symptoms and adverse events outcome results.	
Chen et al; preprint;[84] 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;[85] preprint; 2020	Patients with moderate COVID-19 infection. 18 assigned to hydroxychloroquine 200 mg twice a day for 10 days, 18 assigned to chloroquine and 12 assigned to standard of care	Mean age 47.4 ± 14.46, male 45.8%, hypertension 16.7%, diabetes 18.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Chen et al;[86] 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;[87] Jun et al; peer-	Patients with mild to severe COVID-19	Mean age 48.6 ± 3.7, male 0.7%,	Lopinavir-ritonavir 6.6%, umifenovir	High for mortality and invasive mechanical	

reviewed; 2020	infection. 15 assigned to hydroxychloroquine 400 mg once a day for 5 days and 15 assigned to standard of care	hypertension 26.6%, diabetes 6.6%, chronic lung disease 3.3%	73.3%, IFN 100%	ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abd-Elsalam et al;[88] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to hydroxychloroquine 400 mg twice on day one followed by 200 mg tablets twice daily for 15 days and 97 assigned to standard of care	Mean age 40.7 ± 19.3, male 58.8%, chronic kidney disease 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-19 PREP trial;[89] 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;[90] 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	Mean age 66 ± 16.2, male 59.4%, hypertension 57.8%, diabetes 32%, chronic lung disease 7%, asthma 15.6%, coronary heart disease	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	

	days and 61 assigned to standard of care	26.6%, chronic kidney disease 7.8%, cerebrovascular disease 6.2%		Notes: Concealment of allocation probably inappropriate.	
PrEP_COVID trial;[91] 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;[92] Abella et al; peer-reviewed; 2020	Patients exposed to COVID-19. 64 assigned to hydroxychloroquine 600 mg a day for 8 weeks and 61 assigned to standard of care	Median age 33 ± 46, male 31%, hypertension 21%, diabetes 3%, asthma 17%	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	
WHO SOLIDARITY trial;[93] 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;[72] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to	Mean age 57.7 ± 8.4, male 59%, hypertension NR%, diabetes 27.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution,	

	Febuxostat 80 mg per day and 30 assigned to hydroxychloroquine	chronic lung disease 1.9%		infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-19 PEP (University of Washington) trial; Barnabas et al;[94] 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;[95] 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;[96] 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;[97] Dubee et al; preprint; 2020	Patients with mild to moderate COVID-19. 124 assigned to	Median age 77 ± 28, male 48.4%, hypertension 53.4%,	Steroids 9.6%, lopinavir-ritonavir 1.2%, azithromycin	Low for mortality and mechanical ventilation; low for symptom	

	hydroxychloroquine 800 mg once followed by 400 mg a day for 8 days and 123 assigned to standard of care	diabetes 17.3%, COPD 11.2%, cerebrovascular disease 17.3%, obesity 27.7%	8.4%	resolution, infection and adverse events	
Q-PROTECT trial;[98] 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	

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;[99] preprint; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to icatibant 30 mg every 8 hours for 4 days, and 10 assigned to iC1e/K	Mean age 51.6 ± 11.5, male 53.3%, hypertension 50%, diabetes 46.7%,%, asthma 3.3%, obesity 43.3%	NR	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information

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;[100] 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 ⨁◯◯◯

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;[101] Esquivel-	Patients with mild to moderate COVID-19	Median age 38 ± 63, male 54%,	Hydroxychloroquine 100%, lopinavir-	High for mortality and invasive mechanical	**Mortality:** No information

Moynelo et al; preprint; 2020	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)	hypertension 22.2%, diabetes 4.7%, asthma 6.3%, coronary heart disease 6.3%, any comorbidities 50.8%	ritonavir 100%, antibiotics 100%	ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** 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;[102] preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to interferon beta-1a 44 µg subcutaneous, three times a week and 39 assigned to standard of care	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, coronary heart disease 28.4%, chronic kidney disease 3.7%, cancer 11.1%	Steroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, immunoglobulin 30.8%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 1.07 (95%CI 0.90 to 1.26); RD 2.3% (95%CI -3.3% to 8.6%); Moderate certainty ⊕⊕⊕◯ **Invasive mechanical ventilation:** RR 0.98 (95%CI 0.83 to 1.17); RD -0.2% (95%CI -2% to 2%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** Very
WHO SOLIDARITY;[93] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 2050 assigned to	age < 70 years 61% , male 62%, hypertension %, diabetes 25%, COPD	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom	

	Interferon beta-1a three doses over six days of 44µg and 2050 assigned to standard of care	6%, asthma 5%, coronary heart disease 21%,		resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Monk P et al;[103] 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 27.5% (95%CI 1.1% to 42.3%); 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;[104] peer-reviewed; 2020	Patients with severe COVID-19. 33 assigned to Interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to standard of care	Median age 60 ± 10.5, male 59%, hypertension 40.9%, diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, coronary heart disease 30.3%, chronic kidney disease NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%	Steroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

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;[105] peer-reviewed; 2020	Patients with moderate COVID-19. 40 assigned to interferon kappa plus TFF2 5 mg/2 mg once a day for six days and 40 assigned to standard of care	Mean age 35.2 ± 11.2, male 63.7%, hypertension 5%, diabetes 3.7%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection**

					(prophylaxis studies): No information **Adverse events:** Very low certainty ⊕◯◯◯
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; Kumar et al;[106] 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 **Uncertainty in potential benefits and harms. Further research is needed.**					
Study; publication status	**Patients and 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; NCT04422561, Shouman et al; Other; 2020	Patients exposed to COVID-19. 203 assigned to ivermectin 15 to 24 mg a day and 101 assigned to standard of care	Mean age 38.72 ± 15.94, male 51.3%	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):** Very low certainty ⨁◯◯◯ **Adverse events:** No information
Mohiuddin et al;[107] 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;[108] peer-reviewed; 2020	Patients with mild to moderate COVID-19. 32 assigned to ivermectin 200 mg once and 30 assigned to standard of care	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Hashim HA et a (Alkarkh Health	Patients with mild to critical COVID-19. 70	Mean age 48.7 ± 8.6, male %	Steroids 100%, azithromycin 100%,	High for mortality and mechanical ventilation;	

Directorate-Baghdad) trial;[109] Hashim et al; preprint; 2020	assigned to Ivermectin plus doxycycline 200 mg/kg two or three doses + 100 mg twice a day for 5 to 10 days and 70 assigned to standard of care			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);[110] preprint; 2020	Patients mild to moderate COVID-19. 100 assigned to ivermectin 400 mg/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);[110] preprint; 2020	Patients with severe COVID-19. 100 assigned to ivermectin 400 mg/Kg once for 4 days and 100 assigned to hydroxychloroquine	Mean age 58.9 ± 19.5, male 71%, hypertension 16%, diabetes 20%, COPD %, asthma 13%, coronary heart disease 7.5%	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Elgazzar et al (prophylaxis);[110]	Patients exposed to COVID-19. 100	NR	NR	High for mortality and mechanical ventilation;	

preprint; 2020	assigned to ivermectin 400 mg/Kg twice (second dose after one week) and 100 assigned to standard of care			high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Krolewiecki et al;[111] 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;[112] 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	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.	
Ahmed et al;[113] peer-reviewed; 2020	Patients with mild COVID-19. 22 assigned to ivermectin 12 mg a day for 5 days and 23 assigned to ivermectin plus	Mean age 42 , male 46%,	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Concealment of	

	doxycycline			allocation probably inappropriate.	

Intravenous immunoglobulin (IVIG)

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Sakoulas et al;[114] 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;[115] 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;[116] peer-reviewed; 2020	Patients with severe COVID-19. 52 assigned to IVIG 400 mg/Kg daily for three doses and 32 assigned to standard	Mean age 53 ± 13, male 77.4%, hypertension 20.2%, diabetes 21.4%, COPD 1.2%, asthma %, coronary heart disease	NR	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events	

	of care	%, chronic kidney disease 4.7%, cancer 1.2%,		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;[117] 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 **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Wang et al;[118] 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.	

Lincomycin

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

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

status	analyzed				of care and GRADE certainty of the evidence
RCT					
Guvenmez et al;[30] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600 mg twice a day for 5 days and 12 assigned to azithromycin 500 mg on first day followed by 250 mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
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;[119] Cao et al; peer-reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to Lopinavir-Ritonavir 400/100 mg daily for 14 days and 100 assigned to standard of care	Median age 58 ± 9.5, male 60.3%, Diabetes 11.6%, disease 6.5%, cancer 3%	Steroids 33.7%, remdesivir NR%, IFN 11.1%, ATB 95%	Low for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might	**Mortality:** RR 1.02 (95%CI 0.92 to 1.22); RD 0.7% (95%CI -2.6% to 4%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 1.07 (95%CI 0.98 to

				have introduced bias to symptoms and adverse events outcomes results.	1.17); RD 0.8% (95%CI -0.2% to 2%); High certainty ⊕⊕⊕⊕ **Symptom resolution or improvement:** RR 1.03 (95%CI 0.92 to 1.15); RD 1..7% (95%CI -4.4% to 8.3%); Moderate certainty ⊕⊕⊕◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.6 (95%CI 0.37 to 0.98); RD -2.2% (95%CI -3.4% to -0.09%); Low certainty ⊕⊕◯◯
ELACOI trial;[120] 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;[121] 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;[75] 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500 mg twice a day for 10 days and 12 assigned to lopinavir-ritonavir 400/100 mg twice a day for 10	Mean age 44 ± 21, male 59.1%	NR	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of	

	days			allocation probably inappropriate.	
Zheng et al; preprint;[122] 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;[123] 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 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.	
WHO SOLIDARITY - trial;[93] Pan et al; preprint; 2020	Patients with moderate to critical COVID-19. 1399 assigned to lopinavir-ritonavir 200/50 mg twice a day for 14 days and 1372 assigned to standard of care	Age 61% < 70 years, male 62%, diabetes 25%, COPD 6%, asthma 5%, coronary heart disease 21%	Steroids 15.1%, convalescent plasma 0.5%, Anti IL6 2.1%	Low for mortality and invasive mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and	

				adverse events outcomes results.	

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;[124] 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 **Adverse events:** No information
Shi et al;[125] preprint; 2020	Patients with severe COVID-19. 65 assigned to mesenchymal stem cell three infusions with 4.0×107 cells each and 35 assigned to standard of care	Mean age 60.3 ± 8.4, male 56%, hypertension 27%, diabetes 17%, COPD 2%	Steroids 22%	Low for mortality and mechanical ventilation	
Lanzoni et al;[126] 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.	

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;[127] preprint ; 2020	Patients with mild to critical COVID-19. 46 assigned to mouthwash with hydrogen peroxide 2% and chlorhexidine gluconate mixed solution three times a day and 46 assigned to standard of care	Mean age 49, male 78.2%, hypertension 37%, diabetes 41.3%, coronary heart disease 6.5%, chronic kidney disease 12%, c obesity 31.5%	Steroids 53.2%, remdesivir 26%, hydroxychloroquine 21.7%, lopinavir-ritonavir 54.3%, azithromycin 57.6%, convalescent plasma 13%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

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;[128] Mohamed et al; preprint; 2020	Patients with COVID-19. 10 assigned to mouthwash with	Median age 28.9 ± nr, male 80%	NR	High for mortality and mechanical ventilation; high for symptom	**Mortality:** No information **Invasive mechanical**

	povidone iodine or essential oils 3 times a day and 10 assigned to mouthwash with water or no mouthwash			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
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;[129] 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

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Nasal hypertonic saline

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

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Risk of bias and study limitations	Interventions effects vs standard of care and GRADE certainty of the evidence
RCT					
Kimura et al;[130] 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;[131] Rocco et al;	Patients mild COVID-19. 194 assigned to	Age range 18 - 77 , male 47%,	NR	Low for mortality and mechanical ventilation;	**Mortality:** No information

preprint; 2020	nitazoxanide 500 mg three times a day for 5 days and 198 assigned to standard of care	comorbidities 13.2%		high for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results. Significant lost 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
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;[122] 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					
Bruce et al;[132] peer-reviewed; 2020	Patients with moderate to severe COVID-19 infection. 54 received NSAID and 1168 received alternative treatment schemes	Age < 65 31.7%, male 56.5%, hypertension 50.3%, diabetes 27%, coronary heart disease 22.3%, chronic kidney disease 38.7%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function)	**Mortality:** OR 0.82 (95%CI 0.66 to 1.02); Very low certainty ⨁◯◯◯
Jeong et al;[133] 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;[134] peer-reviewed; 2020	Patients with mild to severe COVID-19 infection. 224 received NSAID and 896 received alternative treatment schemes	Median age 54 ± 23, male 41.5%, chronic lung disease 3.9%, asthma 5.4%, coronary heart disease 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%	Steroids 7.1%	High for mortality and invasive mechanical ventilation Notes: Non-randomized study with retrospective design. Propensity score and matching were implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, and phase of the outbreak	
Rinott et al;[135] 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;[136]	Patients exposed to	Median age 51 ± 23,	Steroids 2.2%,	High for mortality	

preprint; 2020	COVID-19 infection. 535519 received NSAID and 1924095 received alternative treatment schemes	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%,	hydroxychloroquine 0.6%	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;[137] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 466 received NSAID and 839 received alternative treatment schemes	Mean age 61 ± 16.3, male 53.8%, hypertension 56.2%, diabetes 30.1%, chronic lung disease 8.2%, asthma 8.8%, coronary heart disease 15.9%, chronic kidney disease 17.5%, immunosuppression 1%, cancer 6.4%,	NR	High for mortality Notes: Non-randomized study with retrospective design. Regression was implemented to adjust for potential confounders (not specified)	
Esba et al;[138] 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).	

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;[139] 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:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** 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;[140] 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;[141] 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;[142] 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;[143] preprint; 2020	Patients with severe COVID-19. 18 assigned to progesterone 100 mg twice a day for 5 days and 22 assigned to standard of care	Mean age 55.3 ± 16.4, male 100%, hypertension 48%, diabetes 25%, obesity 45%	Steroids 60%, remdesivir 60%, hydroxychloroquine 2.5%, tocilizumab 12.5%, azithromycin 50%, convalescent plasma 5%	High for mortality and mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⨁◯◯◯

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; Sigamani et al;[144] 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

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;[145] Amat-Santos et al; preprint; 2020	Patients exposed to COVID-19. 50 assigned to Ramipril 2.5 mg a day progressively increased to 10 mg a day and 52 assigned to standard of care	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%, diabetes 20.65%, chronic lung disease 7.35%, coronary heart disease 22.45%, chronic kidney disease 34.15%, cerebrovascular	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	**Mortality:** Very low certainty ⨁◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** No information

		disease 11.15%		to symptoms and adverse events outcomes results.	**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;[146] preprint; 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%	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

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;[147] peer-reviewed; 2020	Patients with mild to critical COVID-19 infection. 541 assigned to remdesivir intravenously 200 mg loading dose on day 1 followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death and 522 assigned to standard of care	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, coronary heart disease 11.6%,	NR	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** RR 0.94 (95%CI 0.82 to 1.08); RD -2% (95%CI -5.9% to 2.6%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.65 (95%CI 0.39 to 1.11); RD -4.1% (95%CI -7.1% to -1.3%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.17 (95%CI 1.03 to 1.33); RD 9.4% (95%CI 1.7% to 18.3%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.8 (95%CI 0.48 to 1.33); RD -1% (95%CI -2.8% to 1.8%); Low certainty ⊕⊕◯◯
SIMPLE trial; Goldman et al;[148] 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;[149] 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	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	

	in single daily infusions and 79 assigned to standard of care				
SIMPLE 2 trial; Spinner et al;[150] peer-reviewed; 2020	Patients with moderate COVID-19 infection. 384 assigned to remdesivir 200 mg on day 1 followed by 100 mg a day for 5 to 10 days and 200 assigned to standard of care	Median age 57 ± 9, male 61.3%, hypertension 42%, diabetes 40%, asthma 14%, coronary heart disease 56%	Steroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	Some Concerns for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Additional treatments unbalanced between arms which suggests that patients might have been treated differently.	
WHO SOLIDARITY;[93] 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;[151] peer-reviewed; 2020	Patients with moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100 assigned to standard of care	Mean age 45 ± 15, male 56%	Lopinavir-ritonavir 15.5%, IFN 9%, umifenovir 18%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** Very low certainty ⊕◯◯◯

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;[123] 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;[152] 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;[153] peer-reviewed; 2020	Patients with severe COVID-19 infection. 22 assigned to ruxolitinib 5mg twice a day and 21 assigned to standard of care	Mean age 63 ± 10, male 58.5%, hypertension 39%, diabetes 19.5%, coronary heart disease 7.3%,	Steroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and invasive mechanical ventilation; low for symptom resolution, infection and adverse events	**Mortality:** No information **Invasive mechanical ventilation:** No information **Symptom resolution or improvement:** Very low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

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;[154] 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**
Sadeghi et al;[155] peer-reviewed;	Patients with moderate to severe	Median age 58 ± 13, male 20.21%,	Steroids 30.2%, lopinavir-ritonavir	High for mortality and invasive mechanical	

2020	COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60 mg once a day for 14 days and 33 assigned to standard of care	hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%, coronary heart disease 15.1%, cancer 4.5%, obesity 25.7%	48.4%, antibiotics 89.4%	ventilation; high for symptom resolution, infection and adverse events Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation probably inappropriate.	**infection (prophylaxis studies):** No information **Adverse events:** No information
Yakoot et al;[156] 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.	

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;[157] Corral-Gudino et al; preprint; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to methylprednisolone 40mg twice daily for 3 days followed by 20 mg twice daily for 3 days and 29 assigned to standard of care	Mean age 69.5 ± 11.5, male 61.9%, hypertension 47.6%, diabetes 17.5%, chronic lung disease 7.9%, cerebrovascular disease 12.7%	Hydroxychloroquine 96.8%, lopinavir-ritonavir 84.1%, azithromycin 92%	High for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably	**Mortality:** RR 0.89 (95%CI 0.78 to 1.02); RD -3.6% (95%CI -7.3% to 0.6%); Moderate certainty ⨁⨁⨁◯ **Invasive mechanical ventilation:** RR 0.84 (95%CI 0.67 to 1.04); RD -1.8%

				inappropriate.	(95%CI -3.8% to 0.4%); Moderate certainty ⨁⨁⨁◯ **Symptom resolution or improvement:** RR 1.49 (95%CI 1.22 to 1.84); RD 27.1% (95%CI 12.1% to 46.5%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe adverse events:** RR 0.89 (95%CI 0.68 to 1.17); RD -0.6% (95%CI -1.7% to 0.9%); Low certainty ⨁⨁◯◯
Metcovid trial;[158] 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;[159] 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;[160] Villar et al; unpublished; 2020	Patients with severe to critical COVID-19. Seven assigned to dexamethasone 20 mg a day for 5 days followed by 10 mg a day for 5 days and 12 assigned to standard of care	NR	NR	Low for mortality and invasive mechanical ventilation Notes: RoB judgment from published SR	
CoDEX trial;[161] Tomazini et al; peer-reviewed; 2020	Patients with critical COVID-19. 151 assigned to dexamethasone 20 mg a day for 5 days	Mean age 61.4 ± 14.4, male 62.5%, hypertension 66.2%, diabetes 42.1%, coronary heart disease	hydroxychloroquine 21.4%, azithromycin 71.2%, ATB 87%	Low for mortality and invasive mechanical ventilation; high for symptom resolution, infection and adverse	

	followed by 10 mg a day for 5 days and 148 assigned to standard of care	7.7%, chronic kidney disease 5.3%, obesity 27%		events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
REMAP-CAP trial;[162] 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;[160] 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;[163] Dequin et al; peer-reviewed; 2020	Patients with severe to critical COVID-19. 76 assigned to Hydrocortisone 200mg a day progressively reduced to 50mg a day for 7 to 14 days and 73 assigned to standard of care	Median age 64.7 ± 19.3, male 69.8%, hypertension %, diabetes 18.1%, chronic lung disease 7.4%, immunosuppression 6%	Remdesivir 3.4%, hydroxychloroquine 46.9%, lopinavir-ritonavir 14.1%, tocilizumab 2%, azithromycin 34.2%	Low for mortality and invasive mechanical ventilation; Low for symptom resolution, infection and adverse events	

Steroids-SARI trial;[160] 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;[164] 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;[165] 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.	

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;[166] Gonzalez Ochoa et al; preprint; 2020	Patients with mild (early within 3 days of onset) COVID-19. 124 assigned to sulodexide 500 RLU twice a day for 3 weeks and 119 assigned to standard of care	Median age 52 ± 10.6, male 47.4%, hypertension 34.2%, diabetes 22.2%, COPD 23%, coronary heart disease 21%,	Steroids 62.5%, hydroxychloroquine 33.7%, ivermectin 43%	Some Concerns for mortality and mechanical ventilation; some concerns for symptom resolution, infection and adverse events Notes: Significant loss to follow up.	**Mortality:** Very low certainty ⊕◯◯◯ **Invasive mechanical ventilation:** Very low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯

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;[167] 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 may not affect mortality but probably reduces invasive mechanical ventilation requirements. However certainty of the evidence is low for mortality outcome because of 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 and GRADE certainty of the evidence
RCT					
COVACTA trial; Rosas et al;[168] preprint; 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 1.08 (95%CI 0.79 to 1.48); RD 2.6% (95%CI -6.9% to 15.8%); Low certainty ⊕⊕◯◯ **Invasive mechanical ventilation:** RR 0.73 (95%CI 0.57 to 0.94); RD -3.1% (95%CI -5% to -7%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** RR 1.04 (95%CI 0.96 to 1.12); RD 2.2% (95%CI -2.2% to 6.6%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No
Wang et al;[169] 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;[68] peer-reviewed; 2020	Patients with moderate to critical COVID-19 infection. 13 assigned to	Mean age 72 ± 40, male 54%, hypertension 42.3%, diabetes 11.5%,	NR	High for mortality and invasive mechanical ventilation; High for symptom resolution,	

	favipiravir 3200 mg once followed by 600mg twice a day for 7 days, 7 assigned to tocilizumab 400 mg once or twice and 5 assigned to favipiravir plus tocilizumab	coronary heart disease 23.1%		infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Adverse events:** RR 0.87 (95%CI 0.72 to 1.05); RD -0.7% (95%CI -1.5% to 2.7%); Moderate certainty ⊕⊕⊕◯
RCT-TCZ-COVID-19 trial;[170] 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;[171] 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;[172] 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	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	

	of care			to symptoms and adverse events outcomes results.	
EMPACTA trial;[173] Salama et al; preprint; 2020	Patients with moderate to severe COVID-19. 249 assigned to tocilizumab 8 mg/kg once and 128 assigned to standard of care	Mean age 55.9 ± 14.4, male 59.2%, hypertension 48.3%, diabetes 40.6%, COPD 4.5%, asthma 11.4%, coronary heart disease 1.9%, cerebrovascular disease 3.4%, obesity 24.4%	Steroids 59.4%, remdesivir 54.6%,	Low for mortality and mechanical ventilation; low for symptom resolution, infection and adverse events	

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;[174] 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;[64] 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;[120] 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;[175] 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;[176] 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;[177] 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;[178] 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
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;[179] 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**
SHADE trial;[180] Rastogi et al; peer-reviewed; 2020	Patients with mild to moderate COVID-19. 16 assigned to	Mean age 48.7 ± 12.4, male 50%,	NR	High for mortality and mechanical ventilation; High for symptom	

	vitamin D 60000 IU a day for 7 days and 24 assigned to standard of care			resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**studies):** No information **Adverse events:** Very low certainty ⊕◯◯◯
Murai et al;[181] preprint; 2020	Patients with severe COVID-19. 117 assigned to vitamin D 200,000 IU once and 120 assigned to standard of care	Mean age 56.3 ± 14.6, male 56.3%, hypertension 52.5%, diabetes 35%, COPD %, asthma 6.3%, coronary heart disease 13.3%, chronic kidney disease 1%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

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;[182] 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
Abd-Elsalam et al;[183] 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 **Adverse events:** No information
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;[184] 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: 0.89 (CI 95% 0.78 - 1.02) Based on data from 7885 patients in 10 studies	**330** per 1000	**294** per 1000 Difference: **36 fewer per 1000** (CI 95% 73 fewer - 7 more)	**Moderate** Due to serious imprecision[1]	Steroids probably decreases mortality
Invasive mechanical ventilation 28 days	Relative risk: 0.84 (CI 95% 0.67 - 1.04) Based on data from 5806 patients in 4 studies Follow up 28	**116** per 1000	**97** per 1000 Difference: **19 fewer per 1000** (CI 95% 38 fewer - 5 more)	**Moderate** Due to serious imprecision[2]	Steroids probably decreases invasive mechanical ventilation
Symptom resolution or improvement 28 days	Relative risk: 1.49 (CI 95% 1.22 - 1.84) Based on data from 510 patients in 3 studies	**554** per 1000	**825** per 1000 Difference: **271 more per 1000** (CI 95% 122 more - 465 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	**54** per 1000	**48** per 1000 Difference: **6 fewer per 1000** (CI 95% 17 fewer - 9 more)	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Steroids may have little or no difference on severe adverse events

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

Summary of findings table 2.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** standard of care	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	**330** per 1000	**310** per 1000 Difference: **20 fewer per 1000** (CI 95% 59 fewer - 26 more)	**Low** Due to serious imprecision, Due to serious risk of bias[1]	Remdesivir may decrease mortality slightly
Invasive 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	**116** per 1000	**75** per 1000 Difference: **41 fewer per 1000** (CI 95% 71 fewer - 13 more)	**Low** Due to serious risk of bias, Due to serious imprecision[2]	Remdesivir may decrease invasive 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	**554** per 1000	**648** per 1000 Difference: **94 more per 1000** (CI 95% 17 more - 183 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	**54** per 1000	**43** per 1000 Difference: **11 fewer per 1000** (CI 95% 28 fewer - 18 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 invasive 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** standard of care	**Absolute effect estimates** HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 15 days	Relative risk: 1.08 (CI 95% 0.99 - 1.19) Based on data from 7824 patients in 6 studies Follow up Median 15 days	**330** per 1000	**356** per 1000 Difference: **26 more per 1000** (CI 95% 3 fewer - 63 more)	**Moderate** Due to serious risk of bias[1]	HCQ probably increases mortality
Mechanical ventilation 15 days	Relative risk: 1.05 (CI 95% 0.99 - 1.22) Based on data from 6607 patients in 5 studies Follow up Median 15 days	**116** per 1000	**122** per 1000 Difference: **6 more per 1000** (CI 95% 1 fewer - 26 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% 0.9 - 1.22) Based on data from 5308 patients in 3 studies Follow up 28 days	**554** per 1000	**582** per 1000 Difference: **28 more per 1000** (CI 95% 55 fewer - 122 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 - 1.11) Based on data from 5799 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% 0.77 - 1.57)	**54** per 1000	**59** per 1000	**Low**	

	Based on data from 3234 patients in 5 studies	Difference: **5 more per 1000** (CI 95% 12 fewer - 31 more)	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** standard of care	**Absolute effect estimates** 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	**330** per 1000	**337** per 1000 Difference: **7 more per 1000** (CI 95% 26 fewer - 40 more)	**Moderate** Due to serious imprecision[1]	Lpv probably has little or no difference on mortality
Invasive 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	**116** per 1000	**124** per 1000 Difference: **8 more per 1000** (CI 95% 2 fewer - 20 more)	**High**	Lpv does not reduce invasive mechanical ventilation
	Relative risk: 1.03 (CI 95% 0.92 - 1.15)	**554** per 1000	**571** per 1000	**Moderate** Due to serious risk of bias[2]	Lpv probably has little or no difference on

Symptom resolution or improvement 28 days	Based on data from 5239 patients in 2 studies Follow up 28 days	Difference: **17 more per 1000** (CI 95% 44 fewer - 83 more)		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	**54** per 1000 **32** per 1000 Difference: **22 fewer per 1000** (CI 95% 34 fewer - 1 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** standard of care	CP	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 0.84 (CI 95% 0.64 - 1.11) Based on data from 1376 patients in 9 studies Follow up Median 28 days	**330** per 1000	**274** per 1000 Difference: **56 fewer per 1000** (CI 95% 119 fewer - 36 more)	**Very Low** Due to serious imprecision, Due to serious risk of bias, Due to serious inconsistency[1]	It is uncertain if CP reduces mortality
Mechanical ventilation 28 days	Relative risk: 0.78 (CI 95% 0.51 - 1.17) Based on data from 545 patients in 2 studies Follow up Median 28 days	**116** per 1000	**90** per 1000 Difference: **26 fewer per 1000** (CI 95% 57 fewer - 20 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether CP increases or decreases mechanical ventilation
	Relative risk: 1.03 (CI 95% 0.89 - 1.2)	**554** per 1000	**571** per 1000	**Very Low**	We are uncertain whether CP increases

Symptom resolution or improvement 28 days	Based on data from 653 patients in 3 studies Follow up 28 days	Difference: **17 more per 1000** (CI 95% 61 fewer - 111 more)	Due to serious risk of bias, Due to serious imprecision, Due to very serious risk of bias[3]	or decreases 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 studies	**54** per 1000 **68** per 1000 Difference: **14 more per 1000** (CI 95% 9 fewer - 49 more)	**Very Low** Due to serious risk of bias, Due to serious imprecision, Due to very serious imprecision[4]	We are uncertain whether cp increases or decreases severe adverse events
Severe adverse events	Based on data from 20000 patients in 1 studies	Observed risk of severe adverse events were: TRALI 0.1%, TACO 0.1%, severe allergic reactions 0.1%	**Very Low** Due to very serious risk of bias[5]	We are uncertain whether lpv increases or decreases severe adverse events

1. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** Point estimates vary widely; **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: Very Serious.** Wide confidence intervals;
3. **Risk of bias: Very Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Serious.** Low number of patients;
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: Very Serious.** Low number of patients, Wide confidence intervals;
5. **Risk of bias: Very Serious.** Although adverse events were rare, we assume that some might have been missed and assumed as related to disease progression. RCT are needed to determine interventions safety.

Summary of findings table 6.

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** standard of care	**Absolute effect estimates** TCZ	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 1.08 (CI 95% 0.79 - 1.48)	**330** per 1000	**356** per 1000	**Low**	

	Based on data from 806 patients in 3 studies Follow up Median 28 days	Difference: **26 more per 1000** (CI 95% 69 fewer - 158 more)	Due to serious imprecision, Due to very serious imprecision[1]	Tcz may have little or no difference on mortality
Mechanical ventilation 28 days	Relative risk: 0.73 (CI 95% 0.57 - 0.94) Based on data from 641 patients in 3 studies Follow up Median 28 days	**116** per 1000 **85** per 1000 Difference: **31 fewer per 1000** (CI 95% 50 fewer - 7 fewer)	**Low** Due to serious imprecision and inconsistency with mortality outcome [2]	Tcz probably decreases mechanical ventilation requirement
Symptom resolution or improvement 28 days	Relative risk: 1.04 (CI 95% 0.96 - 1.12) Based on data from 433 patients in 3 studies Follow up 28 days	**554** per 1000 **576** per 1000 Difference: **22 more per 1000** (CI 95% 22 fewer - 66 more)	**Low** Due to very serious imprecision[3]	Tcz probably has little or no difference on symptom resolution or improvement
Severe adverse events	Relative risk: 0.87 (CI 95% 0.72 - 1.05) Based on data from 873 patients in 4 studies	**54** per 1000 **47** per 1000 Difference: **7 fewer per 1000** (CI 95% 15 fewer - 3 more)	**Moderate** Due to serious imprecision[4]	Tcz probably has little or no difference on severe adverse events

1. **Imprecision: Very Serious.** 95%CI includes significant mortality reduction and increase;
2. **Imprecision: Serious.** 95% included significant and trivial reduction mechanical ventilation requirement reduction; **Incosisntecy: Serious.** Mortality outcome shows a different effect direction
3. **Imprecision: Serious.** 95%CI includes significant benefits and absence of benefits ;
4. **Imprecision: 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** standard of care	ACO	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality: Therapeutic dose (i.e enoxaparin 1mg/kg every 12	Relative risk: 2.02 (CI 95% 0.7 - 5.8) Based on data from 2409 patients in 5 studies	**330** per 1000	**667** per 1000	**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

h) vs. prophylactic dose (i.e enoxaparin 40mg a day)[1] 28 days		Difference: **337 more per 1000** (CI 95% 99 fewer - 770 more)		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	**330** per 1000 **96** per 1000 Difference: **234 fewer per 1000** (CI 95% 287 fewer - 119 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. Intermediate 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 standard of care 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	**330** per 1000 **290** per 1000 Difference: **40 fewer per 1000** (CI 95% 85 fewer - 11 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. (Link to interactive version)

Population: Patients with COVID-19 infection
Intervention: Interferon Beta-1a

Comparator: Standard of care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard of care	IFN	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk: 1.07 (CI 95% 0.9 - 1.26) Based on data from 4181 patients in 2 studies Follow up Median 28 days	**330** per 1000	**353** per 1000 Difference: **23 more per 1000** (CI 95% 33 fewer - 86 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 - 1.17) Based on data from 3921 patients in 2 studies Follow up 28 days	**116** per 1000	**114** per 1000 Difference: **2 fewer per 1000** (CI 95% 20 fewer - 20 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 81 patients in 1 study Follow up 28 days	**554** per 1000	**589** per 1000 Difference: **35 more per 1000** (CI 95% 150 fewer - 225 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	**554** per 1000	**829** per 1000 Difference: **275 more per 1000** (CI 95% 11 more - 423 more)	**Low** Due to very serious imprecision[4]	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. **Imprecision: Very Serious.** 95%CI includes significant benefits and absence of benefits

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