Message

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Sent: 7/19/2020 1:05:16 PM
To: Stephen Hahn [redacted] Shah, Anand (FDA/OC) [redacted] Caputo, Michael (HHS/ASPA) [redacted]
Subject: FW: COVID-19 NMA manuscript resubmitted
Attachments: BMJ-2020-059724.R1_Proof_hi SUBMITTED 19Jul2020.pdf

Hi Dr. Hahn and Anand and Michael, I share this so confidentially. Yikes…and I thought of it long and hard as the group submitted last night to BMJ after revisions…so I am part of the large international research group and one of the senior researchers in this network meta-analysis as seen in the list of authors. You would know the one reason why I stand out among this group of some the world's top researchers which I am proud of and made the personal decision to reveal it. I was told that had I not played such a prominent role in this project started in Feb before I came on deck, that they would have not wanted me in it and I expected this since coming to DC and experiencing the push back which is so terrible. But a lot of the work I did so folk had no choice and some was my own work…anyway, I share this submission (embargoed) so highly confidentially, please share with no one not even in people who work or report to you…please. But I weighed the balance and this is so important and such an emergency and while I have not done this before and will not again, I share this embargoed so that you are primed of what we found if it could help your decision-making to help the USA and the globe as the US leads the world, rightly. You two are an example. So I trust you and Michael, I trust him as a brother. This is for your eyes only but can inform your decision-making behind the scenes as it will be in print maybe one week.

I draw your attention to "Time to symptom resolution"…we included 13 RCTs for that outcome enrolling 2,282 participants. Remember, with Network meta-analysis (NMA), the approach is not simple pair-wise modelling of a treatment to its comparator but we include the indirect evidence in the models (briefly, in NMA we may have evidence of A vs C and B vs C where C is the common comparator e.g. placebo, but not A vs B (head to head) that we are interested in and NMA allows us to speculate mathematically 'if' they were actually compared and we include the direct and that indirect evidence in the model)…anyway, we found that in patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care. For hydroxy there was no other benefit and there was apparent risk of adverse events.

Again, I would never do this but do it here for we have lives on the line and we are searching for a treatment or combination and I want to help the administration and you two as the top regulators in this push. I am so confident in you and the team in beating this virus and the whole administration…yes, it is wearing on us for this is tough, and we are being fought by the other side and media which is horrendous for we have a very serious emergency and the people the public seek just simple, honest, direct guidance and allow them to be informed so they can make common sense 'best' decisions for themselves.

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Time to symptom resolution Thirteen RCTs enrolling 2,282 participants31 34-39 41-43 45 46 50 53 55 64 reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. Patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care.

Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

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Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

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RAS, JB, DZ, LG, and RBP were the core team leading the systematic review. JB, RC, SAF, RV, PA, SM, YW, ZY, IR, AD, TD, AI, AQ, CS, LY, FF, QL, XH, LLS, BF, and AV participated in study identification and selection. DZ, EK, NS, RV, AA, YW, KH, HPH, MH, CF, SM, QL, AQ, LY, and FF participated in data collection. LG, BS, LH, QI, DHA, GG, GT, and LT participated in data analysis. RBP, HPH, AI, RM, TD, NS, and DC participated in assessment of the certainty of the evidence. SM, EL, BR, TA, PV, GG, MM, JN, ML, TT, BT, FF, and GR provided advice at different stages. RAS, RBP and GHG drafted the manuscript. All authors approved the final version of the manuscript. RAC is the guarantor of this article.

Competing interests declaration
All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and will declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Ethics approval: Not applicable. All the work was developed using published data.

Transparency declaration

RS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient involvement

Patients were involved in the interpretation of results and the generation of parallel recommendations, as part of the BMJ Rapid Recommendations initiative.

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What is already known/ what this paper adds

Despite huge efforts to identify effective pharmacologic interventions for COVID-19 disease, evidence for effective treatment remains limited.

This living systematic review and network meta-analysis provides a comprehensive picture and assessment of the evidence published as of 8 July 2020 and will be updated periodically

The certainty of the evidence for most interventions tested thus far is low or very low.

In patients with severe COVID-19, glucocorticoids probably decrease mortality and mechanical ventilation. Hydroxychloroquine, lopinavir-ritonavir, and remdesivir may reduce time to symptom resolution.

Abstract

Objectives: To compare the effects of therapies for treatment of COVID-19

Design: Living systematic review and network meta-analysis (NMA).

Data sources: U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database, which includes 25 electronic databases up to 8 July 2020

Study selection: We included randomized clinical trials (RCTs) in which persons with suspected, probable, or confirmed COVID-19 were randomized to pharmaceuticals or standard care/placebo for treatment. Pairs of reviewers independently screened titles and abstracts, and full texts, of potentially eligible articles.

Methods: After duplicate data abstraction, we conducted a Bayesian-random effects network meta-analysis for each outcome of interest. We assessed the risk of bias of the included studies using a modification of the Cochrane Risk of Bias 2.0 tool, and the certainty of the evidence using the GRADE approach for NMA. We classified interventions in groups from the most to the least effective/ harmful following GRADE guidance using a minimally contextualized approach.

Results: We included 25 RCTs. The certainty of the evidence for the majority of comparisons is very low because of risk of bias (lack of blinding) and very serious imprecision. Glucocorticoids were the only intervention with evidence for a reduction in death compared to standard care (37 fewer per 1000 patients, 95% credible interval [CI] 63 fewer to 11 fewer, moderate certainty) and mechanical ventilation (31 fewer per 1000, CI 47 fewer to 9 fewer, moderate certainty). Three drugs may reduce symptom duration compared to standard care: hydroxychloroquine (-4.5 days, low certainty), remdesivir (-2.6 days, moderate certainty), and lopinavir-ritonavir (-1.2 days, low certainty). Hydroxychloroquine may increase the risk of adverse events when compared to the other interventions and remdesivir probably does not substantially increase the risk of adverse effects. No other interventions included enough patients to meaningfully interpret adverse effects leading to drug discontinuation.

Conclusion: Glucocorticoids probably reduce mortality and mechanical ventilation compared to standard care. The effectiveness of most interventions is very uncertain because most of the RCTs so far have been small and have important study limitations.

Protocol: The protocol is included as a supplement.

Background

As of 18 July 2020, over 14.1 million people have been infected with COVID-19; of these, 600,000 have died.[1] Despite huge efforts to identify effective interventions for its prevention and treatment- which have resulted in almost 1500 trials completed or under way-[2] evidence of effective treatment remains limited.

Faced with the pressures of a global pandemic, healthcare workers around the world are prescribing medications off-label for which there is only very low quality evidence. The result - this appears to be certainly the case for the very well-publicized example of hydroxychloroquine - may be no benefit and appreciable harm. Timely evidence summaries and associated guidelines may ameliorate the problem.[3] Clinicians, patients, guideline bodies, and government agencies are also facing the challenges of interpreting the results from trials that are being published at a rate never seen before. This environment makes it necessary to produce well-developed summaries that distinguish more from less trustworthy evidence.

Living systematic reviews (SRs) and network meta-analyses (NMAs) address the main limitation of traditional reviews, that of providing a picture of the relevant evidence only at a specific timepoint.[4] This is crucial in the context of COVID-19, in which the picture is constantly changing. The ability of living NMA to present a complete, broad, and updated view of the evidence makes it ideal to inform the development of practice recommendations. NMA, rather than pairwise meta-analysis provides useful information about the comparative effectiveness of treatments that were not tested head-to-head. The lack of such direct comparisons is certain to limit inferences in the COVID-19 setting. Moreover, the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head-to-head.[5]

The objective of this living SR and NMA is to compare the effects of pharmacologic therapies for treatment of COVID-19. This SR is part of the *BMJ Rapid Recommendations* project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*. Our living NMA will directly inform *BMJ Rapid Recommendations*[6] on COVID-19 treatments, triggered to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available.

Methods

A protocol provides the detailed methods of this SR, including all updates (available as supplementary material). We report this living SR following the guidelines of the PRISMA checklist for NMA.[7] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[8] The linked BMJ *Rapid Recommendations* the guideline panels approved all decisions relevant to data synthesis.

Eligibility criteria

We included randomized clinical trials (RCT) in persons exposed to COVID-19 or with suspected, probable or confirmed COVID-19 that compared pharmaceuticals for treatment against one another or against no intervention, placebo, or standard care. We included trials regardless of publication status (peer-reviewed, in press, or pre-print) or language. We applied no restriction based on severity of illness or setting and included trials of Chinese medicines if the drug was one or more specific molecules with a defined molecular weight dosing.

We excluded RCTs evaluating vaccination, blood products, nutrition, traditional Chinese herbal medicines that include more than one molecule or a molecule without specific molecular weighted dosing and non-drug supportive care interventions. RCTs including patients with COVID-19 that evaluated these interventions were identified and categorized separately.

Information sources

We perform daily searches Monday to Friday in the U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies—the most comprehensive database of COVID-19 research articles[9]. The database includes 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO COVID-19 website, CDC COVID-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The daily searches are designed to match the update schedule of the database and to capture eligible studies the day of or day after their publication. We filtered the results from the CDC's database through a validated and highly sensitive machine learning model to identify RCTs.[10] We tracked preprints of RCTs until publication and updated data to match that in the peer-reviewed publication when discrepant and reconciled corrections and retractions.

In addition, we searched six Chinese databases on a biweekly basis: Wanfang, CBM, CNKI, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for COVID-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomized trials. The Supplementary Material includes the Chinese literature search strategy.

We monitor living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) COVID-19 Repository by the Epistemonikos Foundation and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[11]

We searched all English information sources from 1 December 2019 and until 8 July 2020 and Chinese literature from the conception of the databases to 26 June 2020.

Study selection

Using a SR software, Covidence,[12] pairs of trained and calibrated reviewers independently screened all titles and abstracts followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extracted data independently using a standardised, pilot-tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities,

setting and type of care, and severity of COVID-19 symptoms for studies of treatment), and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analyzed and the number of participants that experienced an event for dichotomous outcomes).

Outcomes of interest were selected based on their importance to patients and were informed by clinical expertise in the SR team and in the linked guideline panel responsible for the BMJ Rapid Recommendations. The panel includes unconflicted clinical experts, recruited to ensure global representation, and patient-partners. Outcomes were rated from 1-9 based on importance to individual patients (9 being most important) and any outcome rated 7 or higher by any panel member was included. Selected outcomes included mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), adverse events leading to discontinuation (within 28 days), viral clearance (closest to 7 days +/- 3 days), duration of hospitalization, ICU length of stay, time to symptom resolution or clinical improvement, and time to viral clearance. Outcomes of interest for prophylaxis of COVID-19 include mortality, infection with COVID-19, hospitalization, adverse events leading to discontinuation, and time to symptom resolution or clinical improvement. Time to viral clearance was included because it may be a surrogate for transmissibility, although this is uncertain.[13]

Because of the inconsistent reporting observed across trials, in the updates we will use a hierarchy for the outcome mechanical ventilation in which we will include information from the total number of patients who received ventilation over a time period if available (as done for this analysis), but we will also include the number at the time point at which most of the patients were mechanically ventilated if that is the only way in which this outcome is reported.

Reviewers resolved discrepancies by discussion and, when necessary, by adjudication by a third party.

We update the data collected from included studies when they were published as preprint and as soon as the peer-review publication becomes available if studies initially included as preprints.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0)[14] to rate trials as either 'low risk of bias', 'some concerns – probably low risk of bias', 'some concerns – probably high risk of bias' and 'high risk of bias', across the following domains: bias arising from the randomization process, bias due to departures from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported results, including deviations from the registered protocol, and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated at 'some concerns – probably high risk of bias' or 'high risk of bias' and at low risk of bias if all domains were rated at 'some concerns – probably low risk of bias' or 'low risk of bias'. Reviewers resolved discrepancies by discussion and, when not possible, by adjudication by a third party.

Data synthesis

We conducted NMA using a Bayesian framework.[15] In this report, we conducted an NMA for pharmacological treatments of COVID-19 that included all patients, regardless of severity of disease.

a. Summary measures

We summarized the effect of interventions on dichotomous outcomes using the odds ratio (OR) and its 95% credible intervals (CI). For continuous outcomes, we used the mean difference (MD) and its 95% CI in days for ICU length of stay and duration of mechanical ventilation because we expected similar durations across RCTs. For time to symptom resolution and length of hospital stay, we first performed the analyses using the relative effect measure ratio of means (RoM) and its 95% CI before calculating MD in days because we expected substantial variation between studies.[16]

b. Treatment nodes

Treatments were grouped into common nodes based on molecule but not dose or duration. For intervention arms with more than one medication, we created a separate node and included drugs from the same class within the same node. Chloroquine and hydroxychloroquine were included in the same node for COVID-19 specific effects and separated for disease-independent adverse effects. We drew network plots using the *networkplot* command of Stata version 15.1 (StataCorp, College Station, Texas, USA) with thickness of edges of the nodes based on the number of studies.[17]

c. Statistical analysis

For most outcomes, we conducted random-effects NMAs using a Bayesian framework with the same priors for the variance and effect parameters.[15] For networks where the outcome were particularly sparse, we conducted fixed-effect NMA.[18] We will use a plausible prior for variance parameter, and uniform prior for the effect parameter suggested by Turner *et al* based on empiric data.[19] For all analyses, we used three Markov-chains with 100,000 iterations after an initial burn-in of 10,000 and a thinning of 10. We used node-splitting models to assess local incoherence and to obtain indirect estimates.[20] All NMAs were performed using the *gemtc* package of R version 4.0.0 (RStudio, Boston, MA).[21]

Some treatment nodes with very few total participants and very few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that enrolled a total of at least 100 patients or had at least 20 events. For this iteration, the analyses included treatment nodes with fewer than 100 patients and 20 events, but the results are not reported.

Certainty of the evidence

We assessed the certainty of evidence using the GRADE approach for NMA.[5 22] Two people with GRADE experience rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.[23] Judgments of imprecision for this SR were made using a minimally contextualized approach, with a null effect as the threshold of importance.[24] The minimally contextualized approach considers only whether credible intervals include the null effect and thus does not consider whether plausible effects, captured by credible intervals, include both important and trivial effects.[25] We created GRADE evidence summaries (Summary of Findings tables) in the MAGIC Authoring and

publication platform (www.magicapp.org) to provide user-friendly formats for clinicians and patients, and allow re-use in the context of clinical practice guidelines for COVID-19.

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was OR or RoM. For the outcomes mortality and mechanical ventilation, we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.[26] For all other outcomes, we used the mean or median from all studies in which participants received standard of care for each outcome. We calculated absolute effects using the transitive risks model[27] using *R2jags* package in R.[28]

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualized framework that focuses on the treatment effect estimates and the certainty of the evidence.[29]

Subgroup and sensitivity analysis

When a comparison was dominated by a single study (defined as >90% contribution in fixed effects), we conducted our primary analysis with a fixed effects model for that comparison.[18] We planned to perform subgroup analyses of preprints vs. peer reviewed studies and high vs. low risk of bias. We will perform additional subgroup analyses in the future if directed by the linked independent Rapid Recommendation guideline panels; in this case there was no such direction.

Results

Following screening of 6,516 titles and abstracts, and 109 full-texts, we identified 25 unique RCTs that evaluated pharmacological treatments as of 8 July 2020 (**Figure 1**).[30-54] Searches of living evidence retrieval services identified one additional eligible RCT.[55] Fifteen RCTs have been published in peer-reviewed journals; and ten only as preprints. Most trials were registered (23/25; 92%), published in English (23/25; 92%) and evaluated treatment in hospitalized patients with COVID-19 (24/25; 96%). Nearly two-thirds were conducted in China (16/25; 64%). Of the 25 included pharmacological trials, 6 evaluated treatment against active comparator(s), 12 evaluated treatment against standard care or placebo and 2 evaluated different durations/doses of the same treatment. Our NMA was performed on 26 June 2020 and includes 19 RCTs.[31 32 34-38 40 43-51 53] Table 1 presents the characteristics of the included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the Supplementary Material.

The RCTs not included in the analysis are: 1) two RCTs evaluating different durations of the same drug because both arms would have been classified within the same treatment node;[32 40] 2) one RCT evaluating lincomycin vs azithromycin,[56] which was excluded because neither arm was connected to the network; 3) three RCTs, evaluating colchicine,[57] febuxostat,[58] and methylprednisolone[52] all versus standard care were excluded because they were identified after, or the data was available after the analysis was completed.

Two trials did not have publicly accessible protocols or registrations.[36 59] Of the trials with publicly accessible protocols or registrations, 16 reported results for one or more of our outcomes of interest that were not prespecified in protocols/registrations. No other discrepancies

between the reporting of our outcomes of interest in trial reports and protocols/registrations were noted.

Three studies were initially posted as preprints and subsequently published after peer review.[32 45 54 60-62] In one study, mortality was not reported in the preprint but was reported in the peer reviewed paper.[45 61] There were no substantive differences between the preprint and peer reviewed publications for the other two studies. One RCT did not report outcomes in the groups as randomized; the authors shared outcome data with us in the groups as randomized.[52]

All analyses reached convergence based on trace plots and Brooks-Gelman-Rubin statistic <1.05. For glucocorticoids, there were two RCTs with substantial differences in size (RECOVERY enrolled 6425 patients[51] and GLUCOCOVID 63[52]), thus we performed a fixed effects analysis for the direct pairwise analysis for this the outcomes that were reported in both RCTs (mortality and mechanical ventilation). This analysis was separate from the network meta-analyses, which were all random effects. Due to the lack of sufficient data, we did not conduct any of the subgroup or sensitivity analyses specified in the protocol (see Supplementary Material).

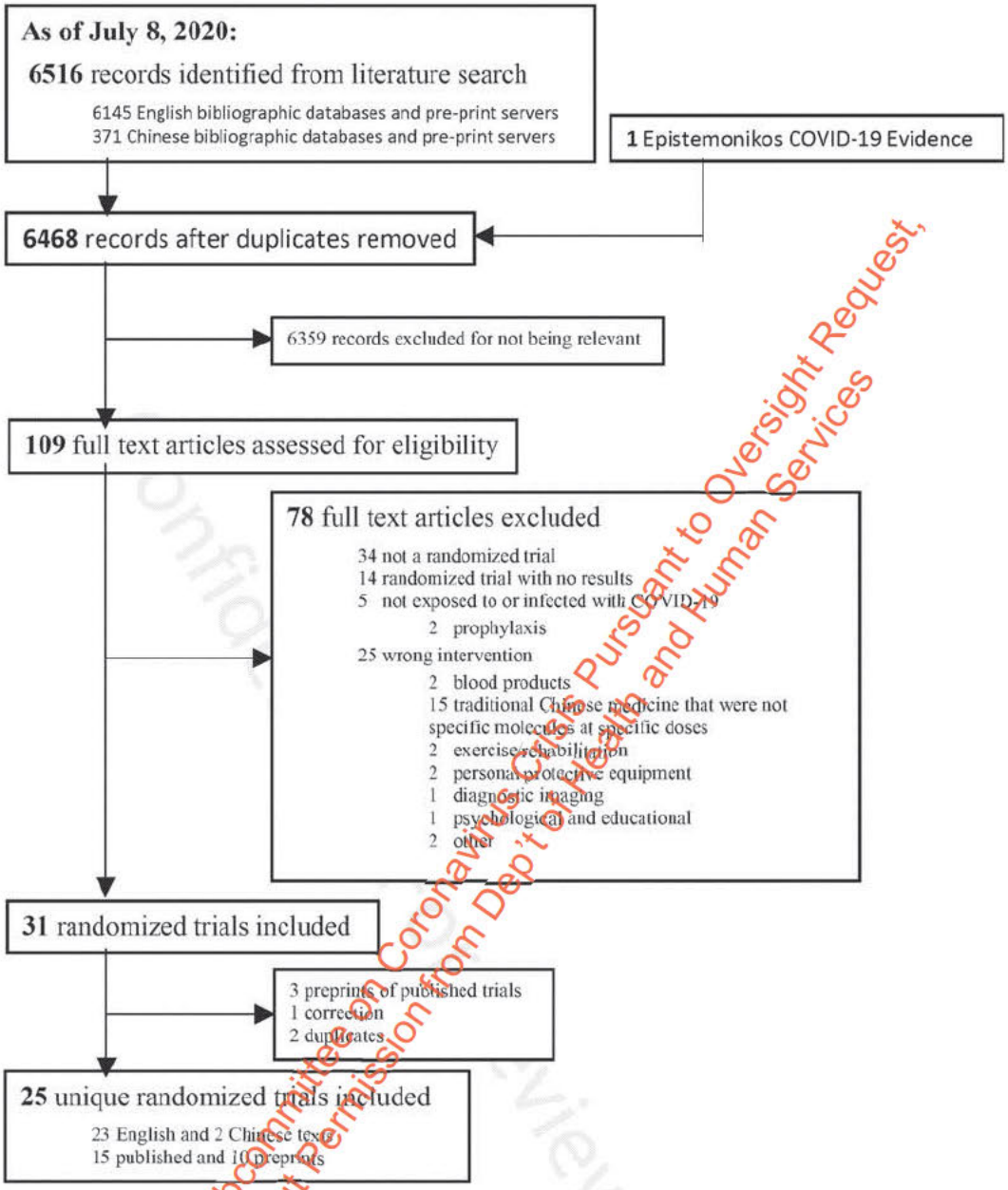

Figure 1: Study Selection

Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies per outcome. Two studies were judged at low risk of bias in all domains.[31 46] All other studies had probably high or high risk of bias in the domains of randomization or deviation from the intended interventions.

Effects of the interventions

The supplementary material presents the network plots depicting the interventions included in the NMA of each outcome. Table 2 presents a summary of the effects of the interventions on the outcomes. The supplementary material presents detailed relative and absolute effect estimates and certainty of the evidence for all comparisons and outcomes. We did not detect statistical incoherence in any of the NMAs.

a. Mortality

The 15 RCTs including 8,654 participants[31 34-37 39 41 43 46 50-53 63 64] addressed mortality. The treatment nodes included in the NMA were glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, remdesivir, umifenovir, and standard care. The network estimates did not reveal a convincing reduction for any of these interventions compared to standard care. The certainty of the evidence was low for the comparison between remdesivir and standard of care, and very low for all other comparisons (Table 2). For glucocorticoids, the direct estimate was more credible than the network estimate (moderate certainty vs. very low certainty) because the direct estimate was more precise. The network estimate, which considers heterogeneity of the entire network, was RR 0.84 CI 0.52 to 1.36. The direct meta-analysis of two RCTs for glucocorticoids versus standard care[51 52] suggested a probable mortality reduction with glucocorticoids: RR 0.88 CI 0.80 to 0.97, RD 37 fewer per 1000 CI 63 fewer to 11 fewer, moderate certainty for risk of bias.

b. Mechanical ventilation

Eight RCTs that enrolled 6,953 participants[31 34 35 39 41 43 46 51 52 63 64] reported mechanical ventilation in patients who were not receiving mechanical ventilation at baseline. The treatment nodes included in the NMA were glucocorticoids, remdesivir, and standard care (Table 2). The network estimate for glucocorticoids was very low certainty because of very serious imprecision RR 0.71 CI 0.29 to 1.73. The direct pairwise direct meta-analysis for glucocorticoids versus standard care[51 52] resulted in higher certainty and suggested a probable reduction with glucocorticoids versus standard care: RR 0.74 CI 0.59 to 0.93, RD 30 fewer per 1000 CI 48 fewer to 8 fewer, moderate certainty for risk of bias.

c. Adverse events leading to discontinuation

Eleven RCTs that enrolled 1,875 participants[31 38 39 41 44-50 53 64] reported adverse effects leading to discontinuing the study drug. The treatment nodes included in the NMA were hydroxychloroquine, remdesivir, and standard care. There was moderate certainty evidence that remdesivir did not incur any additional harm beyond standard care and low certainty evidence that hydroxychloroquine increased the risk of adverse events compared with standard care (Table 2).

d. Viral clearance at 7 days (+/- 3 days)

All ten RCTs that cumulatively enrolled 856 participants[34 37 43 45-48 50 53 55 64] measured viral clearance with PCR cutoff points. The treatment nodes included in the NMA were hydroxychloroquine, lopinavir-ritonavir, remdesivir, and standard care. There was no

convincing evidence that any of the interventions increased the rate of viral clearance (Table 2). The certainty of the evidence was low for the comparison between remdesivir and standard care, and very low for all other comparisons.

e. Duration of hospitalization

Eight RCTs enrolling 855 participants[34 35 37 39 41 46 51 53 55 64] reported duration of hospitalization. The treatment nodes included in the NMA were lopinavir-ritonavir, remdesivir, and standard care. Patients who received lopinavir-ritonavir had fewer days of hospitalization than patients who received standard care but the effect estimate included no difference: RD -1.42 days CI -3.03 to 0.02 (low certainty; Table 2). Remdesivir did not appear to reduce duration of hospitalization (low certainty).

f. ICU length of stay

Two RCTs enrolling 280 participants studied lopinavir-ritonavir (99 patients) and interferon beta 1 (42 patients) versus standard care (139 patients) reported length of ICU stay.[35 39] Standard care was the only treatment node with at least 100 patients and therefore no analyses were performed for this outcome.

g. Duration of mechanical ventilation

Three RCTs and enrolling 557 participants[34 39 46] reported duration of mechanical ventilation. The treatment nodes included in the meta-analysis were remdesivir and standard care. Moderate certainty evidence that remdesivir reduces the duration of mechanical ventilation compared to standard care, MD-5.15 days CI -8.28 to -2.02 (Table 2).

h. Time to symptom resolution

Thirteen RCTs enrolling 2,282 participants[31 34-39 41 43 45 46 50 53 55 64] reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. Patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care.

i. Time to viral clearance

Ten RCTs enrolling 684 participants[35 37 41 43 45 47 48 50 53 55 64] revealed no convincing evidence that any of the interventions reduced the time to viral clearance; at least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. The certainty of the evidence was very low for all comparisons (Table 2).

Discussion

This living SR and NMA provides a comprehensive picture of the evidence for pharmacologic treatments of COVID-19 up to 8 July 2020. The certainty of the evidence for the majority of the comparisons is very low. The only intervention that probably reduces mortality and mechanical ventilation is glucocorticoids, a result driven entirely by the RECOVERY trial.[51] Remdesivir is the only intervention in which moderate certainty exists supporting benefits for both time to symptom resolution and duration of mechanical ventilation, but it remains uncertain whether remdesivir has any impact on mortality and other outcomes important to patients. Remdesivir was the only intervention where all of the data came from RCTs sponsored by a pharmaceutical company. Direct evidence from RCTs in patients with COVID-19 has so far provided

little definitive evidence about adverse effects for most interventions.

Hydroxychloroquine may increase the risk of adverse events leading to drug discontinuation when compared to the other interventions. Notably, this iteration of the living NMA did not include three recently published large RCTs on hydroxychloroquine versus standard care.[65-67] RECOVERY, the largest hydroxychloroquine RCT, suggests that hydroxychloroquine may not reduce mortality and may increase length of hospital stay.[65] These data will be included in the next update. There was no convincing evidence that the other interventions resulted in benefits or harms when compared to standard of care.

Stengths and limitations of our review

Our search strategy and eligibility criteria were comprehensive, without restrictions of language of publication, and provide a full picture of the current evidence. To ensure expertise in all areas, our team is composed of clinical and methods experts trained and calibrated for all stages of the review process. In order to minimize problems with counterintuitive results, the data analysis plan anticipated challenges that arise in NMA when data is sparse.[18] We assessed the certainty of the evidence using the GRADE approach and interpreted the results considering absolute effects. Many of the results for comparisons with sparse data were uninformative and were sometimes implausible. For that reason, we decided to report evidence on treatments that randomized at least 100 patients. In the future, when more data from more treatments are available, our classification of interventions from the most to the least effective will facilitate clear interpretation of results.

The main limitation of the systematic review is the very low quality of the evidence as a result of the current sparse data available. As the many ongoing trials are completed, we anticipate that the effect estimates will quickly become both plausible and informative as the quality of the evidence rises. Only two studies were judged to be at low risk of bias.[31 32 60] The most common limitation was lack of blinding, including the largest trials.

Another limitation of this SR is the limited quality of reporting. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies did not match across studies and thus such studies could not be included in the NMAs. This led the team to propose a hierarchy for the outcome mechanical ventilation as described in the methods. We expect that the relative effect will not vary importantly across methods of measurements.

The living nature of our NMA could conceivably (at least temporarily) amplify publication bias because studies with promising results are more likely to be published and are published sooner than studies with negative results. The inclusion of preprints, many of which have negative results might mediate this risk. Industry-sponsored trials such as those for remdesivir and other patented medications may be particularly at risk for publication bias and positive results for these medications may require more cautious interpretation than generic medications tested in RCTs independent of industry influence. However, the inclusion of preprints in our NMA may introduce bias from simple errors and reporting limitations of preprints. We include preprints because of the urgent need for information and because so many of the studies on COVID-19 are published first as preprints.

For comparisons with sufficient data, the primary limitation of the evidence is lack of blinding, which may introduce bias through differences in co-interventions between randomization groups. We chose to consider the treatment arms that did not receive an active experimental drug (i.e., placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than in studies that were blinded.

It is also possible that study-level meta-analysis may not detect important subgroup modification that would otherwise be detected within trial comparisons.[68] Direct comparisons in which the evidence is dominated by unblinded studies were rated down, consistent with GRADE, for risk of bias and that is reflected in the rating of the quality of evidence from the network estimate.[69] For example, the RECOVERY trial suggested that patients with more severe disease may obtain a greater benefit from dexamethasone than patients with less severe disease.[51]

Our living NMA is informing the development of the *BMJ Rapid Recommendations*. There is, however, an important difference in the methods for assessing the certainty of the evidence between the two. In this SR and living NMA, we are using a minimally contextualized approach for rating the certainty of the evidence, whereas the *BMJ Rapid Recommendations* are using a fully contextualized approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.[24] The contextualization explains potential differences in the certainty of the evidence between the two. The limitations of potentially misleading results when the network is sparse, and the desirability of focusing on direct estimates from larger studies when this is the case, explain differences in the details of the estimates of effect in this NMA and in the associated remdesivir guidelines.

To date, we are aware of two other efforts similar to ours.[68 70] We decided to proceed independently to ensure that the results fully inform clinical decision making for the associated living guidance in BMJ Rapid Recommendations. We are also including a more comprehensive search for the evidence, and several differences in analytic methods which we believe are best suited for this process. It is also important to evaluate the reproducibility and replicability of results from different scientific approaches.

We will periodically update this SR and living NMA. The changes from each version will be highlighted for readers and the most updated version will be the one available in the publication platform. Previous versions will be archived in the supplementary material. This SR and living NMA will also be accompanied by interactive infographics and a website for users to access the most updated results in a user-friendly format.

Conclusions

The evidence suggests that glucocorticoids probably reduce mortality and mechanical ventilation in patients with severe COVID-19. Remdesivir probably reduces length of hospital stay. The effects of most pharmacologic interventions is currently highly uncertain, and no definitive evidence exists that other interventions result in important benefits and harms for any outcomes.

Acknowledgments
We appreciate the input and early contributions of Dr. Kevin Cheung.

Table 1. Study characteristics

Study	Publication status Registration	Number of participants	Country	Mean age	% Male	Comorbidities	Type of care	Severity	% Mechanical ventilation (at baseline)	Treatments (dose and duration)	Outcomes
Beigel, 2020 ACTT-1[31]	Published NCT04280705	1063	United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	58.9	64.3	Coronary artery disease (11.6%) Congestive heart failure (5.0%) Diabetes (29.7%) Hypertension (49.6%) Asthma (11.4%) Chronic oxygen requirement (2.2%) Chronic respiratory disease (7.6%)	Inpatient	Mild/Moderate (11.3%) Severe (88.7%)	44.1	remdesivir (100 mg/day for 10 days) placebo	Mortality Mechanical ventilation Adverse effects leading to discontinuation Time to symptom/clinical improvement
Cao_1, 2020 JOTUS China[34]	Published ChiCTR2000029308	199	China	58.0	60.3	Cerebravascular disease (6.5%) Diabetes (11.6%)	Inpatient	Severe (100%)	16.1	lopinavir-ritonavir (400 mg and 100 mg BID for 14 days) standard care	Mortality Mechanical ventilation Viral clearance Duration of hospitalization ICU length of stay Duration of ventilation Time to symptom/clinical improvement
Cao_2, 2020[35]	Published ChiCTR-OPN-2000029580	43	China	63.0	58.5	Coronary artery disease (7.3%) Diabetes (19.5%) Hypertension (39.0%)	Inpatient	Severe (100%)	12.2	ruxolitinib (5 mg BID) placebo	Mortality Mechanical ventilation Duration of hospitalization Duration of ventilation Time to symptom/clinical improvement Time to viral clearance
Chen_1, 2020[28]	Pre-print ChiCTR2000029559	62	China	44.7	46.8	NR	Inpatient	Mild/Moderate (100%)	NR	hydroxychloroquine (200 mg BID for 5 days) standard care	Adverse effects leading to discontinuation Time to symptom/clinical improvement
Chen_2, 2020[29]	Pre-print ChiCTR2000030254	240	China	NR	46.6	Diabetes (11.4%) Hypertension (28.0%)	NR	Mild/Moderate (88.6%) Severe (10.2%) Critical (1.3%)	NR	favipiravir (600 mg BID for 7 days) umifenovir (200 mg TID for 7 days)	Mortality Time to symptom/clinical improvement
Chen_3, 2020[27]	Published ChiCTR2000029387	101	China	42.5	45.5	Severe heart disease (0%) Severe lung disease (0%)	NR	Mild/Moderate (100%)	NR	ribavirin (400-600 mg TID for 14 days), interferon-α (5 mg BID fo Mortality lopinavir-ritonavir (400 mg and 100 mg BID for 14 days), interfer Viral clearance ribavirin (400-600 mg TID for 14 days), lopinavir-ritonavir (400 m Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance
Chen_4, 2020[33]	Published NCT04261517	30	China	48.6	70.0	Severe heart disease (0%) Diabetes (6.7%) Hypertension (26.7%) Chronic obstructive pulmonary disease (3.3%) Severe lung disease (0%)	Inpatient Intensive care (0%)	Mild/Moderate (100%)	NR	hydroxychloroquine (400 mg/day for 5 days) standard care	Mortality Adverse events leading to discontinuation Viral clearance Time to symptom/clinical improvement Time to viral clearance
Chen_5, 2020[32]	Pre-print ChiCTR2000030054	48	China	46.5	45.8	Diabetes (18.8%) Hypertension (16.7%)	Inpatient	Mild/Moderate (100%)	NR	chloroquine (500 mg/day for 10 days) hydroxychloroquine (300 mg BID for 10 days) standard care	Mortality Adverse events leading to discontinuation Viral clearance Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance
Corral-Gudino, 2020 GLUCOCOVID[52] †	Preprint 2020-001934-37	63	Spain	69.8	61.9	Arrhythmia (0%) Heart disease (12.7%) Diabetes (17.5%) Hypertension (47.6%) Respiratory condition (7.9%)	Inpatient Intensive care NR	Critical (0%)	0	methylprednisolone (40 mg BID for 3 days, then 20 mg BID for 3 standard care	Mortality Mechanical ventilation
Davoudi-Monfared, 2020[36]	Preprint IRCT20100228003449N28	92	Iran	57.8	53.3	Cardiovascular disease(28.4%) Diabetes (27.2%) Hypertension (38.3%) Asthma (1.2%) Chronic obstructive pulmonary disease (1.2%)	Inpatient	Severe (100%)	29.6	interferon β-1a (44 ug/ml TIW for 14 days) standard care	Mortality Mechanical ventilation Adverse events leading to discontinuation Duration of hospitalization ICU length of stay Duration of ventilation Time to symptom/clinical improvement
Goldman, 2020[30] *	Published NCT04292899	402	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	61.5	63.7	Diabetes (22.7%) Hypertension (49.5%) Asthma (12.34%)	Inpatient	Severe (100%)	30.7	remdesivir (100 mg/day for 5 days) remdesivir (100 mg/day for 10 days)	Mortality Mechanical ventilation Adverse events leading to discontinuation Duration of hospitalization Time to symptom/clinical improvement

Guvenmez, 2020[94]	Published	24	Turkey	58.8	62.5	NR	Inpatient	NR	0	lincomycin (600 mg BID for 5 days) azithromycin (250 mg/day for 5 days)	Viral clearance
Horby, 2020 RECOVERY[81]	Pre-print NCT04381936	6425	United Kingdom	66.1	69.6	Heart disease (27.3%) Diabetes (24.1%) Chronic lung disease (20.5%) Tuberculosis (8.4%)	Inpatient	NR	35.7	dexamethasone (6 mg/day for 10 days) standard care	Mortality Mechanical ventilation Duration of hospitalization
Huang, 2020[95]	Published ChiCTR2000029542	33	China	44.0	58.1	Cerebrovascular disease (4.5%) Diabetes (9.1%) Hypertension (18.2%)	Inpatient	Mild/Moderate (63.6%) Severe (36.4%)	NR	chloroquine (500 mg BID for 10 days) lopinavir-ritonavir (400 mg and 100 mg BID for 10 days)	Viral clearance Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance
Hung, 2020[6]	Published NCT04276688	127	China	51.3	53.5	Coronary artery disease (7.9%) Cerebrovascular disease (1.6%) Diabetes (13.4%) Hypertension (28.4%) Obstructive sleep apnea (1.6%) Tuberculosis (1.6%)	Inpatient	Mild/Moderate (100%)	0	lopinavir-ritonavir (400 mg and 100 mg BID for 14 days), ribavirin lopinavir-ritonavir (400 mg and 100 mg BID for 14 days)	Mortality Mechanical ventilation Adverse effects leading to discontinuation Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance
Li_1, 2020 ELACOI[96]	Pre-print NCT04252885	86	China	49.4	46.5	Cardiovascular disease(2.3%) Diabetes (2.3%) Hypertension (10.5%) Respiratory condition (0%)	Inpatient	Mild/Moderate (100%)	0	lopinavir-ritonavir (400 mg and 100 mg BID for 7 to 14 days) umifenavir (200 mg TID for 7 to 14 days) standard care	Mortality Adverse effects leading to discontinuation Viral clearance Time to viral clearance
Lou, 2020[97]	Pre-print ChiCTR2000029544	30	China	52.5	72.4	Cardiovascular disease(13.8%) Diabetes (6.9%) Hypertension (20.7%) Chronic obstructive pulmonary disease (0%)	Inpatient Intensive care (0%)	Critical (0%)	0	baloxavir marboxil (240 mg/day for up to 3 doses on days 1, 4, an lopinavir (400 mg BID for 14 days) standard care	Mortality Mechanical ventilation Viral clearance Time to symptom/clinical improvement Time to viral clearance
Silva Berta, 2020 *ClinicoCOVID-19[98]	Published NCT04333537	81	Brazil	51.1	75.3	Cardiovascular disease (9.1%) Diabetes (25.5%) Hypertension (45.5%) Asthma (7.4%) Tuberculosis (3.6%)	Inpatient Intensive care (45.7%)	Severe (100%)	NR	chloroquine (600 mg BID for 10 days) chloroquine (450 mg/day for 5 days)	Mortality
Tang, 2020[85] [a]	Published ChiCTR2000029868	150	China	46.1	55.0	Cardiovascular disease (0%) Diabetes (14.0%) Hypertension (6.0%)	Inpatient	Mild/Moderate (99.6%) Severe (1.0%)	NR	hydroxychloroquine (800 mg/day for 31 to 71 days) standard care	Mortality Adverse effects leading to discontinuation Viral clearance Time to symptom/clinical improvement Time to viral clearance
Wang, 2020[6]	Published NCT04257656	237	China	65.0	59.3	Cardiovascular disease (7.2%) Diabetes (23.7%) Hypertension (43.2%)	Inpatient	Severe (100%)	16.1	remdesivir (100 mg/day for 10 days) placebo	Mortality Mechanical ventilation Adverse events leading to discontinuation Viral clearance Duration of hospitalization Duration of ventilation Time to symptom/clinical improvement
Zheng, 2020[8]	Pre-print ChiCTR2000029496	89	China	46.7	47.2	Severe heart disease (0%) Severe lung disease (0%)	Inpatient	Mild/Moderate (64.4%) Severe (35.6%)	NR	novaferon (20 μg BID for 7 to 10 days) novaferon, lopinavir-ritonavir (200 mg and 50 mg BID for 7 to 10 lopinavir-ritonavir (200 mg and 50 mg BID for 7 to 10 days)	Adverse events leading to discontinuation Viral clearance Time to viral clearance
Zhong, 2020[9]	Pre-print ChiCTR2000029851	17	China	63.0	76.5	Cardiovascular disease (5.5%) Diabetes (23.5%) Hypertension (17.1%)	Inpatient	Critical (100%)	94.1	α-lipoic acid (1200 mg/day for 7 days) placebo	Mortality Adverse events leading to discontinuation
Zhou, 2020[99]	Published	104	China	52.1	57.7	Severe heart disease (0%) Hypertension (0%) Interstitial pneumonia (0%)	Inpatient Intensive care (8.7%)	Mild/Moderate (100%)	NR	diammonium glycyrrhizinate (150 mg TID for 14 days), lopinavir- lopinavir-ritonavir (500 mg BID for 14 days)	Adverse events leading to discontinuation

NR: not reported
*not included in network meta-analysis
†not included in the current iteration of the network meta-analysis but will be included in the next iteration. Corral-Gudino et al, 2020 was included in the pairwise meta-analysis of glucocorticoids.

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