COVID-19

Ongoing Living Update of Potential COVID-19 Therapeutics: Summary of Rapid Systematic Reviews

RAPID REVIEW, 22 September 2020

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. Yet, recognizing that there are numerous ongoing clinical studies, PAHO will periodically update these reviews and corresponding recommendations as new evidence becomes available.

Summary of the evidence

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

Table 1. Interventions effects and certainty in RCT

Intervention	Overall number of studies including the intervention, n=88	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)
Hydroxychloroquine or Chloroquine	17	4	3	3	3	4
Glucocorticoids	12	10	4	3		6
Lopinavir-Ritonavir	7	2	1	1		1
Convalecent plasma	5	4	2	3		1
Favipravir	4			2		
Remdesivir	4	3	2	3		3
Ivermectin	3	1	1		1	
Azithromycin	2	2		1		1
Colchicine	2	1	1			
IVIG	2	2	1			1
Leflunomide	2					
Sofosbuvir/Daclatasvir	2	1	1			
Tocilizumab	2	1	1	1		2
Umifenovir	2					
99mTc-MDP	1					
Anticoagulants	1	1				
Aprepitant	1					
Auxora	1	1	1			
Azvudine	1					
Baloxavir	1			1		
Bromhexine Hydrochloride	1			1		
CIGB-325	1			1		1
Electrolyzed saline	1	1		1		
Darunavir-Cobicistat	1					
Febuxostat	1					
Icatibant	1	1				
iC1e/K	1	1				
IFN-alpha2b + IFN-gamma	1					
IFX-1	1	1				1
Interferon beta-1a	1	1	1	1		
Interferon beta-1b	1	1	1	1		
Lincomicin	1					
Mesenchimal cell tranplantation	1			1		
Nasal hypertonic saline	1			1		
Novaferon	1					
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
Telmisartan	1	1	1			
Triazavirin	1	1		1		1
Vitamin C	1	1	1	1		
Vitamin D	1					
α-Lipoic acid	1	1				

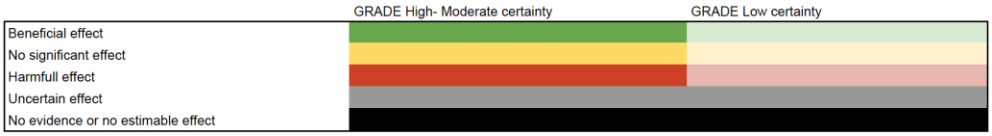
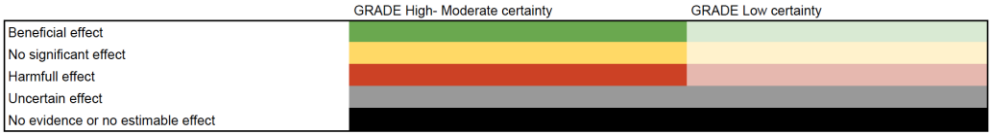


Table 2. Interventions effects and certainty in non-RCT

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	3	3				
Colchicine	1	1				
Convalecent plasma	4	3				1*
Ivermectin	1	1				
NSAID	5	5				
Tocilizumab	9	9				

* Only specific transfusion related adverse events



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 46 therapeutic options (Table 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.

• The results of three RCT suggest that remdesivir may reduce mortality and improve time to symptom resolution. However, certainty of the evidence is low and further research is needed to confirm or discard these findings.

• The body of evidence on hydroxychloroquine and Lopinavir-Ritonavir, including anticipated RECOVERY Trial findings shows no benefit in terms of reducing mortality or reduced time to clinical improvement. Three 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 four RCT assessing convalescent plasma in COVID-19 patients showed a non-statistically significant trend towards reduction in mortality and mechanical ventilation requirements. However, certainty of the evidence is low and further research is needed to confirm or discard these findings.

• Currently, as to tocilizumab, the results of one RCT providing low certainty evidence suggest no mortality reduction with a trend towards less mechanical ventilation requirement and faster symptom resolution. Further research is needed to confirm or discard those findings.

• Currently, as to ivermectin, 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 exploran 46 intervenciones para el manejo de pacientes con COVID-19 (Tabla 3).

• El cuerpo de evidencia sobre los esteroides incluye diez estudios aleatorizados y controlados (ECA) y muestra que esquemas con dosis bajas a moderadas (la dosis utilizada en el estudios 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 consistentes luego de agregar al análisis estudios en los que pacientes con SDRA de otras etiologías fueron aleatorizados a recibir corticosteroides o manejo estándar.

• Los resultados de tres ECA sugieren que remdesivir podría reducir la mortalidad 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 adecuadamente diseñados para confirmar o descartar estos hallazgos.

• El cuerpo de la evidencia sobre hidroxicloroquina y lopinavir-ritonavir, incluidos los resultados preliminares del estudio RECOVERY, no muestra beneficios en la reducción de la mortalidad o en el plazo necesario para la mejoría clínica. Tres 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 proveniente de estudios adecuadamente diseñados es necesaria para confirmar o descartar estos hallazgos.

• Los resultados de cuatro ECA que evaluaron el uso de plasma de convaleciente en pacientes con COVID-19 mostraron una tendencia no estadísticamente significativa hacia una reducción en la mortalidad y la necesidad de ventilación mecánica invasiva. Sin embargo, la certeza en la evidencia es baja y se necesita más información de estudios adecuadamente diseñados para confirmar o descartar estos hallazgos.

• Hasta el momento, en relación con el tocilizumab, los resultados de un ECA sugieren ausencia de beneficios en mortalidad con una tendencia hacia la reducción en los requerimientos de ventilación mecánica e incremento en la velocidad de resolución de los síntomas. Sin embargo, la certeza en la evidencia es baja y más información de estudios adecuadamente diseñados es necesaria para confirmar o descartar estos hallazgos.

• Hasta el momento, en relación con la ivermectina hay evidencia de muy baja certeza, por lo que sus efectos son inciertos. Se necesita más información de estudios adecuadamente diseñados 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 sugieren que 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 resultó muy baja, por lo que se necesita más información de estudios adecuadamente diseñados para confirmar o descartar estos hallazgos.

• El uso 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 especiales 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 adecuadamente diseñados 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.

Background

The vast amount of data that will be coming will present important challenges and it must be interpreted quickly so that the correct most optimal treatment decisions can be made with as less harm to patients, and that manufacturers and supply chains can scale up production rapidly. This will ensure that reportedly successful drugs can be administered to as many patients and in as timely a manner as possible. Moreover, if evidence indicates that a medication is potentially suboptimal and not effective, then the many ongoing clinical trials could change focus and pivot onto more promising alternatives. Additionally, many are using drugs already in huge volumes and also via compassionate or single use applications.[1] It is absolutely imperative therefore that prescribers be given the most updated research evidence fast to inform if what was done was optimal or if it is not optimal or even harmful to patients. The following evidence-database was compiled to orient the published studies thus far and will endeavor to add to this table list as research is released into the public space.

Methods

Search methods

We systematically searched in L·OVE (Living OVerview of Evidence) platform for COVID-19, a system that maps PICO 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 website.[2]

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 the day before release on September 22, 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 ID, DOI, trial registry ID), 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.

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.

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, mechanical ventilation, symptom resolution or improvement, infection (prophylaxis studies) and severe adverse events).[3]

No electronic database search restrictions were imposed. If meta-analytical pooling was and is possible from retrieved evidence, this review would seek to do this to derive more precise estimates of effect and derive additional statistical power.

In addition to RCT, we included and will continue to include comparative non-RCT which report on effects of specific interventions that are being extensively used within the region (table 2.). For some of these interventions (TCZ and NSAID) we only incorporated non-RCT that included, at least, 100 patients. We presented results of RCT and non-RCT separately.[4]

For any meta-analytical pooling if and when data allowed, we pooled all studies. We presented the combined analysis relative and absolute effects. To assess interventions' absolute effects, we applied relative effects to baseline risks (risks with no intervention). We extracted mortality and mechanical ventilation baseline risks from 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 RCT. For mortality there were some drug instances whereby we provide systematic-review (meta-analysis) evidence indirectly related to COVID-19 patients 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 relevant biases to the estimates of effect.[6] For non-RCT potential residual confounding was assumed in all cases and certainty of the evidence was downgraded twice for RoB. The GRADE approach was used to assess the certainty on the body of evidence, for every comparison, on an outcome basis (Table 3).

Results

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 very 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 severity of disease, comorbidities, previous or concomitant COVID-19 treatment. The Risk of Bias assessment of each randomized controlled trial is presented in table 4.

Main findings

Corticosteroids

We identified 11 RCT including 7914 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. RECOVERY trial was the biggest with 2104 patients assigned to dexamethasone and 4321 to standard of care. All ten studies included patients with severe to critical disease as mortality in the control groups ranged from 14.2% to 61.4%. In the RECOVERY trial a subgroup analysis by baseline respiratory support received informed significant differences favoring those with oxygen requirement. 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 significantly 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 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 patients with ARDS. No significant differences between subgroups of studies using different steroids were observed. (Figures 2 and 3)

Figure 1: All-cause mortality with corticosteroids use vs. standard of care in randomized control trials including COVID-19 patients

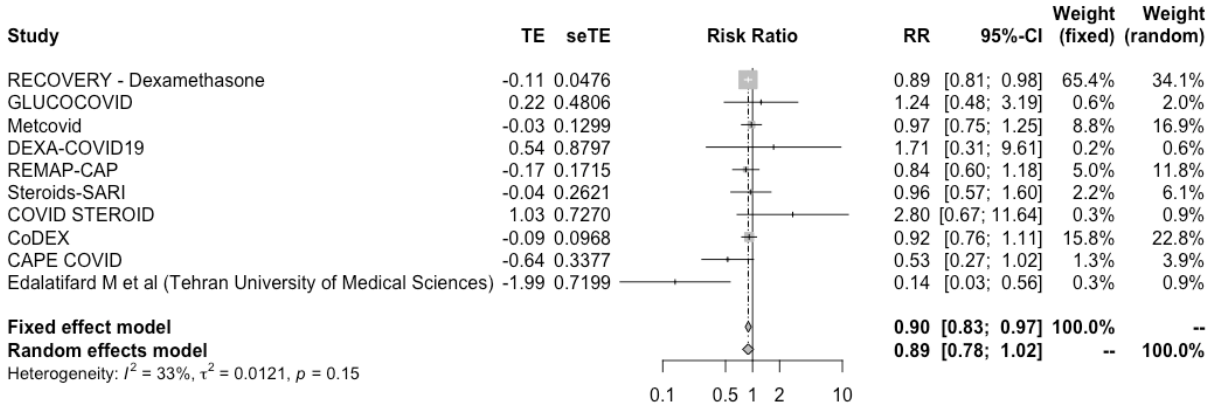


Figure 2. All-cause mortality with corticosteroids use vs. standard of care in randomized control trials including COVID-19 patients and ARDS non-COVID-19 patients

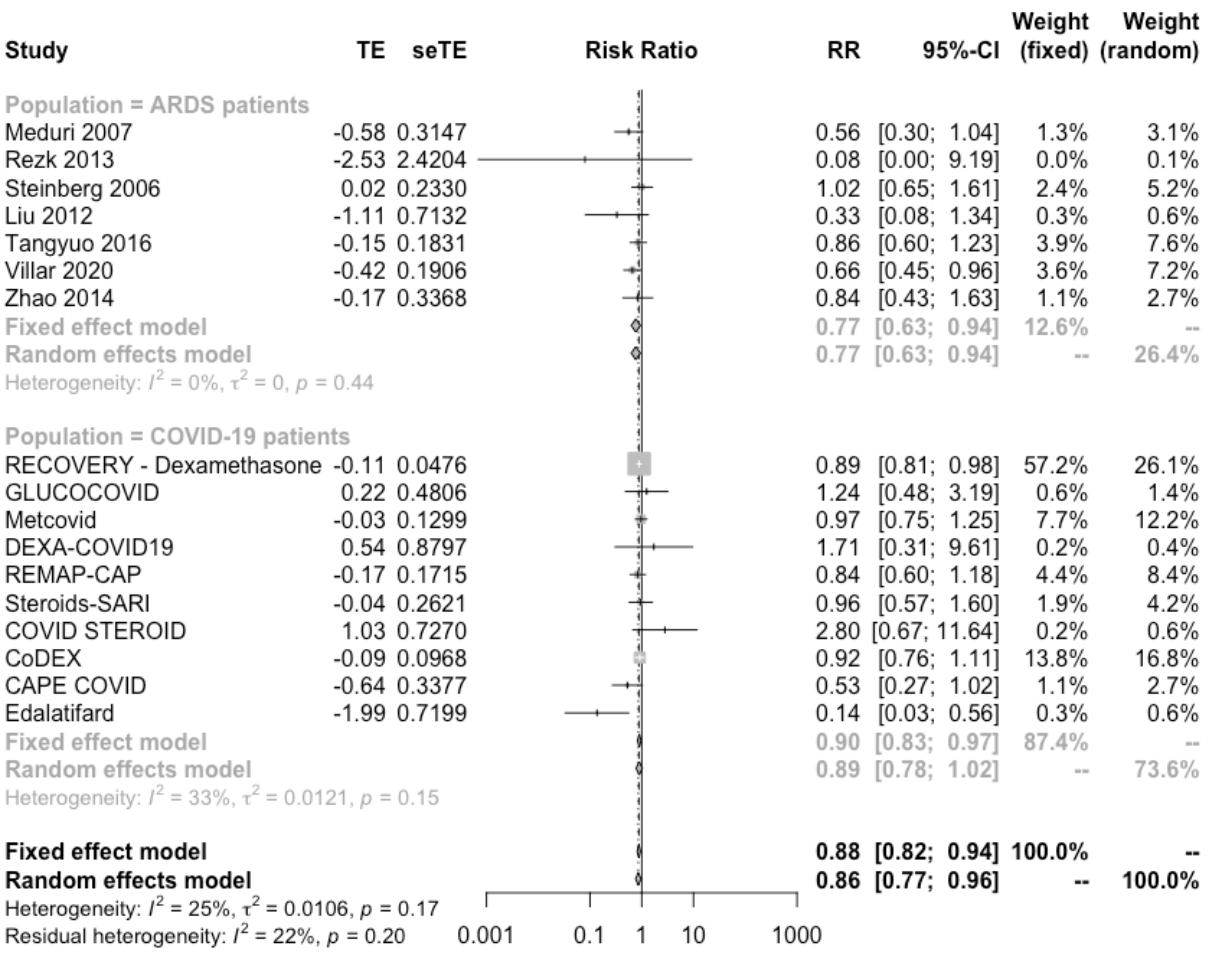
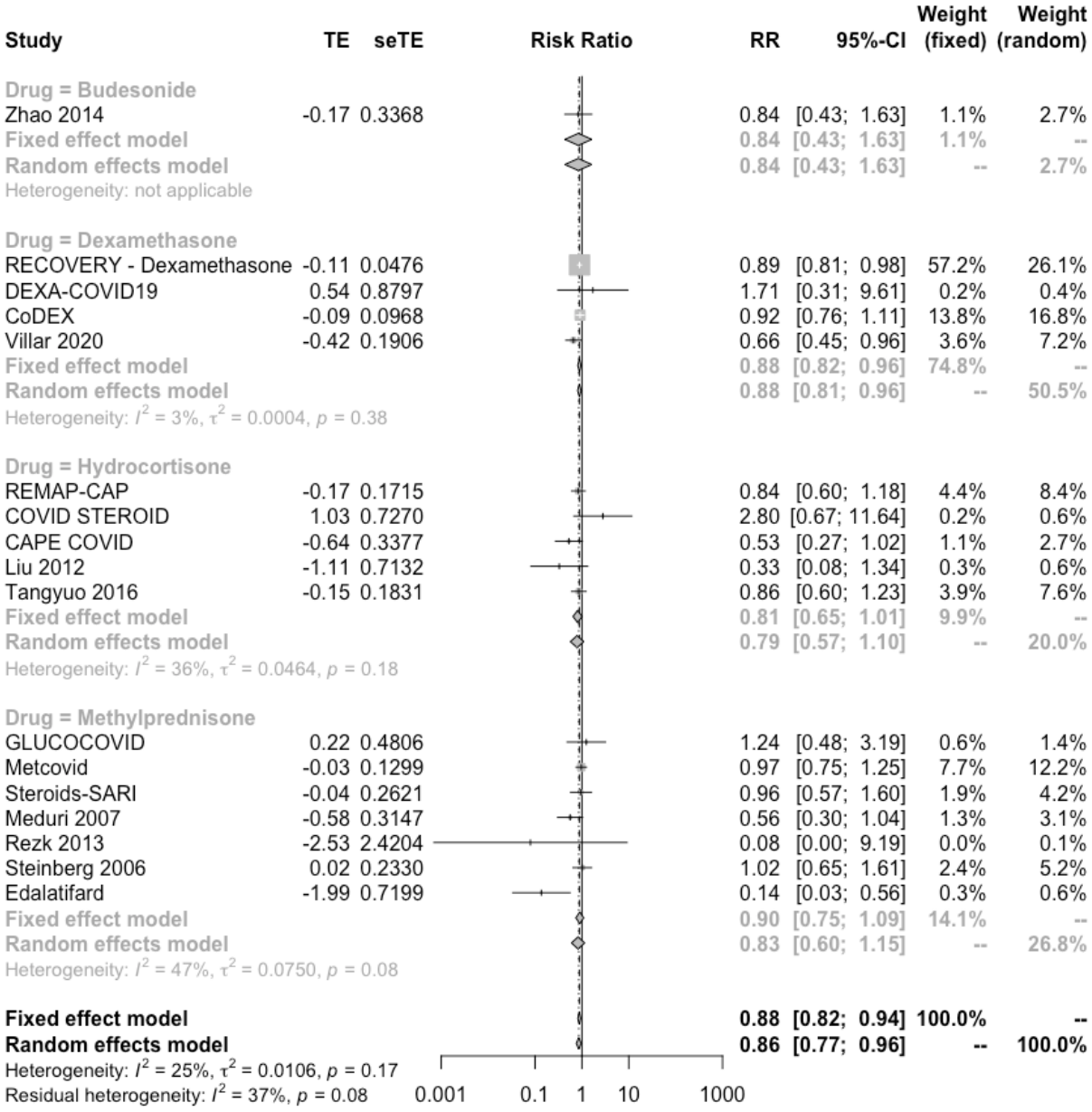


Figure 3. All-cause mortality by type of corticosteroids vs. standard of care in randomized control trials including COVID-19 patients and ARDS non-COVID-19 patients



Remdesivir

We identified 4 RCT including 2277 in which remdesivir was compared against standard of care or other treatments. ACTT-1 trial is the biggest with 538 patients assigned to remdesivir and 521 to standard of care. Three studies included patients with severe disease as the 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 reduce mortality, RR 0.78 (95%CI 0.56 to 1.08); RD -7.3% (95%CI -14.5% to 2.6%); Low certainty ⊕⊕◯◯ (figure 4.)
- It is uncertain if remdesivir affects mechanical ventilation requirement; Very low certainty ⊕◯◯◯
- Remdesivir may improve time to symptom resolution, RR 1.17 (95%CI 1.03 to 1.33); RD 3.8% (95%CI 0.7% to 7.4%); Low certainty ⊕⊕◯◯ (figure 5.)
- Remdesivir may not significantly increase the risk of severe adverse events, RR 0.91 (95%CI 0.52 to 1.59); RD -0.5% (95%CI -2.6% to 3.2%); Low certainty ⊕⊕◯◯

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

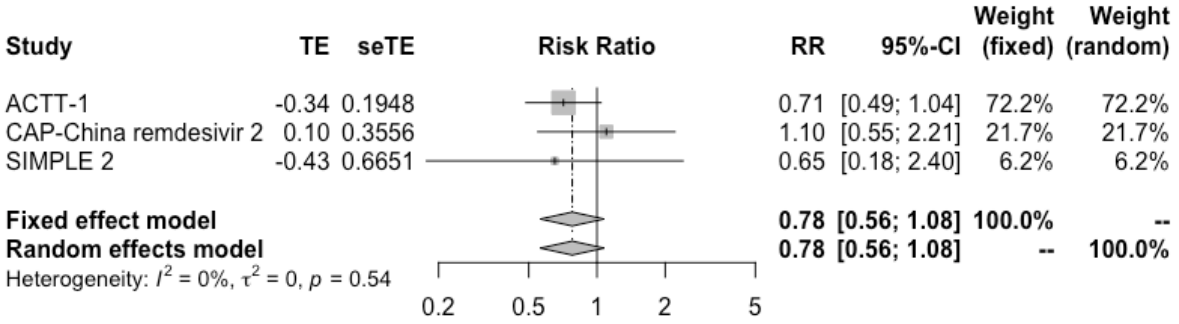
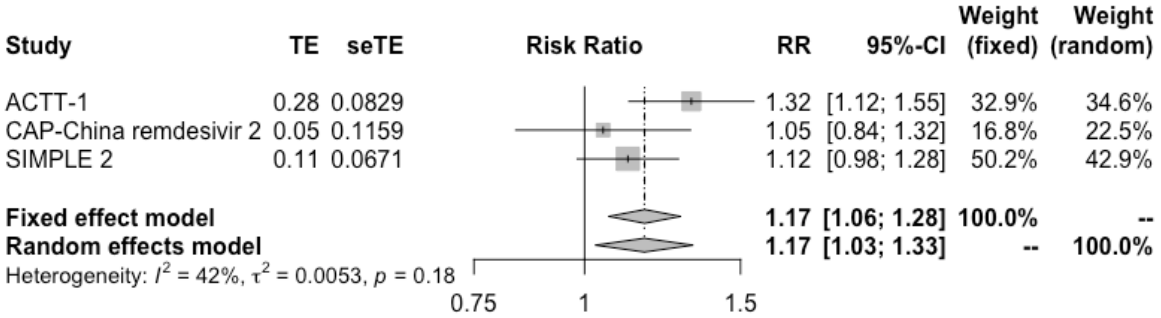


Figure 5. Symptom resolution or improvement with remdesivir use vs. standard of care in randomized control trials including COVID-19 patients



Hydroxychloroquine and Chloroquine

We identified 16 RCT including 10066 patients in which hydroxychloroquine or chloroquine was compared against standard of care or other treatments. RECOVERY trial was the biggest with 1561 patients assigned to dexamethasone and 3155 to standard of care. In RECOVERY trial patients had severe disease as mortality risk in the control arm was 24.9%. The remaining studies included patients with non-severe disease as mortality risk in the control arms ranged from 0 to 5.2%. Additionally we identified three studies in which hydroxychloroquine was used in healthy persons to prevent COVID-19 infection. Our results showed:

- Hydroxychloroquine or Chloroquine probably does not reduce mortality, RR 1.08 (95%CI 0.97 to 1.19); RD 2.6% (95%CI to 1% to 6.3%); Moderate certainty ⊕⊕⊕◯ (figure 6.)
- Hydroxychloroquine or Chloroquine probably does not reduce mechanical ventilation requirement; RR 1.1 (95%CI 0.89 to 1.35); RD 1.2% (95%CI to 1.3% to 4%); Moderate certainty ⊕⊕⊕◯
- Hydroxychloroquine or Chloroquine may not improve time to symptom resolution, RR 1.1 (95%CI 0.92 to 1.31); RD 5.5% (95%CI -4.4% to 17.2%); Low certainty ⊕⊕◯◯
- Hydroxychloroquine or Chloroquine may marginally reduce COVID-19 symptomatic infection in exposed individuals, RR 0.84 (95%CI 0.64 to 1.02); RD -2.8% (95%CI -6.3% to 0.3%); Very Low certainty ⊕◯◯◯ (figure 7.)
- It is uncertain if Hydroxychloroquine or Chloroquine increase the risk of severe adverse events, RR 1.02 (95%CI 0.56 to 1.86); RD 0.1% (95%CI -2.3% to 4.6%); Very Low certainty ⊕◯◯◯

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

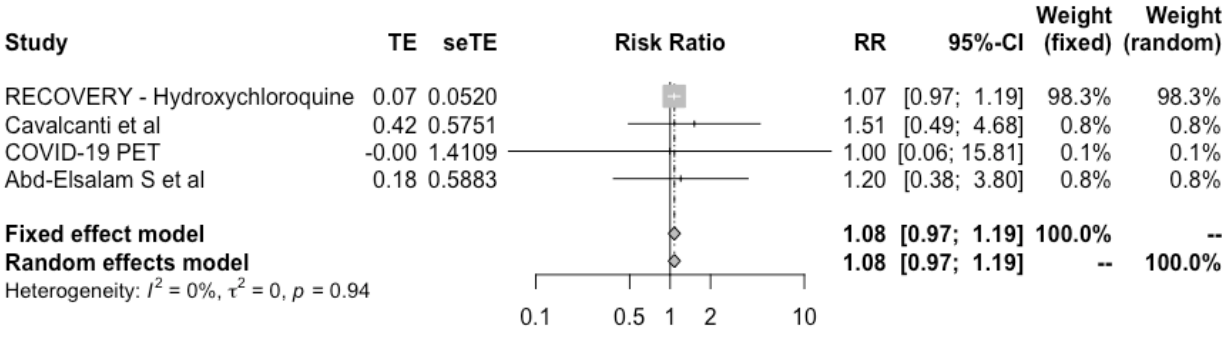
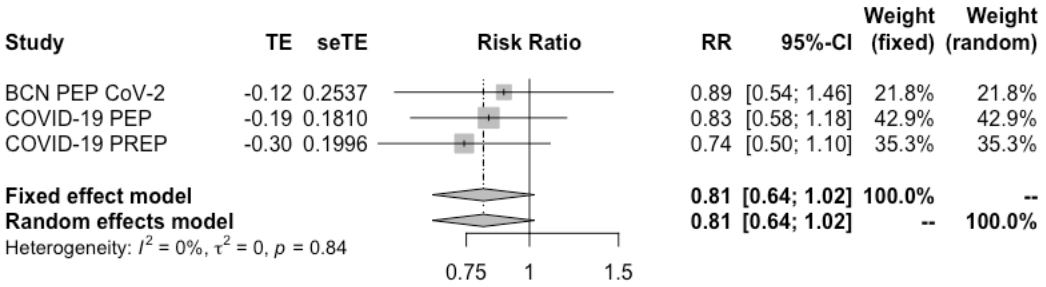


Figure 7. Symptomatic infection with hydroxychloroquine or chloroquine use vs. no prophylaxis in randomized control trials including persons exposed to COVID-19



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).

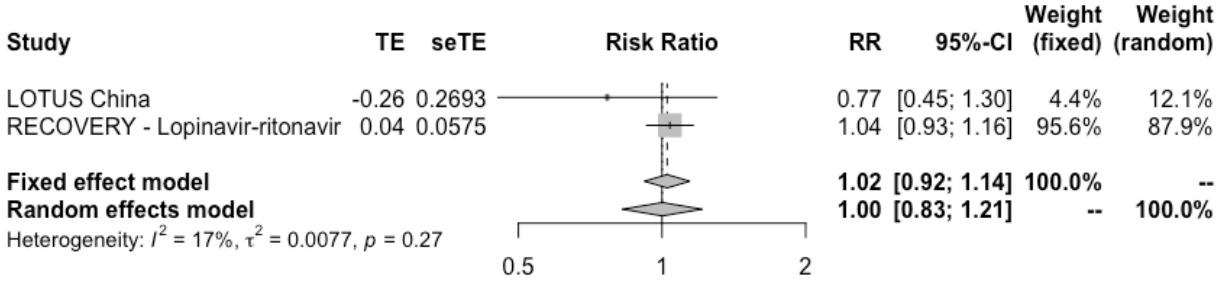
Lopinavir-Ritonavir

We identified 6 RCT including 5391 patients in which lopinavir-ritonavir was compared against standard of care or other treatments. RECOVERY trial was the biggest with 1596 patients assigned to dexamethasone and 3376 to standard of care. Two studies provided information on mortality outcome, both included patients with severe disease as mortality risk in control arms were 21.3 and 25%. Our results showed:

- Lopinavir-Ritonavir probably does not reduce mortality, RR 1 (95%CI 0.83 to 1.21); RD 0% (95%CI -5.6% to 6.9%); Moderate certainty ⊕⊕⊕◯ (figure 8.)

- It is uncertain if lopinavir-ritonavir affects mechanical ventilation requirement; Very low certainty ⊕◯◯◯
- It is uncertain if lopinavir-ritonavir affects symptom resolution or improvement; Very low 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 8. All-cause mortality with lopinavir-ritonavir vs. standard of care in randomized control trials including COVID-19 patients

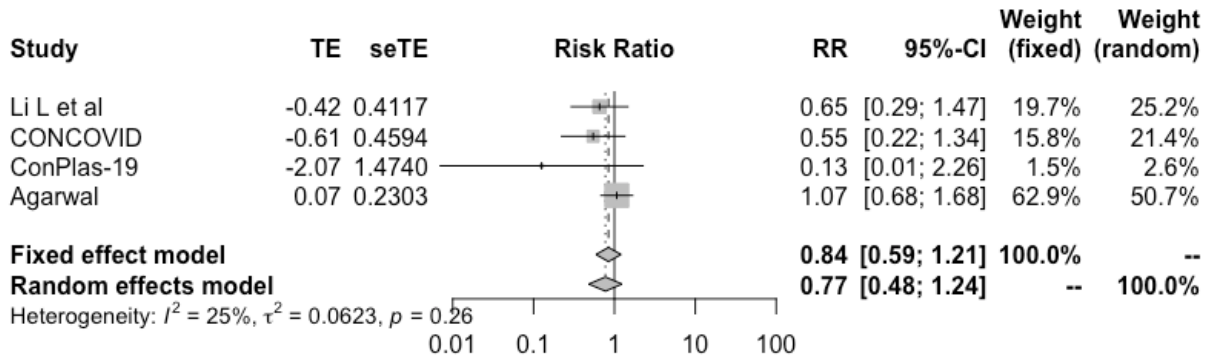


Convalescent plasma

We identified 4 RCT including 734 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. All studies included severe patients as mortality in the control arms ranged from 10% to 25.6%. Convalescent plasma was administered in one or two infusions to symptomatic patients in all cases. Our results showed:

- Convalescent plasma may reduce mortality, RR 0.77 (95%CI 0.48 to 1.24); RD -7.6% (95%CI -17.1% to 7.9%); Low certainty ⊕⊕◯◯ (figure 9.)
- Convalescent plasma may reduce mechanical ventilation requirements, RR 0.79 (95% CI 0.44 to 1.44); RD -2.4% (95%CI -6.5% to 5.1%); Low certainty ⊕⊕◯◯.
- It is uncertain if convalescent plasma affects symptom resolution or improvement; Very low certainty ⊕◯◯◯
- Specific adverse events related to convalescent plasma infusion are probably rare: Transfusion related circulatory overload 0.14%; Transfusion related lung injury 0.22%; Severe allergic transfusion reaction 0.06%

Figure 9: All-cause mortality with convalescent plasma vs. standard of care in randomized control trials including COVID-19 patients



In addition, we identified one study in which patients were randomized to early CP administration (at the time they were randomized) or late CP administration (only if clinical deterioration was observed). All patients in the early arm arm received CP while 43.3% of patients in the late arm received CP. Results showed no mortality reduction (OR 4.22, 95%CI 0.33 to 53.57) nor mechanical ventilation requirement reduction (OR 2.98, 95%CI 0.41 to 21.57) with early convalescent plasma infusion, although the certainty of the evidence was very low ⊕◯◯◯ because of imprecision.

Tocilizumab

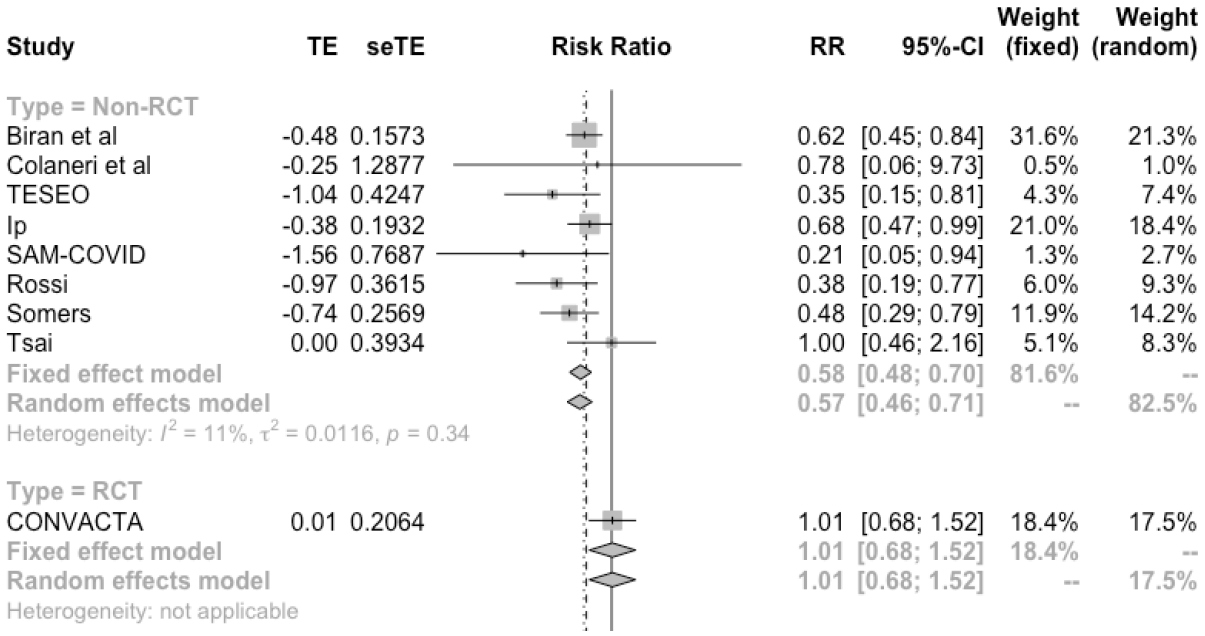
We identified 1 RCT including 438 patients in which tocilizumab was compared against standard of care or other treatments and informed on mortality outcome. The study included severe patients as mortality in the control arm was 19.4%. Our results showed:

- Tocilizumab may not reduce mortality, RR 1.01 (95%CI 0.68 to 1.52); RD 0.5% (95%CI -10.6% to 17.2%); Low certainty ⊕⊕◯◯ (figure 10.)
- Tocilizumab may marginally reduce mechanical ventilation requirements, RR 0.76 (95%CI 0.53 to 1.09); RD -2.8% (95%CI -5.4% to 1%); Low certainty ⊕⊕◯◯
- Tocilizumab may slightly improve time to symptom resolution, HR 1.26 (95%CI 0.97 to 1.64); RD 8.4% (95%CI -1.1% to 18%); Low certainty ⊕⊕◯◯
- Tocilizumab may not significantly increase severe adverse events, RR 0.91 (95%CI 0.7 to 1.18); RD -0.4% (95%CI -1.6% to 1%); Low certainty ⊕⊕◯◯

In addition, we identified nine non-RCT that included more than 100 individuals and informed on mortality comparing patients that were treated with or without tocilizumab. Our results showed:

- Pooled estimates from non-RCT suggest possible reduction in mortality (RR 0.57 95%CI 0.46 to 0.71) but certainty is very low ⊕◯◯◯ (figure 10.). These findings should be interpreted with extreme caution as they are exposed to risk of bias due to potential baseline patient prognostic imbalances

Figure 10: All-cause mortality with tocilizumab vs. standard of care in randomized control trials and non-randomized control trials including COVID-19 patients



Anticoagulants

Thromboembolic complications in patients infected with COVID-19 are relatively frequent.[8] As for hospitalized patients with severe medical conditions current guidelines recommend thromboprophylactic measures to be adopted 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.

NSAID

We identified 5 non-RCT that included at least 100 patients, in which COVID-19 mortality risk was assessed in patients exposed and not exposed to NSAIDs. Populations included varied between studies as Wong et al. included persons exposed to COVID-19 (living in a region affected by the pandemic) and the rest included patients with confirmed COVID-19 infection. Our results showed:

- No association between NSAID exposure and mortality, OR 0.95 (95%CI 0.81 to 1.11); Very Low certainty ⊕◯◯◯ (figure 11.)

Figure 11: All-cause mortality in patients exposed to NSAID vs. not exposed to NSAID in non-randomized control trials including persons exposed or infected with COVID-19

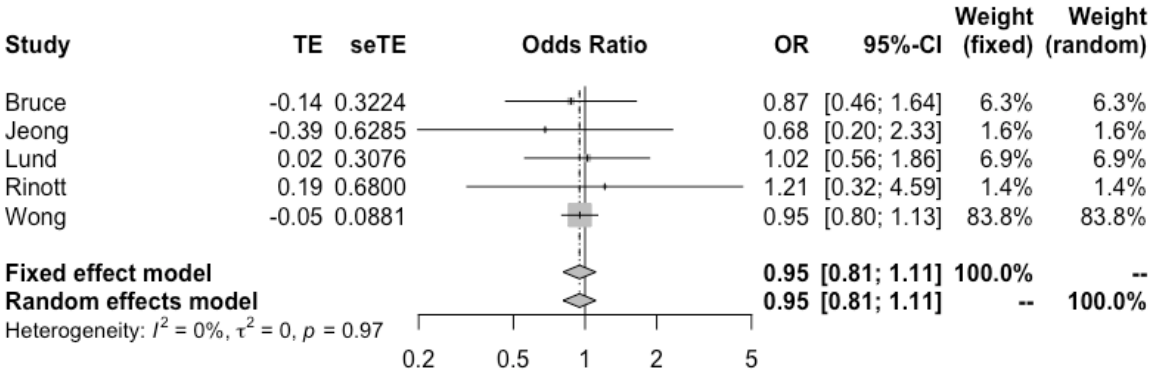


Table 3. Description of included studies and interventions effects

Study; publication status	Patients and interventions analyzed	Comorbidities	Additional interventions	Rob and study limitations	Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence
99mTc-MDP **Uncertainty in potential benefits and harms. Further research is needed.**					
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 SOC	Median age 61 ± 20, male 42.9%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **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.**					
RCT					
HESACOVID trial;[11] Bertoldi Lemos et al; Peer reviewed; 2020	Patients critical COVID-19. 10 assigned to LMWH therapeutic dose and 10 assigned to	Mean age 56.5 ± 13, male 80%, hypertension 35%, diabetes 35%, CHD 10%,	Steroids 70%, hydroxychloroquine 25%, azithromycin 90%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** No

	LMWH prophylactic dose	immunosuppression 5%		Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** 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. 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%, CHD 56.7%, CKD 10.7%, immunosuppression 2.9%, cancer 12.3%	Hydroxychloroquine 58.6%, lopinavir-ritonavir 50.8%, tocilizumab 15%, ATB 58%	High for mortality Notes: Non-randomized study. Retrospective design. Regression was implemented to adjust for potential confounders (age, sex, race, ethnicity, BMI, smoking status, dibetes immunosupression, heart disease, pulmonary disease, kidney disease, cancer, hyperlipidemia, need	

				for ICU admission, mechanical ventilation, pharmacological treatments, laboratory measurments)	
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. Retrospective design. Regression was implemented to adjust for potential confounders (age, sex, clinical parameters and concomitant interventions)	
Aprepitant **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Mehboob et al;[15] 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 SOC	Mean age 54.2 ± 10.91, male 61.1%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Auxora Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Miller et al;[16] 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 9 assigned to SOC	Mean age 60 ± 12, male 46.1%, hypertension 46.1%, diabetes 38.4%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate. Analysis performed on a subgroup (patients that requires HFNC were excluded form primary analysis).	**Mortality:** Very Low certainty ⨁◯◯◯ **Mechanical ventilation:** Very Low certainty ⨁◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Azithromycin Azithrimycin may not affect mortality. However certainty of the evidence is low because of imprecision. Further research is needed.					
RCT					
Sekhavati et al;[17] Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 56 assigned to azithromycin 500 mg twice-daily and 55 assigned to SOC	Mean age 57.1 ± 15.73, male 45.9%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 1.05 (95%CI 0.83 to 1.33); RD 1.6% (95%CI -5.6% to 10.9%); Low certainty ⨁⨁◯◯ **Mechanical ventilation:** No information **Symptom resolution or improvement:** Very Low certainty ⨁◯◯◯ **Symptomatic**
Guvenmez et al;[18] Peer reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to Lincomicin 600mg	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	twice a day for 5 days and 12 assigned to Azithromycin 500mg on first day followed by 250mg a day for 5 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
COALITION II trial;[19] Furtado et al; Peer reviewed; 2020	Patients severe COVID-19. 214 assigned to azithromycin 500mg once a day for 10 days and 183 assigned to SOC	Median age 59.8 ± 19.5, male 66%, hypertension 60.7%, diabetes 38.2%, chronic lung disease 6%, asthma %, CHD 5.8%, CKD 11%, cerebrovascular disease 3.8%, immunosuppression %, cancer 3.5%, obesity %	Steroids 18.1%, remdesivir %, hydroxychloroquine %, lopinavir-ritonavir 1%, tocilizumab %, azithromycin %, convalescent plasma %, oseltamivir 46%, ATB 85%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Azvudine **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Ren et al;[20] Peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 10 assigned to Azvudine 5mg once a day and 10 assigned to SOC	Median age 52 ± 59, male 60%, hypertension 5%, diabetes 5%, CHD 5%	Antivirals 100%, ATB 40%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Baloxavir Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Lou et al;[21] 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 favipravir and 10 assigned to SOC	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, CHD 13.8%	Antivirals 100%, IFN 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Bromhexine Hydrochloride **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Li T et al;[22] Peer reviewed; 2020	Patients severe to critical COVID-19. 12 assigned to Bromhexine Hydrochloride 32mf three times a day for 14 days and 6 assigned to SOC	Median age 52 ± 15.5, male 77.8%, hypertension 33.3%, diabetes 11.1%	Steroids 22.2%, IFN 77.7%	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 **Mechanical ventilation:** No information **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information
CIGB-325 **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
ATENEA-Co-300 trial;[23] Cruz et al; Preprint; 2020	Patients mild to moderate COVID-19. 10 assigned to CIGB-325 2.5 mg/kg/day during 5-consecutive days) and 10 assigned to SOC	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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **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.**					
RCT					
GRECCO-19 trial;[24] Deftereos et al; Peer reviewed; 2020	Patients with severe COVID-19 infection. 50 assigned to Colchicine 1.5mg once followed by 0.5mg twice daily until hospital discharge or 21 days and 55 assigned to SOC	Median age 64 ± 11, male 58.1%, hypertension 45%, diabetes 20%, chronic lung disease 4.8%, CHD 13.3%, immunosupression 3.75%	Hydroxychloroquine 98%, Lopinavir-ritonavir 31.4%, tocilizumab 3.8%, azithromycin 92%	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information

Lopes et al;[25] Preprint; 2020	Patients with moderate to severe COVID-19 infection. 19 assigned to Colchicine 0.5mg three times a day, for 5 days followed by 0.5mg twice daily for 5 days and 19 assigned to SOC	Median age 50.75 ± 26.2, male 40%, diabetes 31.4%, chronic lung disease 14.2%, CHD 40%	Steroids 40%, hydroxychloroquine 100%, azithromycin 100%, convalescent plasma NR%, heparin 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Non-RCT					
Scarsi et al;[26] 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%, CHD 69.4%, cancer 15%	Steroids 43%, hydroxychloroquine 51.6%, lopinavir-ritonavir 25.7%	High for mortality Notes: Non-randomized study. 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 ⨁◯◯◯
Convalescent plasma **Convalescent plasma may modestly reduce mortality in patients with moderate to critical COVID-19 infection. However certainty of the evidence is low because of risk of bias and imprecision. Further research is needed to clarify these potential relevant effects and address intervention's safety.**					
RCT					
Li et al;[27] Peer	Patients with	Median age 70 ± 8,	Steroids 39.2%,	High for mortality and	**Mortality:** RR 0.77

reviewed; 2020	moderate to critical COVID-19 infection. 52 assigned to CP 4 to 13 mL/kg of recipient body weight and 51 assigned to SOC	male 58.3%, hypertension 54.3%, diabetes 10.6%, CHD 25%, CKD 5.8%, cerebrovascular disease 17.45%, cancer 2.9%, liver disease 10.7%	antivirals 89.3%, ATB 81%, IFN 20.2%, IVIG 25.4%	mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	(95%CI 0.48 to 1.24); RD -7.6% (95%CI -17.1% to 7.9%); Low certainty ⊕⊕◯◯ **Mechanical ventilation:** RR 0.79 (95%CI 0.44 to 1.44); RD -2.4% (95%CI -6.5% to 5.1%); Low certainty ⊕⊕◯◯ **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
CONCOVID trial; Gharbharan et al;[28] Preprint; 2020	Patients with moderate to critical COVID-19 infection. 43 assigned to CP 300ml once or twice and 43 assigned to SOC	Median age 62 ± 18, male 72%, hypertension 26%, diabetes 24.4%, chronic lung disease 26.7%, CHD 23.2%, CKD 8.1%, immunosuppression 12.8%, cancer 9.3%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	
Avendaño-Solá et al;[29] Preprint; 2020	Patients severe COVID-19. 38 assigned to CP 250-300 ml once and 43 assigned to SOC	Mean age 60.8 ± 15.5, male 54.3%, hypertension 39.5%, diabetes 20.9%, chronic lung disease 12.3%, asthma NR%, CHD 18.5%, CKD 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 mechanical ventilation; 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;[30] Agarwal et al; Preprint; 2020	Patients severe COVID-19. 235 assigned to CP 200ml twice in 24hs and 229 assigned to SOC	Median age 52 ± 18, male 76.3%, hypertension 37.3%, diabetes 43.1%, chronic lung disease 3.2%, CHD 6.9%, CKD 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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias	

				to symptoms and adverse events outcomes results.	
Balcells et al;[31] Preprint; 2020	Patients moderate to severe COVID-19. 28 assigned to CP at enrolment, 200mg twice and 30 assigned to CP 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%, CHD %, CKD 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 mechanical ventilation; 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 ⊕◯◯◯ **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;[32] Peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 5000 received CP	Median age 62.3 ± 79.3, male 63.1%	NR	Low for specific transfusion related adverse events	
Liu et al;[33] Preprint; 2020	Patients with severe to critical COVID-19 infection. 39 received CP and 156 received alternative treatment schemes	Mean age 55 ± 13, male 64%, diabetes 21%, asthma 8%, CKD 3%, cancer 5%, obesity 54%	Steroids 57.4%, hydroxychloroquine 94.4%, azithromycin 84.1%, ATB 72.3%	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (exact matching was enforced on the administration of hydroxychloroquine and azithromycin, intubation status and duration, length of	**Mortality:** Very Low certainty ⊕◯◯◯ **Adverse events:** Transfusion related circulatory overload 0.14%; Transfusion related lung injury 0.22%; Severe allergic transfusion reaction 0.06%

				hospital stay, and oxygen requirement on the day of transfusion)	
Rogers et al;[34] Preprint; 2020	Patients with severe to critical COVID-19 infection. 64 received CP and 177 received alternative treatment schemes	Median age 61 ± 25, male 54.8%, hypertension 40.7%, diabetes 23.7%, chronic lung disease 14.9%, CHD 13.7%, CKD 10.8%, cancer 4.6%, obesity 39.4%	NR	High for mortality Notes: Non-randomized study. Retrospective design with matched control group. Regresion was implemented to adjust for potential confounders (age, gender, race, baseline oxygen requirements, remdesivir use, and corticosteroid use)	
Salazar et al;[35] Peer reviewed; 2020	Patients with severe to critical COVID-19 infection. 136 received CP and 251 received alternative treatment schemes	Mean age NR ± NR, male 58.4%, hypertension 34.7%, diabetes 26.7%, chronic lung disease 10.8%, CHD 10.3%, CKD 13.9%	Steroids 54.8%, remdesivir 3.5%, hydroxychloroquine 16.5%, lopinavir-ritonavir 1.6%, tocilizumab 19.6%, azithromycin 60.3%	High for mortality Notes: Non-randomized study. Prospective design with matched control group. Propensity score was implemented to adjust for potential confounders (age, gender, race, baseline oxygen requirements, remdesivir use, and corticosteroid use.)	
Darunavir-Cobicistat **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
DC-COVID-19 trial;[36] Chen et al; Peer reviewed; 2020	Patients with mild COVID-19 infection. 15 assigned to Darunavir-Cobicistat 800mg/150mg once a day for 5 days and	Mean age 47.2 ± 2.8, male NR, diabetes 6.6%, CHD 26.6%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	**Mortality:** No information **Mechanical ventilation:** No information

	15 assigned to SOC			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Electrolyzed saline **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
TX-COVID19 trial;[37] Delgado-Enciso et al; Preprint; 2020	Patients mild to moderate COVID-19. 45 assigned to electrolyzed saline nebulizations 4 times a day for 10 days and 39 assigned to SOC	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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very Low certainty ⊕◯◯◯ **Adverse events:** No information
Favipravir **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Chen et al; Preprint;[38] 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to Favipravir 1600mg	Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	**Mortality:** No information **Mechanical ventilation:** No

	twice the first day followed by 600mg twice daily for 7 days and 120 assigned to Umifenovir 200mg three times daily for 7 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	information **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Ivashchenko et al;[39] Peer reviewed; 2020	Patients with moderate COVID-19 infection. 20 assigned to Favipravir 1600mg once followed by 600mg twice a day for 12 days, 20 assigned to Favipravir and 20 assigned to SOC	Mean age NR ± NR, male NR	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Lou et al;[21] 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 Favipravir and 10 assigned to SOC	Mean age 52.5 ± 12.5, male 72.4%, hypertension 20.7%, diabetes 6.9%, CHD 13.8%,	Antivirals 100%, IFN 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Doi et al;[40] Peer reviewed; 2020	Patients mild COVID-19. 44 assigned to Favipravir (early) 1800mg on day 1 followed by 800mg twice daily for 10 days and 45 assigned to Favipravir (late) 1800mg on day 6 followed by 800mg twice daily for 10 days	Median age 50 ± 26.5, male 61.4%, comorbilidades 39%	Steroids 2.3%, ATB 12.5%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Febuxostat Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Davoodi et al;[41] Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to Febuxostat 80mg 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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Hydroxychloroquine and chloroquine HCQ/CQ probably does not reduce mortality, mechanical ventilation nor significantly improves time to symptom resolution with moderate certainty. When used prophylactically in persons exposed to COVID-19 it may marginally reduce the risk of infection. However certainty of the evidence is very low because of risk of bias and imprecision. HCQ/CQ may also be associated with a small increase in severe adverse events.					
RCT					
CloroCOVID19 trial;[42] Borba et al; Peer reviewed; 2020	Patients with severe COVID-19 infection. 41 assigned to CQ 600mg twice a day for 10 days and 40 assigned to CQ 450mg twice on day 1 followed by 450mg 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%, CHD 17.9%, CKD 7.4%, alcohol use disorder 27.5%, HIV 1.8%, tuberculosis 3.6%,	Azithromycin 100%, oseltamivir 89.7%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** RR 1.08 (95%CI 0.97 to 1.19); RD 2.6% (95%CI -1% to 6.3%); Moderate certainty ⊕⊕⊕◯ **Mechanical ventilation:** RR 1.1 (95%CI 0.89 to 1.35); RD 1.2% (95%CI -1.3% to 4%); Moderate certainty ⊕⊕⊕◯ **Symptom resolution or improvement:** RR
Huang et al;[43] Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500mg twice a day	Mean age 44 ± 21, male 59.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	for 10 days and 12 assigned to Lopinavir-Ritonavir 400/100mg twice a day for 10 days			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	1.1 (95%CI 0.92 to 1.31); RD 5.5% (95%CI -4.4% to 17.2%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** RR 0.84 (95%CI 0.64 to 1.02); RD -2.8% (95%CI -6.3% to 0.3%); Very Low certainty ⊕◯◯◯ **Severe Adverse events:** RR 1.02 (95%CI 0.56 to 1.86); RD 0.1% (95%CI -2.4% to 4.6%); Very Low certainty ⊕◯◯◯
RECOVERY - Hydroxychloroquine trial;[44] Horby et al; Preprint; 2020	Patients with Mild to critical COVID-19 infection. 1561 assigned to HCQ 800mg once followed by 400mg twice a day for 9 days and 3155 assigned to SOC	Mean age 65.3 ± 15.3, male %, diabetes 26.9%, chronic lung disease 21.9%, asthma NR%, CHD 25.4%, CKD 7.8%, HIV 0.4%	NR	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.	
BCN PEP CoV-2 trial;[45] Mitja et al; Preprint; 2020	Patients exposed to COVID-19. 1116 assigned to HCQ 800mg once followed by 400mg x once a day for 6 days and 1198 assigned to SOC	Mean age 48.6 ± 19, male 27%, diabetes 8.3%, chronic lung disease 4.8%, CHD 13.3%, Nervous system disease 4.1%	NR	Some concerns 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. Significant number of patients excluded from analysis.	
COVID-19 PEP trial;[46] Boulware et al; Peer reviewed; 2020	Patients exposed to COVID-19. 414 assigned to HCQ 800 mg once followed by 600 mg daily for a total course of 5 days and 407 assigned to SOC	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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Significant loss of information that	

				might have affected the studies results.	
Cavalcanti et al trial;[47] Cavalcanti et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 159 assigned to HCQ 400mg twice a day for 7 days, 172 assigned to HCQ + AZT and 173 assigned to SOC	Mean age 50.3 ± 14.6, male 58.3%, hypertension 38.8%, diabetes 19.1%, chronic lung disease 1.8%, asthma 16%, CHD 0.8%, CKD 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 mechanical ventilation; 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;[48] Kamran et al; Preprint; 2020	Patients with mild COVID-19 infection. 349 assigned to HCQ 400mg twice a day once then 200mg twice a day for 4 days and 151 assigned to SOC	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;[49] Skipper et al; Peer reviewed; 2020	Patients with mild COVID-19 infection. 212 assigned to HCQ 1400mg once followed by 600mg once a day for 5 days and 211 assigned to SOC	Median age 40 ± 9, male 44%, hypertension 11%, diabetes 4%, chronic lung disease %, asthma 11%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
BCN PEP CoV-2 trial;[50] Mitja et al; Preprint; 2020	Patients with mild COVID-19 infection. 136 assigned to HCQ 800mg once followed by 400mg a day for 6 days and 157 assigned to SOC	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;[51] 2020	Patients with mild to moderate COVID-19 infection. 75 assigned to HCQ 1200 mg daily for three days followed by 800 mg daily to complete 7 days and 75 assigned to SOC	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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outomes results.	
Chen et al; Preprint;[52] 2020	Patients with moderate COVID-19 infection. 31 assigned to HCQ 200mg twice a day for 5 days and 31 assigned to SOC	Mean age 44 ± 15.3, male 46.8%,	ATB 100%, IVIG 100%, antivirals 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Chen et al;[53] Preprint; 2020	Patients with moderate COVID-19 infection. 18 assigned to HCQ 200mg twice a day for 10 days, 18 assigned to CQ and 12 assigned to SOC	Mean age 47.4 ± 14.46, male 45.8%, hypertension 16.7%, diabetes 18.7%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Chen et al;[54] Preprint; 2020	Patients with mild to severe COVID-19 infection. 21 assigned to HCQ 400mg twice on day one followed by 200mg twice a day for 6 days and 12 assigned to SOC	Mean age 32.9 ± 10.7, male 57.6%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

HC-nCoV trial;[55] Jun et al; Peer reviewed; 2020	Patients with mild to severe COVID-19 infection. 15 assigned to HCQ 400mg once a day for 5 days and 15 assigned to SOC	Mean age 48.6 ± 3.7, male 0.7%, hypertension 26.6%, diabetes 6.6%, chronic lung disease 3.3%	Lopinavir-ritonavir 6.6%, umifenovir 73.3%, IFN 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Abd-Elsalam et al;[56] Peer reviewed; 2020	Patients with mild to severe COVID-19 infection. 97 assigned to HCQ 400 mg twice on day one followed by 200 mg tablets twice daily for 15 days and 97 assigned to SOC	Mean age 40.7 ± 19.3, male 58.8%, CKD 3.1%, obesity 61.9%, comorbidities 14.3%, liver disease 1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
COVID-19 PREP trial;[57] Rajasingham et al; Preprint; 2020	Patients exposed to COVID-19. 989 assigned to HCQ 400mg 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 SOC	Median age 41 ± 15, male 49%, hypertension 14%, asthma 10%	NR	Low for infection and adverse events	
Icatibant / iC1e/K **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Mansour et al;[58] Preprint; 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to Icatibant 30 mg every 8 h 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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might	**Mortality:** Very Low certainty ⨁◯◯◯ **Mechanical ventilation:** No information **Symptom resolution or**

				have introduced bias to symptoms and adverse events outcomes results.	**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.**					
RCT					
Vlaar et al;[59] Preprint; 2020	Patients with severe COVID-19 infection. 15 assigned to IFX-1 800mg IV with a maximum of 7 doses and 15 assigned to SOC	Mean age 60 ± 9, male 73%, hypertension 30%, diabetes 27%, obesity 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 ⊕◯◯◯ **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** Very Low certainty ⊕◯◯◯
Interferon alpha-2b + Interferon gamma **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
ESPERANZA trial;[60] Esquivel-Moynelo et al; Preprint; 2020	Patients with mild to moderate COVID-19 infection. 30 assigned to IFN-alpha2b + IFN-gamma Twice a week	Median age 38 ± 63, male 54%, hypertension 22.2%, diabetes 4.7%, asthma 6.3%, CHD 6.3%, any comorbidities 50.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%, convalescent plasma NR%, ATB 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	**Mortality:** No information **Mechanical ventilation:** No information

	for two weeks (SC) and 33 assigned to IFN-alpha2b Thrice a week (IM)			Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Interferon beta-1a **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Davoudi-Monfared et al;[61] Preprint; 2020	Patients with severe COVID-19 infection. 42 assigned to Interferon beta-1a 44 microg subcutaneous, three times a week and 39 assigned to SOC	Mean age 57.7 ± 15, male 54.3%, hypertension 38.3%, diabetes 27.2%, chronic lung disease 1.2%, asthma 1.2%, CHD 28.4%, CKD 3.7%, cancer 11.1%	Steroids 53%, hydroxychloroquine 97.5%, azithromycin 14.8%, ATB 81%, IVIG 30.8%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Interferon beta-1b **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Rahmani et al;[62] Peer reviewed; 2020	Patients severe COVID-19. 33 assigned to	Median age 60 ± 10.5, male 59%, hypertension 40.9%,	Steroids 21.2%, ATB 51.5%, antivirals 100%	High for mortality and mechanical ventilation; High for symptom	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical**

	Interferon beta-1b 250 mcg subcutaneously every other day for two consecutive weeks and 33 assigned to SOC	diabetes 31.8%, chronic lung disease 4.5%, asthma NR%, CHD 30.3%, CKD NR%, cerebrovascular disease NR%, immunosuppression NR%, cancer 3%, obesity NR%		resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**ventilation:** Very Low certainty ⨁◯◯◯ **Symptom resolution or improvement:** Very Low certainty ⨁◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Ivermectin **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Zagazig University trial;[63] Shouman et al; Other; 2020	Patients exposed to COVID-19. 203 assigned to ivermectin 15 to 24mg a day and 101 assigned to SOC	Mean age 38.72 ± 15.94, male 51.3%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⨁◯◯◯ **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;[64] Preprint; 2020	Patients mild to moderate COVID-19. 60 assigned to ivermectin + Doxi 200µgm/kg single dose + 100 mg BID for 10days and 56 assigned to HCQ +AZT	Mean age 33.9 ± 14.1, male 72.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Podder et al;[65] Peer reviewed;	Patients mild to moderate COVID-19.	Mean age 39.16 ± 12.07, male 71%	NR	High for mortality and mechanical ventilation;	

2020	32 assigned to ivermectin 200mg once and 30 assigned to SOC			High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Non-RCT					
Rajter et al;[66] Preprint; 2020	Patients with moderate to severe COVID-19 infection. 173 received Ivermectin and 107 received alternative treatment schemes	Mean age 59.6 ± 17.9, male 54.6%, hypertension 17.9%, diabetes 32.1%, chronic lung disease 10%, CHD 15.4%, CKD 8.6%, cancer 6.1%, obesity 40.7%	Hydroxychloroquine 92.9%, azithromycin 86.1%	High for mortality Notes: Non-randomized study. Retrospective design. Regression was implemented to adjust for potential confounders (age, sex, comorbidities of diabetes, chronic lung disease, cardiovascular disease, and hypertension, smoking status, severity of pulmonary involvement, BMI, peripheral white blood count, absolute lymphocyte count, and use of hydroxychloroquine and azithromycin)	**Mortality:** Very Low certainty ⨁◯◯◯
IVIG **IVIG may reduce mortality in patients with severe COVID-19 infection. However, certainty of the evidence was low and further research is needed to confirm or discard those findings.**					
RCT					
Sakoulas et al;[67] Preprint; 2020	Patients with severe COVID-19 infection. 16 assigned to IVIG 0.5 g/kg/day for 3 days and 17 assigned	Mean age 54 ± NR, male 60.6%, hypertension 33.3%, diabetes 36.3%, chronic lung disease	Steroids 78.7%, remdesivir 51.5%, convalescent plasma 15.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	**Mortality:** RR 0.41 (95%CI 0.19 to 0.87); RD -19.4% (95%CI -26.7% to 4.3%); Low certainty

	to SOC	12%, CHD 3%, CKD 3%, immunosuppression 3%		Notes: Non-blinded study. Concealment of allocation probably inappropriate.	⊕⊕◯◯ **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;[68] Preprint; 2020	Patients severe to critical COVID-19. 30 assigned to IVIG 5gr a day for 3 days and 29 assigned to SOC	Mean age 56 ± 16, male 69.5%, hypertension 22%, diabetes 27.1%, chronic lung disease 3.3%,	NR	Some Concerns for mortality and mechanical ventilation; Some Concerns for symptom resolution, infection and adverse events Notes: Concealment of allocation probably inapropiate.	
Leflunomide **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Hu et al;[69] Peer reviewed; 2020	Patients with mild to critical COVID-19 infection. 5 assigned to Leflunomide 50mg every 12hs (three doses) followed by 20mg a day for 10 days and 5 assigned to SOC	Mean age 52.5 ± 11.5, male 30%, hypertension 60%, chronic lung disease 10%	Umifenovir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Wang et al;[70] Peer reviewed; 2020	Patients moderate to severe COVID-19. 24 assigned to Leflunomide 100 mg on the first day followed by 20mg a day for 8 days and 24 assigned to SOC	Median age 55.7 ± 21.5, male 50%, hypertension 27.2%, diabetes 4.5%, chronic lung disease 4.5%, CHD 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 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.					
RCT					
Guvenmez et al;[18] Peer reviewed; 2020	Patients with moderate COVID-19 infection. 12 assigned to lincomycin 600mg twice a day for 5 days and 12 assigned to Azithromycin 500mg on first day followed by 250mg a day for 5 days	Mean age 58.7 ± 16, male 70.8%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **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.**					
RCT					
LOTUS China trial;[71] Cao et al; Peer reviewed; 2020	Patients with severe to critical COVID-19 infection. 99 assigned to Lopinavir-Ritonavir 400/100mg daily for 14 days and 100 assigned to SOC	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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** RR 1 (95%CI 0.83 to 1.21); RD 0% (95%CI -5.6% to 6.9%); Moderate certainty ⊕⊕⊕◯ **Mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic**
ELACOI trial;[72] Li et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to	Mean age 49.4 ± 14.7, male 41.7%	Steroids 12.5%, IVIG 6.3%	Low for mortality and mechanical ventilation; High for symptom resolution, infection	

	Lopinavir-Ritonavir 200/50mg twice daily for 7-14 days, 35 assigned to Umifenovir and 17 assigned to SOC			and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**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 ⨁⨁◯◯
RECOVERY - Lopinavir-ritonavir trial;[73] Horby et al; Press communication; 2020	Patients with mild to critical COVID-19 infection. 1596 assigned to Lopinavir-Ritonavir 400/100mg twice a day for 10 days and 3376 assigned to SOC	Mean age NR ± NR, male NR	NR	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.	
Huang et al; Peer reviewed;[43] 2020	Patients with moderate to severe COVID-19 infection. 10 assigned to CQ 500mg twice a day for 10 days and 12 assigned to Lopinavir-Ritonavir 400/100mg twice a day for 10 days	Mean age 44 ± 21, male 59.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Zheng et al; Preprint;[74] 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to Novaferon 40 microg twice a day (inh), 30 assigned to Novaferon + Lopinavir-Ritonavir 40 microg twice a day (inh) +	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

	400/100mg a day and 29 assigned to Lopinavir-Ritonavir				
Chen et al; Preprint;[75] 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to Ribavirin 2gr IV loading dose followed by orally 400-600mg every 8hs for 14 days, 36 assigned to Lopinavir-Ritonavir and 32 assigned to Ribavirin + Lopinavir-Ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	
Mesenchymal stem cell transplantation **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Shu et al;[76] 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 SOC	Median age 61 ± 10, male 58.5%, hypertension 22%, diabetes 19.5%	Steroids 100%, antibiotics 87.8%, antivirals 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Nasal hypertonic saline Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Kimura et al;[77] Peer reviewed; 2020	Patients mild to moderate COVID-19. 14 assigned to nasal hypertonic saline 250cc twice daily, 14 assigned to nasal hypertonic saline + sufractant and 17 assigned to SOC	Mean age 37.9 ± 15.7, male 53.3%, hypertension 24.4%, diabetes 6.6%, chronic lung disease 15.5%, CHD 4.4%,	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **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.					
RCT					
Zheng et al;[74] Preprint; 2020	Patients with moderate to severe COVID-19 infection. 30 assigned to Novaferon 40 microg twice a day (inh), 30 assigned to Novaferon + Lopinavir-Ritonavir 40 microg twice a day (inh) + 400/100mg a day and 29 assigned to Lopinavir-Ritonavir	Median age 44.5 ± NR, male 47.1%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information
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.**					
Non-RCT					
Bruce et al;[78] 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%, CHD 22.3%, CKD 38.7%,	NR	High for mortality Notes: Non-randomized study. Retrospective design. Regression was implemented to adjust for potential confounders (age, sex, smoking status, CRP levels, diabetes, hypertension, coronary artery disease, reduced renal function)	
Jeong et al;[79] 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%, CKD 2%, cancer 6%	NR	High for mortality and mechanical ventilation Notes: Non-randomized study. Retrospective design. Propensity score and IPTW were implemented to adjust for potential confounders (age, sex, health insurance type, hypertension, hyperlipidaemia, diabetes mellitus, malignancy, asthma, chronic obstructive pulmonary disease, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis,	**Mortality:** OR 0.95 (95%CI 0.81 to 1.11); Very Low certainty ⨁◯◯◯

				osteoarthritis, gastrointestinal, conditions, and use of co-medications)	
Lund et al;[80] 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%, CHD 10.2%, cerebrovascular disease 3.4%, cancer 7.1%, obesity 12.5%	Steroids 7.1%	High for mortality and mechanical ventilation Notes: Non-randomized study. 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;[81] 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%, CHD 12.9%,	NR	High for mortality and mechanical ventilation Notes: Non-randomized study. Retrospective design. No adjustment for potential confounders.	
Wong et al;[82] Preprint; 2020	Patients exposed to COVID-19 infection. 535519 received NSAID and 1924095 received alternative treatment schemes	Median age 51 ± 23, male 42.7%, hypertension 19.6%, diabetes 9.6%, chronic lung disease 2.4%, asthma %, CHD 0.5%, CKD 2.8%, cancer 5.2%,	Steroids 2.2%, hydroxychloroquine 0.6%	High for mortality Notes: Non-randomized study. Retrospective design. Regression was implemented to adjust for potential confounders (age, sex, relevant comorbidities, use of selected prescription drugs, vaccination and deprivation)	

Ramipril Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
RASTAVI trial;[83] Amat-Santos et al; Preprint; 2020	Patients exposed to COVID-19. 50 assigned to Ramipril 2.5mg a day progressively increased to 10mg a day and 52 assigned to SOC	Mean age 82.3 ± 6.1, male 56.9%, hypertension 54.15%, diabetes 20.65%, chronic lung disease 7.35%, CHD 22.45%, CKD 34.15%, cerebrovascular disease 11.15%	NR	Low for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study which might have introduced bias to symptoms and adverse events outcomes results.	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** Very Low certainty ⊕◯◯◯ **Adverse events:** No information
Recombinant Super-Compound Interferon **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Li et al;[84] Preprint; 2020	Patients with moderate to severe COVID-19 infection. 46 assigned to Recombinant Super-Compound Interferon 12 million IU twice daily (nebulisation) 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%, CHD 7.4%, cerebrovascular disease 5.3%, liver disease 6.4%	Steroids 9.6%, ATB 22.3%, IVIG 3.2%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** No information **Symptom resolution or improvement:** Very Low certainty ⊕◯◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No

					information
Remdesivir **Remdesivir may 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.**					
RCT					
ACTT-1 trial; Beigel et al;[85] Peer reviewed; 2020	Patients with mild to critical COVID-19 infection. 541 assigned to Remdesivir intravenously 200mg 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 SOC	Mean age 58.9 ± 15, male 64.3%, hypertension 49.6%, diabetes 29.7%, chronic lung disease 7.6%, CHD 11.6%,	NR	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** RR 0.78 (95%CI 0.56 to 1.08); RD -7.3% (95%CI -14.5% to 2.6%); Low certainty ⊕⊕◯◯ **Mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** RR 1.17 (95%CI 1.03 to 1.33); RD 3.8% (95%CI 0.7% to 7.4%); Low certainty ⊕⊕◯◯ **Symptomatic infection (prophylaxis studies):** No information **Severe Adverse events:** RR 0.91 (95%CI 0.52 to 1.59); RD -0.5% (95%CI -2.6% to 3.2%); Low certainty ⊕⊕◯◯
SIMPLE trial; Goldman et al;[86] Peer reviewed; 2020	Patients with severe COVID-19 infection. 200 assigned to Remdesivir (5 days) 200mg 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 mechanical ventilation; 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;[87] Wang et al; Peer reviewed; 2020	Patients with severe to critical COVID-19 infection. 158 assigned to Remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions and 79	Median age 65 ± 7.5, male 60.5%, hypertension 43%, diabetes 23.7%, CHD 7.2%	Steroids 65.6%, lopinavir-ritonavir 28.4%, IFN 32.2%, ATB 91.1%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	

	assigned to SOC				
SIMPLE 2 trial; Spinner et al;[88] Peer reviewed; 2020	Patients with moderate COVID-19 infection. 384 assigned to Remdesivir 200mg on day 1 followed by 100mg a day for 5 to 10 days and 200 assigned to SOC	Median age 57 ± 9, male 61.3%, hypertension 42%, diabetes 40%, asthma 14%, CHD 56%	Steroids 17%, hydroxychloroquine 21.33%, lopinavir-ritonavir 11%, tocilizumab 4%	Some Concerns for mortality and 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.	
rhG-CSF (in patients with lymphopenia) **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Cheng et al;[89] Peer reviewed; 2020	Patients moderate to severe COVID-19 and lymphopenia. 100 assigned to rhG-CSF six doses and 100 assigned to SOC	Mean age 45 ± 15, male 56%	Lopinavir-ritonavir 15.5%, IFN 9%, umifenovir 18%	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 ⊕◯◯◯ **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.					
RCT					
Chen et al;[75] Preprint; 2020	Patients with mild to moderate COVID-19 infection. 33 assigned to Ribavirin 2gr IV loading dose followed by orally 400-600mg every 8hs for 14 days, 36 assigned to Lopinavir-Ritonavir and 32 assigned to Ribavirin + Lopinavir-Ritonavir	Mean age 42.5 ± 11.5, male 45.5%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information
Ribavirin + Interferon beta-1b **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Hung et al;[90] Peer reviewed; 2020	Patients with mild to moderate COVID-19 infection. 86 assigned to Ribavirin + Interferon beta-1b 400 mg every 12 h (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 SOC	Median age 52 ± 15, male 54%, hypertension 18.3%, diabetes 13.3%, CHD 7.9% cerebrovascular disease 1.5%, cancer 1.5%	Steroids 6.2%, ATB 53.3%	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.	**Mortality:** No information **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.					
RCT					
Cao et al;[91] Peer reviewed; 2020	Patients with severe COVID-19 infection. 22 assigned to Ruxolitinib 5mg twice a day and 21 assigned to SOC	Mean age 63 ± 10, male 58.5%, hypertension 39%, diabetes 19.5%, CHD 7.3%,	Steroids 70.7%, IVIG 43.9%, umifenovir 73%, oseltamivir 27%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** No information **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.					
RCT					
Kasgari et al;[92] Peer reviewed; 2020	Patients with moderate COVID-19 infection. 24 assigned to sofosbuvir/daclatasvir 400/60mg twice daily and 24 assigned to HCQ 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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⊕◯◯◯ **Mechanical ventilation:** Very Low certainty ⊕◯◯◯ **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information
Sadeghi et al;[93] Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 33 assigned to sofosbuvir/daclatasvir 400/60mg once a	Median age 58 ± 13, male 20.21%, hypertension 34.8%, diabetes 42.4%, chronic lung disease 22.7%, asthma 3%,	Steroids 30.2%, lopinavir-ritonavir 48.4%, antibiotics 89.4%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events	

	day for 14 days and 33 assigned to SOC	CHD 15.1%, cancer 4.5%, obesity 25.7%		Notes: Only outcome assessors and data analysts were blinded. Concealment of allocation probably inappropriate.	**Adverse events:** No information
Steroids **Steroids reduce mortality and probably reduce mechanical ventilation requirements in patients with severe COVID-19 infection with moderate certainty. Steroids may not significantly increase the risk of severe adverse events**					
RCT					
GLUCOCOVID trial;[94] 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 20mg twice daily for 3 days and 29 assigned to SOC	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 mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** RR 0.89 (95%CI 0.78 to 1.02); RD -3.6% (95%CI -7.3% to 0.6%); Moderate certainty ⨁⨁⨁◯ **Mechanical ventilation:** RR 0.84 (95%CI 0.67 to 1.04); RD -1.8% (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;[95] 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 SOC	Mean age 55 ± 15, male 64.6%, hypertension 48.9%, diabetes 29.1%, chronic lung disease 0.5%, asthma 2.5%, CHD 6.9%, alcohol use disorder 27%, liver disease 5.5%	Remdesivir 0%, tocilizumab 0%, convalescent plasma 0%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	
RECOVERY - Dexamethasone trial;[96] 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 SOC	Mean age 66.1 ± 15.7, male 64%, diabetes 24%, chronic lung disease 21%, asthma NR%, CHD 27%, CKD 8%, liver disease 2%, any comorbiditie 56%	Steroids NA%, remdesivir 0.08%, hydroxychloroquine 1%, lopinavir-ritonavir 0.5%, tocilizumab 3%, azithromycin 25%	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.	
DEXA-COVID19 trial;[97] Villar et al; Unpublished; 2020	Patients severe to critical COVID-19. 7 assigned to Dexa 20mg a day for 5 days followed by 10mg a day for 5 days and 12 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation Notes: RoB judgment from published SR	
CoDEX trial;[98] Tomazini et al; Peer reviewed; 2020	Patients critical COVID-19. 151 assigned to Dexa 20mg a day for 5 days followed by 10mg a day for 5 days and 148 assigned to SOC	Mean age 61.4 ± 14.4, male 62.5%, hypertension 66.2%, diabetes 42.1%, CHD 7.7%, CKD 5.3%, obesity 27%	hydroxychloroquine 21.4%, azithromycin 71.2%, ATB 87%	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.	
REMAP-CAP trial;[99] Arabi et al; Peer reviewed; 2020	Patients severe to critical COVID-19. 278 assigned to Hydrocortisone 50mg every 6 hours for 7 days and 99 assigned to SOC	Mean age 59.9 ± 13, male 71%, diabetes 32%, chronic lung disease 20.3%, CHD 7.5%, CKD 9.2%, immunosuppression 4.9%	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.	
COVID STEROID trial;[97] Petersen et al; Unpublished; 2020	Patients severe to critical COVID-19. 15 assigned to Hydrocortisone 200mg a day for 7 days and 14 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation Notes: RoB judgment from published SR	

CAPE COVID trial;[100] Dequin et al; Peer reviewed; 2020	Patients 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 SOC	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 mechanical ventilation; Low for symptom resolution, infection and adverse events	
Steroids-SARI trial;[97] Unpublished; 2020	Patients severe to critical COVID-19. 24 assigned to Methylprednisolone 40mg twice a day for 5 days and 23 assigned to SOC	NR	NR	Low for mortality and mechanical ventilation Notes: RoB judgment from published SR	
Farahani et al;[101] Preprint; 2020	Patients severe to critical COVID-19. 14 assigned to Methylprednisolone 1000 mg/day for three days followed by prednisolone 1mg/kg for 10 days, and 15 assigned to SOC	Mean age 64 ± 13.5	Hydroxychloroquine 100%, lopinavir-ritonavir 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.	
Edalatifard et al;[102] Peer reviewed; 2020	Patients severe COVID-19. 34 assigned to Methylprednisolone 250mg/day for 3 days and 28 assigned to SOC	Mean age 58.5 ± 16.6, male 62.9%, hypertension 32.3%, diabetes 35.5%, chronic lung disease 9.7%, CHD 17.7%, CKD 11.3%, cancer 4.8%	Hydroxychloroquine 100%, lopinavir-ritonavir 100%	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	

Telmisartan **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Duarte et al;[103] Preprint; 2020	Patients with mild to severe COVID-19 infection. 38 assigned to Telmisartan 80 mg twice daily and 40 assigned to SOC	Mean age 61.9 ± 18.2, male 61.5%, hypertension 30.7%, diabetes 11.5%, chronic lung disease 11.5%, asthma 1.3%, CKD 2.6%, cerebrovascular disease 7.7%, obesity 12.8%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⨁◯◯◯ **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 may reduce mechanical ventilation requirements and improve time to symptom resolution. However certainty of the evidence is low because of imprecision. Further research is needed.**					
RCT					
COVACTA trial; Rosas et al;[104] Preprint; 2020	Patients Severe COVID-19. 294 assigned to TCZ 8mg/kg once and 144 assigned to SOC	Mean age 60.8 ± 14, male 70%, hypertension 62.1%, diabetes 38.1%, chronic lung disease 16.2%, asthma %, CHD 28%, CKD %, cerebrovascular disease %, immunosuppression %, cancer %, obesity 20.5%	Steroids 42.2%, convalescent plasma 3.6%, Antivirals 31.5%	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** RR 1.01 (95%CI 0.68 to 1.52); RD 0.5% (95%CI -10.6% to 17.2%); Low certainty ⨁⨁◯◯ **Mechanical ventilation:** RR 0.76 (95%CI 0.53 to 1.09); RD -2.8% (95%CI -5.4% to 1%); Low certainty ⨁⨁◯◯
Wang et al;[105] Preprint; 2020	Patients moderate to severe COVID-19. 34 assigned to TCZ	Median age 63 ± 16, male 50.8%, hypertension 30.8%,	NR	High for mortality and mechanical ventilation; High for symptom	**Symptom resolution or improvement:** HR

	400mg once or twice and 31 assigned to SOC	diabetes 15.4%		resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	1.26 (95%CI 0.97 to 1.64); RD 8.4% (95%CI -1.1% to 18%); Low certainty ⨁⨁◯◯ **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** RR 0.91 (95%CI 0.7 to 1.18); RD -0.4% (95%CI -1.6% to 1%); Low certainty ⨁⨁◯◯
Non-RCT					
Biran et al;[106] Peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 210 received TCZ and 420 received alternative treatment schemes	Median age 63.5 ± 18, male 69.2%, hypertension 59%, diabetes 37.5%, chronic lung disease 14.5%, CHD 15%, cerebrovascular disease 4.5%,	Steroids 45.5%, hydroxychloroquine 90%, azithromycin 56%,	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (age, gender, diabetes, chronic obstructive pulmonary disease (COPD) or asthma, hypertension, cancer, renal failure, obesity, oxygenation less than 94%, quick Sequential Organ Failure Assessment (qSOFA) score, use of steroids, C-reactive protein 15 mg/dL or higher, and intubation or mechanical ventilator support)	**Mortality:** Very Low certainty ⨁◯◯◯

Colaneri et al;[107] Peer reviewed; 2020	Patients with moderate to critical COVID-19 infection. 21 received TCZ and 91 received alternative treatment schemes	Median age 63.5 ± 16.9, male 73.2%, hypertension 50%, diabetes 17.8%, chronic lung disease 7.1%, CHD 16%, obesity 28.5%	NR	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (sex, age, LDH, and neutrophils)	
TESEO study;[108] Guaraldi et al; Peer reviewed; 2020	Patients with severe COVID-19 infection. 125 received TCZ and 179 received alternative treatment schemes	Median age 66 ± 21, male 69%, hypertension 25%, diabetes 7%, CHD 8%, CKD 4%, cerebrovascular disease 8%, cancer 3%	NR	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (age, sex, recruiting centre, duration of symptoms, and Subsequent Organ Failure Assessment (SOFA) score)	
Ip et al;[109] Peer reviewed; 2020	Patients with severe to critical COVID-19 infection. 134 received TCZ and 413 received alternative treatment schemes	Median age 67 ± 18, male 65%, hypertension 62.1%, diabetes 37.5%, chronic lung disease 16.2%, CHD 18.2%, cerebrovascular disease 4.7%, cancer 12.4%, obesity 37.1%	Steroids 64.3%, hydroxychloroquine 88.8%, lopinavir-ritonavir %, tocilizumab %, azithromycin 76.6%, convalescent plasma %	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (age, gender, COPD, and renal failure)	
Martínez-Sanz et al; Preprint;[110] 2020	Patients with moderate to severe COVID-19 infection. 260 received TCZ and 969 received alternative treatment schemes	Median age 67 ± 22, male 62.2%, hypertension 22%, diabetes %, chronic lung disease 10.8%, CHD 7.9%, CKD 5.2%	NR	High for mortality Notes: Non-randomized study. Retrospective design. Adjusted estimates not provided.	

SAM-COVID study;[111] Rodríguez-Baño et al; Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 53 received TCZ and 106 received alternative treatment schemes	Median age 68 ± 18, male 74.9%, hypertension 41.5%, diabetes 18.8%, chronic lung disease 9.4%, CHD 18.2%, CKD 1.8%, cancer 3.1%, obesity 9.4%	Remdesivir 0.6%, hydroxychloroquine 94.3%, lopinavir-ritonavir 79.2%, tocilizumab %, azithromycin 66.6%	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (age, gender, race, and comorbidities)	
Rossi et al;[112] Preprint; 2020	Patients with moderate to severe COVID-19 infection. 84 received TCZ and 84 received alternative treatment schemes	Median age 64.6 ± 14.85, male 62%, hypertension 56%, diabetes 39.2%, chronic lung disease 16%, CHD 25%, immunosuppression 4.8%, cancer 7.1%, obesity 31.5%	Hydroxychloroquine 77.3%, lopinavir-ritonavir 5.3%, ATB 100%	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (age, sex, smoking status, history of coronary artery disease, stroke, heart failure or peripheral artery disease, hypertension, chronic kidney disease with eGFR less than 60 mL/min/1m^2, cancer, long-term corticosteroid treatment, use of antibiotics, of antivirals, of corticosteroids, of baricitinib after admission, SpO2/FiO2 ratio at admission, time between admission and inclusion, and SpO2/FiO2 ratio and CRP at inclusion)	

Somers et al;[113] Peer reviewed; 2020	Patients with critical COVID-19 infection. 78 received TCZ and 76 received alternative treatment schemes	Mean age 58 ± 14.9, male 66%, hypertension 66%, diabetes 16%, chronic lung disease 16%, asthma 20%, CHD 23%, CKD 42%	Steroids 25%, remdesivir 3%, hydroxychloroquine 23%	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders (no details of variables included in the model are provided).	
Tsai et al;[114] Preprint; 2020	Patients with severe COVID-19 infection. 66 received TCZ and 66 received alternative treatment schemes	Mean age 62 ± 14, male 75.8%, hypertension 54%, diabetes 30.3%, chronic lung disease 15.5%, asthma %, CHD 9.85%, CKD 5.3%, cerebrovascular disease 9.1%, cancer 2.25%	Hydroxychloroquine 90.1%, lopinavir-ritonavir %, tocilizumab %, azithromycin 62.1%,	High for mortality Notes: Non-randomized study. Retrospective design. Propensity score was implemented to adjust for potential confounders. (age, sex, body mass index, select baseline laboratory values (lactic acid, ferritin, LDH, procalcitonin, serum creatinine, hypertension, and comorbidity score)	
Triazavirin **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Wu et al;[115] Peer reviewed; 2020	Patients 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 SOC	Median age 58 ± 17, male 50%, hypertension 28.8%, diabetes 15.4%, chronic lung disease 5.8%, CHD 15.4%, cerebrovascular disease 7.7%	Steroids 44.2%, hydroxychloroquine 26.9%, lopinavir-ritonavir 9.6%, ATB 69.2%, IFN 48.1%, umifenovir 61.5%, ribavirin 28.9%,	Low for mortality and mechanical ventilation; Low for symptom resolution, infection and adverse events	**Mortality:** Very Low certainty ⊕◯◯◯ **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.**					
RCT					
Chen et al;[38] Preprint; 2020	Patients with moderate to critical COVID-19 infection. 116 assigned to Favipravir 1600mg twice the first day followed by 600mg twice daily for 7 days and 120 assigned to Umifenovir 200mg three times daily for 7 days	Mean age NR ± NR, male 46.6%, hypertension 27.9%, diabetes 11.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** No information **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;[72] Peer reviewed; 2020	Patients with moderate to severe COVID-19 infection. 34 assigned to Lopinavir-Ritonavir 200/50mg twice daily for 7-14 days, 35 assigned to Umifenovir and 17 assigned to SOC	Mean age 49.4 ± 14.7, male 41.7%	Steroids 12.5%, IVIG 6.3%	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.	

Vitamin C Uncertainty in potential benefits and harms. Further research is needed.					
RCT					
Zhang et al;[116] Preprint; 2020	Patients with severe COVID-19 infection. 26 assigned to Vit C 12gr twice a day for 7 days and 28 assigned to SOC	Mean age 67.4 ± 12.4, male 66.7%, hypertension 44.4%, diabetes 29.6%, chronic lung disease 5.6%, CHD 22.2%, CKD 1.85%, cancer 5.6%, nervous system disease 20.4%	NR	High for mortality and mechanical ventilation; High for symptom resolution, infection and adverse events Notes: Non-blinded study. Concealment of allocation probably inappropriate.	**Mortality:** Very Low certainty ⊕◯◯◯ **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.**					
RCT					
COVIDIOL trial; Entrenas Castillo et al;[117] Peer reviewed; 2020	Patients moderate to severe COVID-19. 50 assigned to Vit D 0.532 once followed by 0.266 twice and 26 assigned to SOC	Mean age 52.95 ± 10, male 59.2%, hypertension 34.2%, diabetes 10.5%, chronic lung disease 7.9%, CHD 3.9%, immunosuppression 9.2%, cancer %, obesity %	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.	**Mortality:** No information **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information

					Adverse events: No information
α-Lipoic acid **Uncertainty in potential benefits and harms. Further research is needed.**					
RCT					
Zhong et al;[118] Preprint; 2020	Patients with critical COVID-19 infection. 8 assigned to α-Lipoic acid 1200mg infusion once daily for 7 days and 9 assigned to SOC	Median age 63 ± 7, male 76.5%, hypertension 47%, diabetes 23.5%, CHD 5.9%,	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.	**Mortality:** Very Low certainty ⨁◯◯◯ **Mechanical ventilation:** No information **Symptom resolution or improvement:** No information **Symptomatic infection (prophylaxis studies):** No information **Adverse events:** No information

Table 3. Risk of bias of included Randomized Controlled Trials

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 Mechanical ventilation	Symptoms, infection and adverse events
RECOVERY - Dexamethason	Low	Some Concerns	Low	Low	Low	Low	Some Concerns
RECOVERY - Hydroxychloroc	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-ritona	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 Ur	Low	Some Concerns	Low	Some Concerns	Low	Low	High
Edalatifard M et al (Tehran Ur	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 H	High	Some Concerns	Low	Some Concerns	Low	High	High
Doi Y et al (Fujita Health Univ	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

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