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Drug treatments for covid-19: living systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To compare the effects of treatments for coronavirus disease 2019 (covid-19).

DESIGN

Living systematic review and network meta-analysis.

DATA SOURCES

WHO covid-19 database, a comprehensive multilingual source of global covid-19 literature, up to 3 December 2020 and six additional Chinese databases up to 12 November 2020.

STUDY SELECTION

Randomised clinical trials in which people with suspected, probable, or confirmed covid-19 were randomised to drug treatment or to standard care or placebo. Pairs of reviewers independently screened potentially eligible articles.

METHODS

After duplicate data abstraction, a bayesian network meta-analysis was conducted. Risk of bias of the included studies was assessed using a modification of the Cochrane risk of bias 2.0 tool, and the certainty of the evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach. For each outcome, interventions were classified in groups from the most to the least beneficial or harmful following GRADE guidance.

RESULTS

85 trials enrolling 41 669 patients met inclusion criteria as of 21 October 2020; 50 (58.8%) trials and 25 081 (60.2%) patients are new from the previous iteration; 43 (50.6%) trials evaluating treatments with at least 100 patients or 20 events met the threshold for inclusion in the analyses. Compared with standard care, corticosteroids probably reduce death (risk difference 17 fewer per 1000 patients, 95% credible interval 34 fewer to 1 more, moderate certainty), mechanical ventilation (29 fewer per 1000 patients, 54 fewer to 1 more, moderate certainty), and days free from mechanical ventilation (2.6 fewer, 0.2 fewer to 5.0 fewer, moderate certainty). The impact of remdesivir on mortality, mechanical ventilation, length of hospital stay, and duration of symptoms is uncertain, but it probably does not substantially increase adverse effects leading to drug discontinuation (0 more per 1000, 9 fewer to 40 more, moderate certainty). Azithromycin, hydroxychloroquine, lopinavir/ritonavir, interferon-beta, and tocilizumab may not reduce risk of death or have an effect on any other patient-important outcome. The certainty in effects for all other interventions was low or very low.

CONCLUSION

Corticosteroids probably reduce mortality and mechanical ventilation in patients with covid-19 compared with standard care, whereas azithromycin, hydroxychloroquine, interferon-beta, and tocilizumab may not reduce either. Whether or not remdesivir confers any patient-important benefit remains uncertain.

SYSTEMATIC REVIEW REGISTRATION

This review was not registered. The protocol is included as a supplement.

READERS' NOTE

This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication. This version is the second update of the original article published on 30 July 2020 (*BMJ* 2020;370:m2980), and previous versions can be found as data supplements. When citing this paper please consider adding the version number and date of access for clarity.

Introduction

As of 8 December 2020, more than 67 million people have been infected with severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (covid-19); of these, 1.5 million have died.[1] Despite global efforts to identify effective interventions for the prevention and treatment of covid-19, which have resulted in 2400 trials completed or underway,[2] evidence for effective treatment remains limited.

Faced with the pressures of a global pandemic, healthcare workers around the world are prescribing drugs off-label for which there is only very low quality

evidence. Timely evidence summaries and associated guidelines could 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 encountered previously. This environment makes it necessary to produce well developed summaries that distinguish more trustworthy evidence from less trustworthy evidence.

Living systematic reviews deal with the main limitation of traditional reviews—that of providing an overview of the relevant evidence only at a specific time.[4] This is crucial in the context of covid-19, in which the best evidence is constantly changing. The ability of a living network meta-analysis to present a complete, broad, and updated view of the evidence makes it the best type of evidence synthesis to inform the development of practice recommendations. Network meta-analysis, rather than pairwise meta-analysis, provides useful information about the comparative effectiveness of treatments that have not been 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]

In this living systematic review and network meta-analysis we compare the effects of drug treatments for covid-19. This review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*.[6] This living systematic review and network meta-analysis will directly inform *BMJ* Rapid Recommendations[6] on covid-19 treatments, initiated to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available. The first covid-19 *BMJ* Rapid Recommendation considered the role of remdesivir[7] (box 1). This living network meta-analysis is the third version. The previous versions are available in the supplementary material.

Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster

- Siemieniuk R, Rochwerg B, Agoritsas T, et al. A living WHO guideline on drugs for covid-19 [Update 2]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
  - Living WHO *BMJ* Rapid Recommendations guidance on drugs for covid-19
- World Health Organization. *Therapeutics and COVID-19. Living guideline*. 17 Dec 2020. https://apps.who.int/iris/bitstream/handle/10665/337876/WHO-2019-nCoV-therapeutics-2020.1-eng.pdf.
- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 2]. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
  - Review and network meta-analysis of all available randomised trials that assessed drug treatments for covid-19
- MAGICapp (https://app.magicapp.org/#/guideline/nBkO1E)
  - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices
- Author website (https://www.covid19lnma.com)
  - Interim updates will be available here

Methods

A protocol provides the detailed methods of this systematic review, including all updates (see supplementary file). We report this living systematic review following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for network meta-analyses.[8] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[9] The linked *BMJ* Rapid Recommendations guideline panels approved all decisions relevant to data synthesis.

Eligibility criteria

We included randomised clinical trials in people with suspected, probable, or confirmed covid-19 that compared drugs 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 preprint) or language. No restrictions were applied based on severity of illness or setting and we included trials of Chinese medicines if the drug comprised one or more specific molecules with a defined molecular weight dosing.

We excluded randomised controlled trials 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. Trials that evaluated these interventions were identified and categorised separately.

Information sources

We perform daily searches from Monday to Friday in the World Health Organization (WHO) covid-19 database for eligible studies – a comprehensive multilingual source of global literature on covid-19. Prior to its merge with the WHO covid-19 database on 9 October 2020, we performed daily searches from Monday to Friday in the US Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies.[10] The database includes, but is not limited to the following 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 the day after publication. To identify randomised controlled trials, we filtered the results from the CDC's database through a validated and highly sensitive machine learning model.[11] We tracked preprints of randomised controlled trials until publication and updated data to match that in the peer reviewed publication when discrepant and reconciled corrections and retractions existed.

In addition, we search six Chinese databases monthly: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, 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 randomised trials. The supplementary file 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[12] 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.[13]

We searched all English information sources from 1 December 2019 to 3 December 2020, and the Chinese literature from conception of the databases to 12 November 2020.

Study selection

Using a systematic review software, Covidence,[14] pairs of reviewers, following training and calibration exercises, 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 analysed and the number of participants who experienced an event for dichotomous outcomes). Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party. We updated the data collected from included preprints as soon as the peer review publication became available.

Outcomes of interest were selected based on importance to patients and were informed by clinical expertise in the systematic review team and in the linked guideline panel responsible for the WHO-*BMJ* Rapid Recommendations.[7] The panel includes unconflicted clinical and methodology experts, recruited to ensure global representation, and patient-partners. All panel members rated outcomes from 1 to 9 based on importance to individual patients (9 being most important), and we included any outcome rated 7 or higher by any panel member. 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 either way), admission to hospital, duration of hospital stay, intensive care unit (ICU) length of stay, duration of mechanical ventilation, time to symptom resolution or clinical improvement, time to viral clearance, and days free from mechanical ventilation (within 28 days). Viral clearance at seven days and time to viral clearance were included because both may be surrogates for transmissibility, although this is uncertain.[15]

Because of the inconsistent reporting observed across trials, we used a hierarchy for the outcome mechanical ventilation in which we considered the total number of patients who received ventilation over the study, if available, and the number of patients ventilated at the time point at which most of the patients were mechanically ventilated, if that is the only way in which this outcome was reported.

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 randomised trials (RoB 2.0)[16] to rate trials as either at i) low risk of bias, ii) some concerns—probably low risk of bias, iii) some concerns—probably high risk of bias, or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; bias due to competing risks; and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated as some concerns—probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as some concerns—probably low risk of bias or low risk of bias. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party.

Data synthesis

We conducted the network meta-analysis using a bayesian framework.[17] In this report, we conducted a network meta-analysis of drug treatments for covid-19 that included all patients, regardless of severity of disease.

Summary measures

We summarised the effect of interventions on dichotomous outcomes using the odds ratio and corresponding 95% credible interval. For continuous outcomes, we used the mean difference and corresponding 95% credible interval in days for ICU length of stay, length of hospital stay, and duration of mechanical ventilation because we expected similar durations across randomised controlled trials. For time to symptom resolution and time to viral clearance, we first performed the analyses using the relative effect measure ratio of means and corresponding 95% credible interval before calculating the mean difference in days because we expected substantial variation between studies.[18]

Treatment nodes

Treatments were grouped into common nodes based on molecule and not on dose or duration. For intervention arms with more than one drug, we created a separate 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, TX), with thickness of lines between nodes and size of the nodes based on the inverse of the variance of the direct comparison.[19]

Statistical analysis

For most outcomes, we conducted network meta-analyses and pairwise meta-analyses using a bayesian framework with the same priors for the variance and effect parameters.[17] In previous versions, we used fixed effects for some outcomes because data was sparse or dominated by a single trial. In this update, we used random effects for all outcomes. We used a plausible prior for variance parameter and a uniform prior for the effect parameter suggested in a previous study based on empirical data.[20] 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.[21] All network meta-analyses were performed using the *gemtc* package of R version 3.6.3 (RStudio, Boston, MA)[22] and all pairwise meta-analyses using the *bayesmeta* package.[17]

In the first iteration of this living network meta-analysis, some treatment nodes with few total participants and few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that included at least 100 patients or had at least 20 events, based on our impression of the minimum number of patients/events to possibly provide meaningful results.

Certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach for network meta-analysis.[5 23 24] Two people with experience in using GRADE 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.[24] Judgments of imprecision for this systematic review were made using a minimally contextualised approach, with a null effect as the threshold of importance.[25] The minimally contextualised 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] To evaluate certainty of no benefit (or no effect), we used a 2% risk difference threshold of the 95% credible interval for mortality and mechanical ventilation. In other words, if the entire 95% credible interval was within 2% of the null effect, we would not rate down for imprecision. We decided on this preliminary threshold based on a survey of the authors. In future updates, it will be guided by a survey of patients and guideline panellists. Interim updates and additional study data will be posted on our website (www.covid19lnma.com).

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was an odds ratio or ratio of means. When available, we inferred baseline risk in the usual care group for each outcome from representative observational data (supplementary material). For mortality, we used data from the CDC on patients who were hospitalised with covid-19.[26 27] For mechanical ventilation, duration of invasive mechanical ventilation, duration of hospitalisation, and ICU length of stay we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.[28] For all other outcomes, we used the median from all studies in which participants received standard of care to calculate the baseline risk for each outcome, with each study weighed equally. We calculated absolute effects using the transitive risks model[29] using *R2jags* package in R.[30]

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualised framework, which focuses on the treatment effect estimates and the certainty of the evidence.[31]

Subgroup and sensitivity analysis

Subgroup analyses were performed for specific interventions of interest at the direction of the linked WHO living guideline panel. In this iteration, we performed subgroup analyses for remdesivir, hydroxychloroquine, and lopinavir/ritonavir. The panel requested subgroup analyses by age (children vs. non-elderly adults vs. elderly) and severity (non-severe vs. severe vs. critical). We performed bayesian hierarchical meta-regression with study as a random effect.

Patient and public involvement

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

Results

After screening 20 228 titles and abstracts and 370 full texts, 130 unique randomised controlled trials from 118 publications were identified that evaluated drug treatments as of 3 December 2020 (fig 1).[32-77] A table of excluded full texts is provided in the supplementary file. Searches of living evidence retrieval services identified 27 additional eligible randomised controlled trials.[65-72 78-88] Seventy-three randomised trials have been published in peer reviewed journals, 43 only as preprints, and 17 within two meta-analyses. Most of the trials were registered (117/130; 90%), published in English (113/118; 96%), and evaluated treatment in patients admitted to hospital with covid-19 (112/130; 86%). One quarter of the trials were conducted in China (33/130; 25%), with the remainder distributed globally. Of the 130 included drug trials, the three most commonly studied drugs were (hydroxy)chloroquine (33/130; 25%), followed by corticosteroids (11/130; 8%) and lopinavir/ritonavir (8/130; 6%).

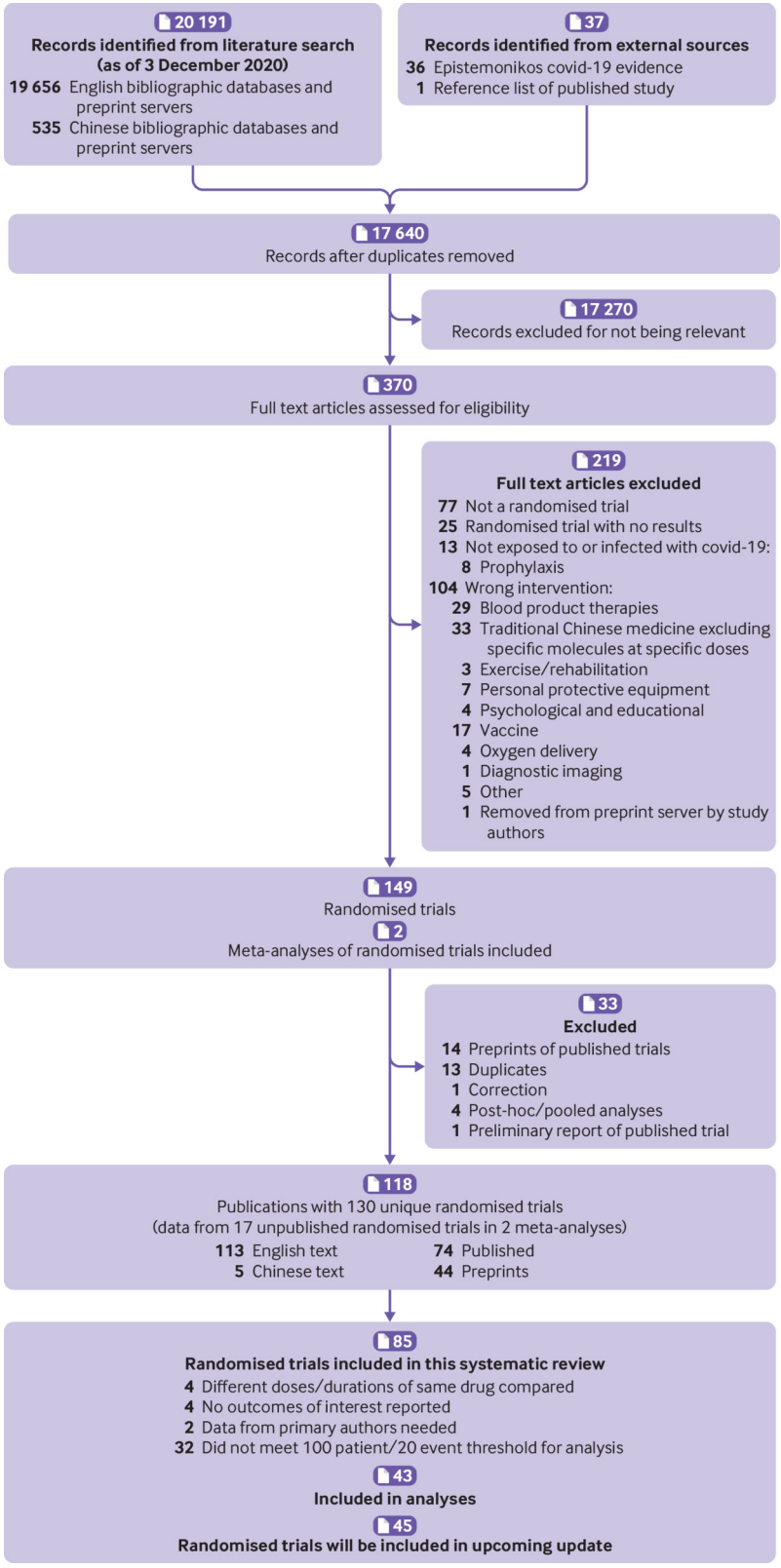


Fig 1 | Study selection

Eighty five randomised controlled trials that evaluated drug treatments were identified up until the date of analysis (21 October 2020). Several of these trials could not be included in the analysis: four trials that evaluated different durations or doses of the same drug, because both arms would have been classified within the same treatment node[35 43 89 90]; two trials with insufficient data[86 91 92]; and four trials that reported no outcomes of interest.[93-96] Of the remaining 75 trials, we analysed 43 (57.3%) reporting on treatments

with at least 100 patients or 20 events to avoid implausible and extremely imprecise estimates.[32 33 37 39 41 47 51 52 76 78 81 83 85 97 -124] Table 1 presents the characteristics of the 85 included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the supplementary file.

Table 1 | Study characteristics

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Abbaspour Kasgari 2020[125]‡	Published, RCT20080804688N1	48	Iran	52.5	37.5	Inpatient; ischemic heart disease (22.9%); diabetes (37.5%); chronic obstructive pulmonary disease (2.1%)	Mild/moderate (100%)	NR	Sofosbuvir-daclatasvir (400 mg and 60 mg once daily for 14 days, ribavirin (600 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; duration of ventilation
Abd-Elsalam 2020[106]	Published, NCT04353336	194	Egypt	40.7	58.8	Inpatient	NR	NR	Hydroxychloroquine (200 mg twice daily for 15 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Altay 2020[126]‡	Preprint, NCT04573153	100	Turkey	35.6	60.0	Outpatient; diabetes (5.0%); hypertension (2.0%)	Mild/moderate (100%)	0	Serine (24 g/day total, given twice daily, for 14 days), N-acetylcysteine (5.1 g/day total, given twice daily, for 14 days), nicotinamide riboside (2 g/day total, given twice daily, for 14 days), L-carnitine tartrate (7.46 g/day total, given twice daily, for 14 days); placebo	Mortality; time to symptom or clinical improvement
Angus 2020; REMAP-CAP[107]	Published, NCT02735707	403	Australia, Canada, Ireland, France, Netherlands, New Zealand, UK, USA	59.9	71.1	Inpatient; intensive care (100%); cardiovascular disease (7.3%); diabetes (32.1%); asthma or chronic obstructive pulmonary disease (16.2%); respiratory disease (19.5%)	Severe (100%)	100	Hydrocortisone (50 mg four times daily for 7 days); hydrocortisone (50 mg four times daily while in shock for up to 28 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; ICU length of stay
Ansarin 2020[127]‡	Published, RCT20080170659N4	78	Iran	59.8	55.1	Inpatient; diabetes (33.3%); hypertension (50.0%)	NR	NR	Bromhexine hydrochloride (8 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; duration of hospital stay

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Beigel 2020; ACTT-1[32]	Published, NCT04280705	1062	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	58.9	64.4	Inpatient; coronary artery disease (11.9%); congestive heart failure (5.6%); diabetes (30.6%); hypertension (50.7%); asthma (11.4%); chronic oxygen requirement (2.2%); chronic respiratory disease (7.6%)	Severe (90.1%)	45.0	Remdesivir (100 mg/day for 10 days); placebo	Mortality; mechanical ventilation; adverse effects leading to discontinuation; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement
Cao 2020; LOTUS China[37]	Published, ChiCTR2000029308	199	China	58.0	60.3	Inpatient; cerebrovascular disease (6.5%); diabetes (11.6%)	Severe (100%)	16.1	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; intensive care unit length of stay; duration of ventilation; time to symptom or clinical improvement
Cao 2020‡[38]	Published, ChiCTR2000029580	43	China	63.0	58.5	Inpatient; coronary artery disease (7.3%); diabetes (19.5%); hypertension (39.0%)	Severe (100%)	12.2	Ruxolitinib (5 mg twice daily); placebo	Mortality; mechanical ventilation; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement; time to viral clearance
Castillo 2020‡; Pilot Covidiol[128]	Published, NCT04366908	76	Spain	53.0	59.2	Inpatient; cardiovascular disease (4.0%); diabetes (10.5%); hypertension (34.2%); previous lung disease (7.9%)	NR	NR	Calcifediol (0.532 mg on day 1, then 0.266 mg on day 3 and 7, and then weekly until discharge or ICU admission); standard care	Mortality; adverse events leading to discontinuation
Cavalcanti, 2020[97]	Published, NCT04322123	667	Brazil	50.3	58.4	Inpatient; intensive care (13.8%); heart failure (1.5%); diabetes (19.1%); hypertension (38.3%); asthma (6.0%); chronic obstructive pulmonary disease (1.8%)	Mild/Moderate (100%)	0	Hydroxychloroquine (400 mg twice daily for 7 days); hydroxychloroquine (400 mg twice daily for 7 days), azithromycin (500 mg/day for 7 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Chen 2020[41]	Preprint, ChiCTR2000029559	62	China	44.7	46.8	Inpatient; NR	Mild/moderate (100%)	NR	Hydroxychloroquine (200 mg twice daily for 5 days); standard care	Time to symptom or clinical improvement
Chen 2020[39]	Preprint, ChiCTR2000030254	240	China	NR	46.6	NR; diabetes (11.4%); hypertension (28.0%)	Mild/moderate (88.6%); severe (10.2%); critical (1.3%)	NR	Favipiravir (600 mg twice daily for 7 days); umifenovir (200 mg three times daily for 7 days)	Mortality; time to symptom or clinical improvement

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Chen 2020[98]	Published, NCT04261517	30	China	48.6	70.0	Inpatient; diabetes (6.7%); hypertension (26.7%); chronic obstructive pulmonary disease (3.3%)	Mild/moderate (100%)	NR	Hydroxychloroquine (400 mg/day for 5 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Chen 2020[52]	Preprint, ChiCTR2000030054	48	China	46.9	45.8	Inpatient; diabetes (18.8%); hypertension (16.7%)	Mild/moderate (100%)	NR	Chloroquine (500 mg/day for 10 days); hydroxychloroquine (200 mg twice daily for 10 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Chen 2020[99]	Preprint, NCT04384380	33	Taiwan	32.9	57.6	Inpatient	Mild/Moderate (100%)	0	Hydroxychloroquine (200 mg twice daily for 7 days); standard care	Mortality; time to viral clearance
Cheng 2020[108]	Published, ChiCTR2000030007	200	China	45.0	56.0	Inpatient	Critical (0%)	27.0	Granulocyte colony-stimulating factor (5 µg/kg/day for 3 days); standard care	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; time to symptom or clinical improvement
Corral-Gudino 2020; GLUCOCOVID[51]	Preprint, 2020-001934-37	63	Spain	69.8	61.9	Inpatient; heart disease (12.7%); diabetes (17.5%); hypertension (47.6%); respiratory condition (7.9%)	Critical (0%)	0	Methylprednisolone (40 mg twice daily for 3 days, then 20 mg twice daily for 3 days); standard care	Mortality; mechanical ventilation
Cruz 2020‡; ATENEA-Co-300[129]	Preprint, IG/OGB300/CV/2001	20	Cuba	45.4	70.0	Inpatient; hypertension (25.0%)	Mild/moderate (90%); severe (10%)	NR	Anti-CK2 synthetic peptide (2.5 mg/kg/day for 5 days); standard care	Time to viral clearance
Dabbous 2020[85]	Preprint, NCT04349241	100	Egypt	36.4	50.0	Inpatient	Mild/moderate (100%)	NR	Favipiravir (600 mg twice daily for 10 days); standard care	Mortality; viral clearance; duration of hospital stay; time to viral clearance
Davoodi 2020‡[130]	Published, IRCT20190727044134N1	60	Iran	57.7	59.3	Outpatient; diabetes (27.8%); lung disease (1.9%)	Mild/Moderate (100%)	0	Febuxostat (80 mg/day for 5 days); hydroxychloroquine (200 mg twice daily for 5 days)	Mortality; admission to hospital

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Davoudi-Monfared 2020[42 104]	Published, RCT20002803N28	92	Iran	58.7	54.3	Inpatient; ischemic heart disease (28.4%); diabetes (27.2%); hypertension (38.3%); asthma (1.2%); chronic obstructive pulmonary disease (1.2%)	Severe (100%)	29.6	Interferon beta-1a (44 µg/ml three times weekly for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; duration of ventilation; time to symptom or clinical improvement
de Alencar 2020[131]‡	Published, U1111-1250-356	140	Brazil	58.5	59.3	Inpatient; diabetes (37.8%); hypertension (46.7%)	Severe (100%)	0.7	N-acetylcysteine (14 g in the first 4 hours, then 7 g in the next 16 hours); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay
Deftereos 2020; GRECCO-19[105]	Published, NCT04326790	110	Greece	64.0	58.1	Inpatient; atrial fibrillation (10.5%); coronary artery disease (13.3%); valvulopathy (4.8%); diabetes (20.0%); hypertension (44.8%); chronic obstructive pulmonary disease (4.8%)	NR	2.9	Colchicine (0.5 mg twice daily for 21 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay
Delgado-Enciso 2020‡; TX-COVID19[132]	Preprint, RPCEC00000309	84	Mexica	47.1	53.6	Outpatient; diabetes (11.9%); hypertension (19.1%); asthma (6.0%)	Mild/moderate (100%)	NR	Electrolyzed saline (15 ml/day for 7 days with successive increases up to 30 ml/day if indicated); standard care	Mortality; admission to hospital; adverse events leading to discontinuation
Dequin 2020; CAPE COVID[109]	Published, NCT02517489	149	France	62.2	69.8	Inpatient; intensive care (100%); cerebrovascular disease (4.0%); diabetes (18.1%); asthma (3.4%); chronic obstructive pulmonary disease (4.0%)	Critical (100%)	81.2	Hydrocortisone (200 mg/day for 7 days, followed by 100 mg once daily for 4 days, and 50 mg once daily for 3 days)	Mortality; mechanical ventilation
Doi 2020[90]*	Published, jRCTs041190120	89	Japan	50.0	61.4	Inpatient	NR	NR	Favipiravir (800 mg twice daily for 10 days starting on day 1 of enrolment); favipiravir (800 mg twice daily for 10 days starting on day 6 of enrolment)	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Duarte 2020[133]‡	Preprint, NCT04355936	82	Argentina	61.9	61.5	Inpatient; stroke (7.7%); diabetes (11.5%); hypertension (30.8%); asthma (1.3%); chronic obstructive pulmonary disease (11.5%)	NR	0	Telmisartan (80 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay
Edalatifard 2020[110]	Published, RCT20200404047N1	68	Iran	58.5	62.9	Inpatient; cardiovascular disease (17.7%); diabetes (35.5%); hypertension (32.3%); respiratory condition (9.7%)	Severe (100%)	37.1	Methylprednisolone (250 mg/day for 3 days); standard care	Mortality; mechanical ventilation; time to symptom or clinical improvement
Esquivel-Moynelo 2020; ESPERANZA[111]	Preprint, RPCEC00000307	79	Cuba	38.0	54.0	Inpatient; cardiac disease (6.4%); diabetes (4.8%); hypertension (22.2%); asthma (6.4%)	Mild/moderate (100%)	NR	Interferon gamma (0.5 MIU twice a week for 14 days); standard care	Mortality; viral clearance; time to viral clearance
Farahani 2020[86]*	Preprint, RCT20200406463N1	29	Iran	64.0	65.5	Inpatient	Mild/moderate (0%)	NR	Methylprednisolone (1000 mg/day for 3 days), prednisolone (1 mg/kg with tapering of dose over 10 days); standard care	Mortality; mechanical ventilation; intensive care unit length of stay
Fu 2020[113]	Published, ChiCTR2000030262	80	China	35.3	63.8	Inpatient; diabetes (3.8%); hypertension (5.0%)	Mild/moderate (100%)	NR	Interferon kappa (2 mg/day for 6 days), trefoil factor 2 (5 mg/day for 6 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to viral clearance
Furtado 2020; COALITION II[112]	Published, NCT04321278	447	Brazil	60.2	64.0	Inpatient; heart failure (5.6%); previous stroke (4.0%); previous myocardial infarction (4.5%); diabetes (38.0%); hypertension (60.9%); chronic obstructive pulmonary disease (6.7%)	Severe (100%)	50.3	Azithromycin (500 mg/day for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; ventilator-free days
Goldman 2020[43]*	Published, NCT04292899	402	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	61.5	63.7	Inpatient; diabetes (22.7%); hypertension (49.9%); asthma (12.3%)	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 hospital stay; time to symptom or clinical improvement
Guvenmez 2020[134]	Published	24	Turkey	58.8	62.5	Inpatient; NR	NR	0	Lincomycin (600 mg twice daily for 5 days); azithromycin (250 mg/day for 5 days)	Viral clearance

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Horby 2020; RECOVERY[50 100]	Published, NCT04381936	6425	UK	66.2	63.6	Inpatient; heart disease (27.3%); diabetes (24.1%); chronic lung disease (21.0%); tuberculosis (0.4%)	NR	15.7	Dexamethasone (6 mg/day for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Horby 2020; RECOVERY[114 135]	Published, NCT04381936	4716	UK	65.3	62.2	Inpatient; heart disease (25.7%); diabetes (27.2%); chronic lung disease (22.2%); tuberculosis (0.3%)	NR	16.8	Hydroxychloroquine (400 mg twice daily for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Horby 2020; RECOVERY[115]	Published, NCT04381936	5040	UK	66.2	61.1	Inpatient; heart disease (26.0%); diabetes (27.5%); chronic lung disease (23.1%); tuberculosis (0.3%)	NR	4.1	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Hu 2020‡[136]	Published, ChiCTR2000030058	10	China	54.9	30.0	Inpatient; hypertension (10.0%); chronic obstructive pulmonary disease (10.0%)	Mild/moderate (100%)	0	Leflunomide (20 mg/day for 10 days); standard care	Mortality; viral clearance; time to symptom or clinical improvement; time to viral clearance
Huang 2020[78]	Published, ChiCTR2000029542	22	China	44.0	59.1	Inpatient; cerebrovascular disease (4.5%); diabetes (9.1%); hypertension (18.2%)	Mild/moderate (63.6%); severe (36.4%)	NR	Chloroquine (500 mg twice daily for 10 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 10 days)	Viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Huang 2020‡[40 137]	Published, ChiCTR2000029387	101	China	42.5	45.5	Inpatient	Mild/moderate (100%)	NR	Ribavirin (400-600 mg three times daily for 14 days), interferon-alfa (5 mg twice daily for 14 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), interferon-alfa (5 mg twice daily for 14 days); ribavirin (400-600 mg three times daily for 14 days), lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), interferon-alfa (5 mg twice daily for 14 days)	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Hung 2020‡[44]	Published, NCT04276688	127	China	51.3	53.5	Inpatient; coronary artery disease (7.9%); cerebrovascular disease (1.6%); diabetes (13.4%); hypertension (28.4%); obstructive sleep apnoea (1.6%); tuberculosis (1.6%)	Mild/moderate (100%)	0	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), ribavarin (400 mg twice daily for 14 days), interferon beta-1b (1-3 mL every other day); lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days)	Mortality; mechanical ventilation; adverse effects leading to discontinuation; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Ivaschenko 2020[116 138 139]	Published, NCT04434248	60	Russia	50.7	50.0	Inpatient; NR	Mild/moderate (100%)	0	Favipiravir (600 mg twice daily for 14 days); favipiravir (800 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement
Jeronimo 2020; Metcovid[117]	Published, NCT04343729	416	Brazil	55.0	65.3	Inpatient; intensive care (35.4%); heart disease (6.6%); diabetes (29.1%); hypertension (48.4%); asthma (2.4%); chronic obstructive pulmonary disease (0.5%); tuberculosis (2.1%)	NR	33.9	Methylprednisolone (0.5 mg/kg twice daily for 5 days); placebo	Mortality; mechanical ventilation; viral clearance; duration of hospital stay
Kimura 2020[140]‡	Published, NCT0447538	54	USA	38.2	53.3	Outpatient; heart disease (4.4%); diabetes (6.7%); hypertension (24.4%); chronic lung disease (15.6%)	NR	NR	Hypertonic saline (250 ml twice daily); hypertonic saline with surfactant (250 ml and 2.5 mg twice daily); standard care	Time to symptom or clinical improvement
Lemos 2020‡; HESACOVID[141]	Published, REBEC RBR-949z6v	20	Brazil	56.5	80.0	Inpatient; cardiovascular disease (10.0%); diabetes (35.0%); hypertension (35.0%)	Critical (100%)	100	Enoxaparin (1 mg/kg/day to 1 mg/kg twice daily for 14 days based on age and creatinine clearance; maximum dose was 140 mg twice daily); standard care	Mortality; venous thromboembolism; clinically-important bleeding; duration of hospital stay; ventilator-free days
Li 2020; ELACOI[53 101]	Published, NCT04252885	86	China	49.4	46.5	Inpatient; cardiovascular disease (2.3%); diabetes (2.3%); hypertension (10.5%)	Mild/moderate (100%)	0	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 7 to 14 days); umifenovir (200 mg three times daily for 7 to 14 days); standard care	Mortality; adverse effects leading to discontinuation; viral clearance; time to viral clearance

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Li 2020[89]*	Preprint, ChiCTR2000029638	96	China	53.6	46.8	Inpatient; cerebrovascular disease (5.3%); heart disease (7.5%); diabetes (9.6%); hypertension (19.2%); chronic obstructive pulmonary disease (1.1%); tuberculosis (3.2%)	Mild/moderate (87.2%); severe (12.8%)	25.5	Recombinant super-combinant interferon (12 MIU twice daily for 28 days); interferon alpha (5 MIU twice daily for 28 days)	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Li 2020[142]‡	Published, NCT04273763	18	China	52.0	77.8	Inpatient; diabetes (11.1%); hypertension (33.3%)	Mild/moderate (100%)	0	Bromhexine hydrochloride (32 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; time to symptom or clinical improvement
Lopes 2020[118]	Preprint, RBR-8jyhxh	38	Brazil	50.8	40.0	Inpatient; cardiovascular disease (40.0%); diabetes (31.4%); respiratory condition (14.3%)	Critical (0%)	2.6	Colchicine (0.5 mg three times daily for 5 days, then 0.5 mg twice daily for 5 days); placebo	Mortality; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay
Lou 2020[45 77]	Preprint, ChiCTR2000029544	30	China	52.5	72.4	Inpatient; cardiovascular disease (13.8%); diabetes (6.9%); hypertension (20.7%)	NR	0	Baloxavir marboxil (80 mg/day for up to 3 doses on days 1, 4, and 7); favipiravir (600 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Lyngbakken 2020*; NO COVID-19[96]	Published, NCT04316377	53	Norway	62.0	66.0	Inpatient; coronary heart disease (9.4%); diabetes (17.0%); hypertension (32.1%); chronic obstructive pulmonary disease or asthma (26.4%)	Mild/moderate (0%)	0	Hydroxychloroquine (400 mg twice daily for 7 days); standard care	NA
Mansour 2020[143]‡	Preprint, U1111-1250-1843	60	Brazil	51.6	53.3	Inpatient; diabetes (46.7%); hypertension (50.0%); asthma (3.3%)	Severe (100%)	NR	Icatibant (30 mg three times daily for 4 days); C1 esterase/kallikrein inhibitor (20 IU/kg on day 1 and 4); standard care	Mortality; duration of hospital stay; intensive care unit length of stay

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Mehboob 2020[144]‡	Preprint, NCT04468646	18	Pakistan	53.3	61.1	Inpatient; carotid artery bypass grafting (5.6%); ischemic heart disease (33.3%); diabetes (38.9%); hypertension (50.0%)	Mild/moderate (27.8%); severe (33.3%); critical (38.9%)	NR	Aprepitant (80 mg/day for 3-5 days); standard care	Mortality
Miller 2020‡; CARDEA[145]	Published, NCT04345614	30	USA	59.3	46.7	Inpatient; diabetes (40.0%); hypertension (46.7%)	Severe (86.7%); critical (13.3%)	13.3	Auxora (1.6 mg/kg given in 4 hours for 3 days); standard care	Mortality; mechanical ventilation; time to symptom or clinical improvement
Mitja 2020[91]†	Published, NCT04304053	353	Spain	41.6	31.4	Outpatient; cardiovascular disease (12.0%); respiratory condition (5.8%)	Mild/moderate (100%)	0	Hydroxychloroquine (400 mg/day for 7 days); standard care	Mortality; mechanical ventilation; admission to hospital; time to symptom or clinical improvement
Mitja 2020†; BCN PEP-CoV-2[101]	Preprint, NCT04304053	352	Spain	42.0	29.0	Outpatient; NR	Mild/moderate (100%)	0	Hydroxychloroquine (400 mg/day for 7 days), cobicistat-boosted darunavir (800 mg/150 mg/day for 7 days); standard care	Mortality; mechanical ventilation; admission to hospital; time to symptom or clinical improvement
Nojomi 2020[82]‡	Preprint, RCT20[illegible]2	100	Iran	56.4	60.0	Inpatient; coronary heart disease (9.0%); diabetes (28.0%); hypertension (39.0%); asthma (2.0%)	Mild/moderate (77.0%); severe (23.0%)	NR	Hydroxychloroquine (400 mg/ day for 1 day), lopinavir-ritonavir (400 mg twice daily for up to 14 days); hydroxychloroquine (400 mg twice daily for 7 to 14 days), umifenovir (200 mg three times daily for 7 to 14 days)	Mortality; mechanical ventilation; duration of hospital stay; time to symptom or clinical improvement

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Pan 2020; SOLIDARITY[76146]	Preprint, NCT04315948	5475	Albania, Argentina, Austria, Belgium, Brazil, Canada, Colombia, Egypt, Finland, France, Honduras, India, Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania, Luxembourg, Macedonia, Malaysia, Norway, Pakistan, Phillipines, Peru, Saudi Arabia, South Africa, Spain, Switzerland	NR	62.9	Inpatient; heart disease (20.9%); diabetes (25.2%); asthma (5.1%); chronic lung disease (5.4%)	NR	8.9	Remdesivir (100 mg/day for 10 days); standard care	Mortality; mechanical ventilation
		1854			59.9	Inpatient; heart disease (20.9%); diabetes (21.8%); asthma (4.7%); chronic lung disease (6.9%)		9.0	Hydroxychloroquine (200 mg twice daily for 10 days); standard care	Mortality; mechanical ventilation
		2791			59.7	Inpatient; heart disease (20.9%); diabetes (24.0%); asthma (4.4%); chronic lung disease (6.6%)		8.2	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation
		4127			63.0	Inpatient; heart disease (21.5%); diabetes (25.0%); asthma (4.2%); chronic lung disease (5.4%)		6.6	Interferon beta-1a (44 µg three times daily for 6 days; patients on high-flow oxygen, ventilators, or ECMO were given 10 µg/day for 6 days); standard care	Mortality; mechanical ventilation
Rahmani 2020[147]	Published, RCT20002800349N27	80	Iran	60.5	59.1	Inpatient; ischemic heart disease (30.0%); diabetes (31.8%); hypertension (56.1%); asthma (4.6%); chronic obstructive pulmonary disease (4.6%)	Severe (100%)	1.5	Interferon beta-1b (250 µg every other day for 14 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; intensive care unit length of stay; time to symptom or clinical improvement
Ren 2020‡[148]	Published, ChiCTR2000029853	20	China	52.0	60.0	Inpatient; cardiovascular disease (5.0%); diabetes (5.0%); hypertension (5.0%)	Mild/moderate (100%)	0	Azvudine (5 mg/day until discharge); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to viral clearance
Rosas 2020; COVACTA[81]	Preprint, NCT04320615	452	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	60.8	69.9	Inpatient; intensive care (56.4%); cardiovascular impairment (28.1%); diabetes (38.1%); hypertension (62.1%); chronic lung disease (16.2%)	Severe (100%)	37.7	Tocilizumab (8 mg/kg, max 800 mg up to two times in 24 hours); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; ventilator-free days; time to symptom or clinical improvement

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Sadeghi 2020[149]‡	Published, RCT20200428046294N2	70	Iran	58.0	51.5	Inpatient; heart failure (15.2%); diabetes (42.4%); hypertension (34.9%); asthma (3.0%); chronic pulmonary disease (22.7%)	Mild/moderate (0%)	0	Sofosbuvir-dedatasvir (400 mg and 60 mg once daily for 14 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; time to symptom or clinical improvement
Salehzadeh 2020[83]	Preprint, RCT20200418047126N1	100	Iran	56.1	41.0	Inpatient; ischemic heart disease (15.0%); diabetes (11.0%); hypertension (11.0%); chronic obstructive pulmonary disease (4.0%)	NR	NR	Colchicine (1 mg/day for 6 days); placebo	Mortality; duration of hospital stay
Sekhavati 2020[119]	Published	111	Iran	57.1	46.0	Inpatient	NR	NR	Azithromycin (500 mg/day for 5 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay
Silva Borba 2020*; CloroCOVID-19[35150]	Published, NCT04323527	81	Brazil	51.1	75.3	Inpatient; intensive care (45.7%); cardiovascular disease (9.1%); diabetes (25.5%); hypertension (45.5%); asthma (7.4%); tuberculosis (3.6%)	Severe (100%)	NR	Chloroquine (600 mg twice daily for 10 days); chloroquine (450 mg/day for 5 days)	Mortality
Skipper 2020[103]	Published, NCT04308668	491	USA, Canada	40.0	45.8	Outpatient; cardiovascular disease (1.2%); diabetes (3.9%); hypertension (11.0%); asthma (10.4%); chronic lung disease (0.4%)	Mild/moderate (100%)	0	Hydroxychloroquine (600 mg/day for 5 days); placebo	Mortality; admission to hospital
Spinner 2020[120]	Published, NCT04292730	596	France, Germany, Hong Kong, Italy, Netherlands, Korea, Singapore, Spain, Switzerland, Taiwan, UK, USA	57.0	61.1	Inpatient; cardiovascular disease (56.3%); diabetes (39.7%); hypertension (42.5%); asthma (13.9%)	Mild/moderate (100%)	0.9	Remdesivir (100 mg/day for 10 days); remdesivir (100 mg/day for 5 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; time to symptom or clinical improvement
Sterne 2020; DEXA-COVID 19[122]	Data from meta-analysis, NCT04325061	19	Spain	60.7	68.4	Inpatient; NR	Critical (100%)	100	Dexamethasone (20 mg/day for 5 days, then 10 mg/day for 5 days); standard care	Mortality
Sterne 2020; COVID STEROID[122]	Data from meta-analysis, NCT04348305	29	Denmark	59.4	79.3	Inpatient; NR	Critical (100%)	51.7	Hydrocortisone (200 mg/day for 7 days); placebo	Mortality

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Sterne 2020; Steroids-SARI[122]	Data from meta-analysis, NCT04244591	47	China	64.6	74.5	Inpatient; NR	Critical (100%)	57.5	Methylprednisolone (40 mg twice daily for 5 days); standard care	Mortality
Sun 2020[80]‡	Published	66	China	49.5	66.7	Inpatient; cardiovascular disease (1.5%); diabetes (9.1%); hypertension (18.2%)	Mild/moderate (100%)	NR	Diammonium glycyrrhizinate (150 mg three times daily)	Mortality
Tang 2020[47 151]	Published, ChiCTR2000029868	150	China	46.1	55.0	Inpatient; diabetes (14.0%); hypertension (6.0%)	Mild/moderate (99.0%); severe (1.0%)	NR	Hydroxychloroquine (800 mg/day for 14 to 21 days); standard care	Mortality; adverse effects leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Tomazini 2020; CoDEX[121]	Published, NCT04327401	299	Brazil	61.4	62.5	Inpatient; intensive care (100%); heart failure (7.7%); diabetes (42.1%); hypertension (66.2%)	Critical (100%)	100	Dexamethasone (20 mg/day for 5 days, then 10 mg/day for 5 days); standard care	Mortality; mechanical ventilation; ventilator-free days; duration of ventilation
Ulrich 2020; TEACH[123]	Published, NCT04369742	128	USA	66.2	59.4	Inpatient; non-hypertensive cardiovascular disease (25.6%); diabetes (32.0%); hypertension (57.8%); asthma (15.6%); chronic obstructive pulmonary disease (7.0%)	Mild/moderate (0%)	1.56	Hydroxychloroquine (200 mg twice daily for 5 days); placebo	Mortality; mechanical ventilation; viral clearance; duration of hospital stay
Vlaar 2020‡; PANAMO[152 153]	Published, NCT04333420	30	Netherlands	60.5	73.3	Inpatient; intensive care (60.0%); diabetes (26.7%); hypertension (30.0%)	Severe (100%)	60.0	IFX-1 (800 mg/day for up to 7 times within 22 days); standard care	Mortality; adverse events leading to discontinuation
Wang 2020[33]	Published, NCT04257656	237	China	65.0	59.3	Inpatient; cardiovascular disease (7.2%); diabetes (23.7%); hypertension (43.2%)	Severe (100%)	16.1	Remdesivir (100 mg/day for 10 days); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement
Wang 2020[93]*	Published	20	China	47.0	45.0	Inpatient; NR	Mild/moderate (100%)	NR	Vitamin C (10 g/60 kg twice daily); standard care	NA
Wang 2020[95]*	Published	60	China	NR	38.3	Inpatient; NR	Mild/moderate (100%)	NR	Lopinavir-ritonavir (2 tablets twice daily); standard care	NA

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Wang 2020[154]	Preprint, ChiCTR2000029765	65	China	63.0	50.8	Inpatient; diabetes (15.4%); hypertension (30.8%)	Mild/moderate (56.9%); severe (43.1%)	15.4	Tocilizumab (400 mg for up to two times in 24 hours); standard care	Duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Wang 2020[155]‡	Published, ChiCTR2000030058	50	China	55.8	45.8	Inpatient; coronary artery disease (2.1%); diabetes (4.2%); hypertension (25.0%); chronic obstructive pulmonary disease (4.2%)	Mild/moderate (81.25%); severe (14.6%); critical (4.2%)	NR	Leflunomide (50 mg twice daily for 1.5 days, then 20 mg/day for 8 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to viral clearance
Wu 2020[156]‡	Published, ChiCTR2000030001	52	China	58.0	50.0	Inpatient; cardiovascular disease (15.4%); cerebrovascular disease (7.7%); diabetes (15.4%); hypertension (28.8%); chronic obstructive pulmonary disease (5.8%)	NR	NR	Triazavirin (250 mg three times daily for 7 days in mildly ill patients, 250 mg four times daily for 7 days in severe or critically ill patients); placebo	Mortality; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Yethindra 2020[124]	Published	30	Kyrgyzstan	36.5	60.0	Inpatient; cardiovascular disease (0%)	Mild/moderate (100%)	NR	Umifenovir (200 mg three times daily for 1 to 5 days); standard care	Mortality; time to symptom or clinical improvement
Yuan 2020[94]*	Preprint, ChiCTR2000029431	21	China	61.0	42.9	Inpatient; NR	Mild/moderate (100%)	NR	99mTC-methylene diphosphate (5 ml/day for 7 days); standard care	NA
Zhang 2020[79]‡	Preprint, NCT04264533	56	China	67.4	66.7	Inpatient; intensive care (100%); coronary heart disease (22.2%); diabetes (29.6%); hypertension (44.4%); chronic lung disease (5.6%)	Mild/moderate (0%)	100	Vitamin C (12 g/50 ml given at 12 ml/hour for 7 days); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; ventilator-free days; duration of ventilation
Zhao 2020[87]‡	Published, NCT04310228	26	China	73.5	53.9	Inpatient; coronary artery disease (23.1%); diabetes (11.5%); hypertension (42.3%)	Mild/moderate (46.2%); severe (50.0%); critical (3.9%)	3.9	Favipiravir (600 mg twice daily for 7 days); tocilizumab (4-8 mg/kg in 100 ml for 1 hr); favipiravir (600 mg twice daily for 7 days), tocilizumab (4-8 mg/kg in 100 ml for 1 hr)	Mortality; mechanical ventilation

Table 1 | Study characteristics *(Continued)*

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Zheng 2020‡[49 157]	Published, ChiCTR2000029496	89	China	46.7	47.2	Inpatient; chronic bronchitis (2.0%)	Mild/moderate (94.4%); severe (5.6%)	NR	Novaferon (20 µg twice daily for 7 to 10 days); novaferon, lopinavir-ritonavir (400 mg and 100 mg twice daily for 7 to 10 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 7 to 10 days)	Adverse events leading to discontinuation; viral clearance; time to viral clearance
Zhong 2020‡[158]	Preprint, ChiCTR2000029851	17	China	63.0	76.5	Inpatient; cardiovascular disease (5.9%); diabetes (23.5%); hypertension (47.1%)	Critical (100%)	94.1	Alpha lipoic acid (1200 mg/day for 7 days); placebo	Mortality; adverse events leading to discontinuation
Zhou 2020‡[159]	Published	104	China	52.1	57.7	Inpatient	Mild/moderate (100%)	NR	Diammonium glycyrrhizinate (150 mg three times daily for 14 days), lopinavir-ritonavir (500 mg twice daily for 14 days); lopinavir-ritonavir (500 mg twice daily for 14 days)	Adverse events leading to discontinuation

NR=not reported

NA=not applicable

* Not eligible to be included in the network meta-analysis.

† Not included in the current iteration of the network meta-analysis but will be included in a future iteration.

‡ This study was part of a treatment node with less than 100 participants or less than 20 events.

Table 2 describes the randomised controlled trials that were identified after the data analysis and that will be included in the next update.

Table 2 | Randomised trials identified after data analysis, which will be included in the next update

Study	Publication status, registration No	No of participants	Treatments
Hermine 2020[160]	Published, NCT04331808	131	Tocilizumab; standard care
Salvarani 2020[161]	Published, NCT04346355	126	Tocilizumab; standard care
Stone 2020[162]	Published, NCT04356937	243	Tocilizumab; placebo
Dubée 2020[163]†	Preprint, NCT04325893	250	Hydroxychloroquine; placebo
Valizadeh 2020[164]	Published, NR	40	Nano-curcumin; placebo
Salama 2020[165]	Preprint, NCT04372186	377	Tocilizumab; placebo
Rocco 2020[166]	Preprint, NCT04552483	392	Nitazoxanide; placebo
Axfors 2020[84]*†	Preprint, NCT04329923	30	Hydroxychloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04345289	2	Hydroxychloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04335552	11	Hydroxychloroquine, azithromycin; hydroxychloroquine; azithromycin; standard care
Axfors 2020[84]*†	Preprint, NL8490	12	Hydroxychloroquine; chloroquine; standard care
Axfors 2020[84]*†	Preprint, NCT04342650	152	Chloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04323527	82	Chloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04315896	152	Hydroxychloroquine; placebo
Axfors 2020[84]*†	Preprint, ChiCTR2000031204	35	Chloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04333654	8	Hydroxychloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04338698	373	Hydroxychloroquine, azithromycin, oseltamivir; hydroxychloroquine, azithromycin; hydroxychloroquine, oseltamivir; azithromycin, oseltamivir; azithromycin; oseltamivir
Axfors 2020[84]*†	Preprint, NCT04345692	16	Hydroxychloroquine; standard care
Axfors 2020[84]*†	Preprint, NCT02735707	142	Hydroxychloroquine; standard care
Axfors 2020[84]*†	Preprint, NCT04342221	27	Hydroxychloroquine; placebo
Axfors 2020[84]*†	Preprint, NCT04340544	16	Hydroxychloroquine; placebo
Ghaderkhani 2020[88]	Preprint, IR.TUMS.VCR.REC.1399.204	53	Arbidol; standard care
Padmanabhan 2020[102]	Preprint, CTRI/2020/05/025013	60	Bacille Calmette-Guérin vaccine; placebo
Self 2020[54]†	Published, NCT04332991	479	Hydroxychloroquine; placebo
Monk 2020[55]	Published, NCT04385095	101	Inhaled nebulised interferon beta-1a (SNG001); placebo
Lenze 2020[56]	Published, NCT04342663	152	Fluvoxamine; placebo
Khamis 2020[57]	Published, NR	89	Inhaled interferon beta-1b, favipiravir; standard care
Brown 2020[58]	Published, NCT04329832	85	Hydroxychloroquine; azithromycin
Feld 2020[59]	Preprint, NCT04354259	60	Peginterferon-lambda; placebo
Cadegiani 2020[60]	Preprint, NCT04446429	130	Dutasteride; placebo
Murai 2020[61]	Preprint, NCT04449718	240	Vitamin D; placebo
Rastogi 2020[62]	Published, NCT04459247	40	Vitamin D; placebo
Jagannathan 2020[63]	Preprint, NCT04331899	120	Peginterferon-lambda-1a; placebo
Omrani 2020[64]	Published, NCT04349592	456	Hydroxychloroquine, azithromycin; hydroxychloroquine; placebo
Krolewiecki 2020[65]	Preprint, NCT004381884	45	Ivermectin; standard care
Elgazzar 2020[66]	Preprint, NR	400	Ivermectin; hydroxychloroquine
Hassan 2020[67]	Preprint, NR	105	Zinc; standard care
Husain 2020[68]	Preprint, NR	64	Doxycycline, oral methyl prednisolone, topical nasal steroid (mometasone); placebo, olfactory training
Niaee 2020[69]	Preprint, IRCT20200408046987N1	180	Ivermectin; placebo
Yakoot 2020[70]	Preprint, DRKS00022203	89	Sofosbuvir, daclatasvir; standard care
Ruzhentsova 2020[71]	Preprint, NCT04501783	168	Favipiravir; standard care
Udwadia 2020[72]	Published, CTRI/2020/05/025114	150	Favipiravir; standard care
Kumar 2020[73]	Preprint, CTRI/2020/05/024959	30	Itolizumab; standard care
Abd-Elsalam 2020[74]	Published, NCT04447534	191	Zinc; standard care
Maldonado 2020[75]	Published, NR	38	Pentoxifylline; standard care

Table 2 | Randomised trials identified after data analysis, which will be included in the next update *(Continued)*

Study	Publication status, registration No	No of participants	Treatments

* Unpublished data from a meta-analysis preprint.

† Part of supplemental analysis evaluating hydroxychloroquine for mortality.

Of the randomised controlled trials included in the analyses, seven did not have publicly accessible protocols or registrations.[80 93 95 119 124 134 159] Of the trials with publicly accessible protocols or registrations, 55 reported results for one or more of our outcomes of interest that were not prespecified in protocols or registrations. No other discrepancies between the reporting of our outcomes of interest in trial reports and protocols or registrations were noted. One trial did not report outcomes in the groups as randomised; the authors shared outcome data with us in the groups as randomised.[51]

Thirteen studies were initially posted as preprints and subsequently published after peer review.[35 47 74 96 100 -102 104 114 115 137 157 167] The supplementary material presents the differences between study preprint and peer reviewed publications. Eight studies had discrepancies in outcome reporting between the preprint and peer-reviewed publication. Three studies had discrepancies with patient baseline characteristics. No substantiative differences were found for the other four studies.

All analyses reached convergence based on trace plots and a Brooks-Gelman-Rubin statistic less than 1.05, except comparisons including umifenovir for mortality and tocilizumab for adverse events leading to discontinuation because no patients randomised to either of these drugs died.

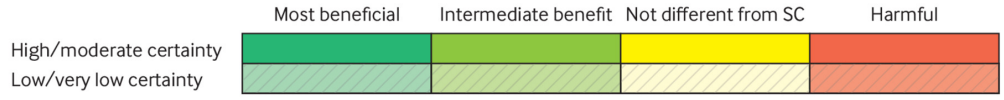
Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies for each outcome. Nine studies were judged at low risk of bias in all domains.[33 35 41 86 103 109 118 122 131] All other studies had probably high or high risk of bias in at least one of the domains.

Effects of the interventions

The supplementary material presents the network plots depicting the interventions included in the network meta-analysis of each outcome. Figure 2 presents a summary of the effects of the interventions on the outcomes. The supplementary file also 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 network meta-analyses.

	Mortality	Mechanical ventilation	Adverse events	Admission to hospital	Viral clearance at 7 days	Duration of hospital stay	ICU length of stay	Duration of mechanical ventilation	Time to symptom resolution	Time to viral clearance	Ventilator free days
Standard care*	130 per 1000	116 per 1000	15 per 1000	43 per 1000	484 per 1000	13 days	13 days	15 days	11 days	10 days	11 days
Azithromycin	6 (-40 to 62)	1 (-60 to 90)				0.4 (-2.9 to 3.9)					-1.7 (-5.1 to 1.8)
Colchicine	-106 (-129 to 42)					-1.6 (-2.8 to -0.3)**					
Corticosteroids	-17 (-34 to 1)	-29 (-54 to 1)			5 (-426 to 458)	-0.9 (-3.4 to 1.7)	-3.8 (-5.9 to -1.8)	-1.4 (-3.4 to 0.62)			2.6 (0.2 to 5.0)
Favipiravir	63 (-113 to 773)				81 (-301 to 399)						
Hydroxy-chloroquine	11 (-11 to 38)	20 (-18 to 76)	16 (-11 to 192)**	-26 (-38 to 12)**	18 (-293 to 334)	0.1 (-1.9 to 2.0)			-2.0 (-4.0 to 0.1)	-0.7 (-4.3 to 4.8)**	
Hydroxy-chloroquine + azithromycin	-48 (-103 to 66)	58 (-32 to 216)				0.6 (-1.2 to 2.4)**					
Interferon beta	2 (-35 to 35)	-13 (-60 to 45)									
Interferon gamma					436 (-215 to 516)						
Interferon kappa+ treefoil factor 2					290 (-334 to 503)						
Lopinavir-ritonavir	-12 (-31 to 10)	10 (-31 to 60)			-235 (-449 to 164)	-0.4 (-1.7 to 0.6)**			-1.0 (-4.1 to 3.2)		
Nitazoxanide											
rhG-CSF	-102 (-124 to -41)	-96 (-108 to -68)				-0.7 (-2.3 to 1.0)**			-0.8 (-4.5 to 4.6)		
Remdesivir	-12 (-35 to 14)	-33 (-65 to 1)	0 (-9 to 40)		14 (-429 to 460)	-0.2 (-1.9 to 1.2)**		-1.3 (-4.1 to 1.5)	-2.0 (-4.2 to 0.9)		
Tocilizumab	5 (-46 to 81)	-35 (-80 to 54)	-8 (-15 to 300)**			-2.5 (-6.9 to 1.8)	-4.5 (-13.8 to 4.9)		-1.8 (-5.0 to 3.4)		4.7 (-4.2 to 13.9)
Umifenovir	-130 (-130 to 870)										



*The expected risk of each outcome with standard care is reported in the grey row. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care
** The best estimate of effect was obtained from direct evidence
Empty cells: there was no evidence for the specific intervention
rSG-CSF: Recombinant human granulocyte colony-stimulating factor

Fig 2 | Summary of effects compared with standard care

Mortality

Seventy two randomised controlled trials including 40 083 participants[3233537-39434447515276798385-87899097-128130-133136137141-145147-149152156158] reported mortality. Thirty eight trials with 37 730 participants[32 33 37 39 47 51 52 76 77 81 83 85 97 -101 103 -110 112 114 115 117 -124 139 147] met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network-meta analysis. The treatment nodes included were azithromycin, colchicine, corticosteroids, favipiravir, hydroxychloroquine, hydroxychloroquine plus azithromycin, interferon beta, lopinavir-ritonavir, remdesivir, rhG-CSF, tocilizumab, umifenovir, and standard care. Random effects network meta-analysis showed that corticosteroids (odds ratio 0.85, 95% credible interval 0.71 to 1.01; risk difference 17 fewer per 1000, 95% credible interval 34 fewer to 1 more; moderate certainty) probably reduce deaths compared to standard care (fig 2). Evidence was less certain for remdesivir (odds ratio 0.90, 0.70 to 1.12; risk difference 12 fewer per 1000, 35 fewer to 14 more; low certainty) and lopinavir-ritonavir (odds ratio 0.90, 0.73 to 1.09; risk difference 12 fewer per 1000, 31 fewer to 10 more; low certainty). Patients randomised to hydroxychloroquine (odds ratio 1.10, 0.90 to 1.35; risk difference 11 more per 1000, 11 fewer to 38 more; low certainty of no benefit) and interferon beta (odds ratio 1.02, 0.70 to 1.32; risk difference 2 more per 1000, 35 fewer to 35 more; low certainty) did not have a lower risk of death than those randomised to standard care. 95% credible intervals included both substantial benefit and harm for azithromycin,

colchicine, favipiravir, hydroxychloroquine plus azithromycin, and tocilizumab (all very low certainty). Very low certainty evidence suggests that rhG-CSF may reduce risk of death compared to standard care. Fixed effects network meta-analysis led to similar results for all treatments compared with standard care: corticosteroids (odds ratio 0.86, 0.77 to 0.95), hydroxychloroquine (odds ratio 1.08, 0.96 to 1.22), interferon beta (odds ratio 1.08, 0.89 to 1.30), lopinavir-ritonavir (odds ratio 0.89, 0.80 to 1.00) and remdesivir (odds ratio 0.92, 0.80 to 1.07).

Mortality data from several small trials on hydroxychloroquine were published in a meta-analysis after the analysis had been completed. To optimally inform the linked WHO guideline panel that considered hydroxychloroquine, we updated the analysis for mortality on 11 November 2020. There were no important differences (supplementary material).

Mechanical ventilation

Forty randomised controlled trials including 33 727 participants[32 33 37 38 43 44 51 76 77 79 81 82 86 87 90 97 100 104 -110 112 114 -117 119 -121 123 125 127 131 133 145 147 149] reported mechanical ventilation. Twenty-one trials with 32 162 participants[32 33 37 51 76 81 97 100 104 106 -110 112 114 115 117 119 -121 123 147] met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis. The treatment nodes included were azithromycin, corticosteroids, hydroxychloroquine, hydroxychloroquine plus azithromycin, interferon beta, lopinavir-ritonavir, remdesivir, rhG-CSF, and standard care (fig 2). Random effects network meta-analysis showed that, compared with standard care, corticosteroids probably reduce risk of mechanical ventilation (odds ratio 0.72, 0.50 to 1.01; risk difference 29 fewer per 1000, 54 fewer to 1 fewer; moderate certainty for risk of bias). Certainty was lower for remdesivir (odds ratio 0.68, 0.41 to 1.00; risk difference 33 fewer per 1000, 65 fewer to 1 more; low certainty) and hydroxychloroquine (odds ratio 1.20, 0.83 to 1.81; risk difference 20 more per 1000, 18 fewer to 76 more; low certainty for risk of bias and imprecision). Evidence for was less certain for azithromycin, hydroxychloroquine plus azithromycin, interferon beta, lopinavir-ritonavir, and tocilizumab, and rhG-CSF (all very low certainty). Fixed effects network meta-analysis led to similar results for all treatments compared with standard care: corticosteroids (odds ratio 0.73, 0.61 to 0.86), remdesivir (odds ratio 0.88, 0.76 to 1.03), hydroxychloroquine (odds ratio 1.16, 0.97 to 1.38), azithromycin (odds ratio 1.13, 0.79 to 1.64), hydroxychloroquine plus azithromycin (odds ratio 1.59, 0.86 to 2.89), interferon beta (odds ratio 0.97, 0.80 to 1.18), and lopinavir-ritonavir (odds ratio 1.16, 0.98 to 1.36).

Adverse events leading to discontinuation

Thirty two randomised controlled trials including 4698 participants[32 33 43 44 47 52 79 81 89 98 101 104 105 113 116 118 -120 125 128 131 -133 137 142 148 152 156 -159] reported adverse effects leading to discontinuation of the study drug. Six trials with 1946 participants[32 47 52 81 93 98] met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis. The treatment nodes included were hydroxychloroquine, remdesivir, tocilizumab, and standard care. Moderate certainty evidence showed that remdesivir did not result in a substantial increase in adverse effects leading to drug discontinuation compared with standard care (odds ratio 1.00, 0.37 to 3.83; risk difference 0 more per 1000, 9 fewer to 40 more). Certainty in evidence for hydroxychloroquine and tocilizumab was very low (fig 2).

Viral clearance at 7 days (3 days either way)

Twenty-four randomised controlled trials including 1857 participants[33 37 47 52 77 78 85 89 90 98 101 108 111 113 116 117 123 134 136 137 148 155 -157] measured viral clearance with polymerase chain reaction cut-off points. Fourteen trials with 1186 participants[33 38 47 52 77 78 85 98 101 111 113 116 117 123] met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis. The treatment nodes included were corticosteroids, favipiravir, hydroxychloroquine, interferon gamma, interferon kappa plus trefoil factor 2, lopinavir-ritonavir, remdesivir, and standard care. We did not find any convincing evidence that any of the interventions increased the rate of viral clearance (fig 2). The certainty of the evidence was low for remdesivir compared with standard care, and very low for all other comparisons.

Admission to hospital

Three randomised controlled trials including 603 participants[103 130 132] reported admission to hospital in patients who were outpatients at baseline. One study of hydroxychloroquine versus placebo was included.[103] There were too few events to make any inferences (odds ratio 0.39, 0.12 to 1.28; risk difference 26 fewer per 1000, 38 fewer to 12 more; low certainty) (fig 2).

Venous thromboembolism

One study including 20 participants[141] reported venous thromboembolism in patients who received an anticoagulant as the active drug. No treatment node contained information on at least 100 patients, therefore no analyses were conducted for this outcome.

Clinically-important bleeding

One study including 20 participants[141] reported clinically important bleeding in patients who received an anticoagulant as the active drug. No treatment node contained information on at least 100 patients, therefore no analyses were conducted for this outcome.

Duration of hospital stay

Thirty-nine randomised controlled trials including 22 807 participants[33 37 38 44 52 78 79 81 -83 85 89 97 100 104 -108 112 -115 117 -120 123 125 127 131 133 137 141 143 147 -149 154 155] reported duration of hospital stay. Twenty trials with 21 440 participants[32 33 37 52 78 81 83 97 100 105 106 108 112 114 115 117 -121 123 154] meeting the threshold of analysing treatments with a minimum of 100 patients or 20 events were included in the network meta-analysis. The treatment nodes included were azithromycin, colchicine, corticosteroids, hydroxychloroquine, hydroxychloroquine plus azithromycin, lopinavir-ritonavir, remdesivir, rhG-CSF, tocilizumab, and standard care. Compared with standard care, duration of hospitalisation was shorter in patients who received colchicine (mean difference −1.57 days, −2.78 to −0.32; low certainty). There was no evidence that azithromycin (very low certainty), corticosteroids (very low certainty), hydroxychloroquine (very low certainty), hydroxychloroquine plus azithromycin (low certainty), lopinavir-ritonavir (low certainty), tocilizumab (very low certainty), or remdesivir (low certainty), rhG-CSF (low certainty) impact length of stay (fig 2).

ICU length of stay

Nine randomised controlled trials including 890 participants reported length of ICU stay.[79 81 104 107 118 119 125 131 147] Two studies randomised at least 100 patients to receive corticosteroids.[81 107] Compared with standard care, length of ICU stay was shorter in patients who received corticosteroids (mean difference −3.83 days, −5.88 to −1.78; low certainty) (fig 2).

Duration of mechanical ventilation

Six randomised controlled trials including 857 participants[32 33 37 79 104 121] reported duration of mechanical ventilation. Three studies with 739 participants[32 33 121] meeting the threshold of analysing treatments with a minimum of 100 patients or twenty events were included in the network meta-analysis. The treatment nodes included corticosteroids, remdesivir, and standard care. There was no evidence that corticosteroids (mean difference −1.41 days, −3.44 to 0.62; low certainty) and remdesivir (mean difference −1.28 days, −4.06 to 1.47; low certainty) reduce duration of mechanical ventilation (fig 2).

Ventilator-free days

Five randomised controlled trials including 1036 participants[79 81 112 121 141] reported ventilator-free days. Three studies with 962 participants meeting the threshold of analysing treatments with a minimum of 100 patients were included in the network-meta analysis.[81 112 121] The treatment nodes included were azithromycin, corticosteroids, tocilizumab, and standard care. Compared to standard care, corticosteroids (mean difference 2.62 days, 0.24 to 4.97; moderate certainty) may increase ventilator-free days. There was no evidence that tocilizumab (low certainty) and azithromycin (very low certainty) increase ventilator-free days (fig 2).

Time to symptom resolution

Thirty two randomised controlled trials including 4424 participants[32 33 37 39 41 44 47 52 77 78 81 82 89 104 106 108 110 116 120 124 126 136 137 140 142 145 147 149 154 156] reported time to symptom resolution. Thirteen trials including 3285 participants[32 33 37 41 47 52 78 81 98 106 108 120 154] meeting the threshold of analysing treatments with a minimum of 100 patients were analysed. The treatment nodes included were hydroxychloroquine, lopinavir-ritonavir, remdesivir, rhG-CSF, tocilizumab, and standard care. There was no evidence that remdesivir (moderate certainty), hydroxychloroquine (low certainty), and lopinavir-ritonavir (low certainty) led to shorter symptom duration than in patients who received standard care (fig 2).

Time to viral clearance

Twenty two randomised controlled trials including 1459 participants[38 44 52 77 78 85 89 98 99 101 106 111 113 129 136 137 148 151 154 -157] reported time to viral clearance. At least 100 patients across five trials[52 98 99 106 151] received hydroxychloroquine and standard care. The certainty of the evidence was very low (fig 2).

Subgroups

Remdesivir have different effects in patients by severity of disease (ratio of odds ratios (ROR) 1.80, CI 1.27 2.59, probability of ROR≤1 = 0.0003). The effects of remdesivir on mortality the three subgroups are: non-severe disease (OR 0.71, 0.33 to 1.46), severe disease (OR 0.73, 0.49 to 1.03), critical disease (OR 1.30, 0.89 to 1.97). Using established criteria, we felt that this subgroup effect had low-to-moderate credibility (supplementary material). No other subgroup was notable for any subgroup effects.

Discussion

This living systematic review and network meta-analysis provides a comprehensive overview of the evidence for drug treatments of covid-19 up to 21 October 2020 and a comprehensive list of drug trials to 3 December 2020. The certainty of the evidence for most of the comparisons was very low. Corticosteroids probably reduce the risk of death and mechanical ventilation, and increase ventilator-free days, results driven almost entirely by the RECOVERY trial.[50]

Whether or not remdesivir has any effect on mortality is uncertain. If one believes the subgroup effect, remdesivir may reduce or have no effect mortality in patients with non-critical disease and may increase or have no effect on mortality in patients with critical illness. The subgroup effect however has only moderate credibility and whether or not remdesivir reduces or increases mortality in any subgroup is uncertain. Direct evidence from randomised controlled trials in patients with covid-19 has so far provided little definitive evidence about adverse effects for most interventions, apart from remdesivir which probably has low risk for adverse effects leading to drug discontinuation.

No other drug was found to have an impact on any patient with at least moderate certainty for any other outcome. Based on three small trials, colchicine may reduce duration of hospitalisation (low certainty) and based on a single small trial, rhG-CSF might reduce mortality and mechanical ventilation in patients with lymphopenia (low certainty).

Compared with the second iteration, there are several important updates (box 2). We now have evidence from several large scale international trials on remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon beta. Unfortunately, the trials showed that none of these interventions had a meaningful effect on any patient important outcomes.

Box 2: Summary of changes since last iteration

- Fifty additional randomised trials (25 081 participants)
- Azithromycin, colchicine, interferon beta, interferon gamma, interferon kappa plus trefoil factor 2, rhG-CSF, tocilizumab are new interventions included in the analyses, but certainty is low or very low for the effects of these interventions
- We changed the previous analyses that were performed in fixed effects to random effects. Moving from fixed to random effects models shifted the 95% CIs to encompass the null effect of glucocorticoids and remdesivir for mortality and mechanical ventilation.
- New evidence suggests that remdesivir may not reduce mortality (low certainty) or time to symptom resolution (moderate certainty). Previously, the evidence suggested a benefit on these outcomes with remdesivir.
- New evidence that glucocorticoids probably reduce length of ICU stay (low certainty) and increase ventilator-free days (moderate certainty)
- Evidence for other interventions is similar to the previous version

Strengths and limitations of this review

Our search strategy and eligibility criteria were comprehensive, without restrictions on language of publication or publication status. To ensure expertise in all areas, our team is composed of clinical and methods experts who have undergone training and calibration exercises for all stages of the review process. To minimise problems with counterintuitive results, we anticipated challenges that arise in network meta-analysis when data are sparse.[168] 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 for which at least 100 people were randomised or for which there were at least 20 events. 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 data is that only nine studies were judged to be at low risk of bias.[33 35 41 86 103 109 118 122 131] The primary limitation of the evidence is lack of blinding, which might introduce bias through differences in co-interventions between randomisation

groups. We chose to consider the treatment arms that did not receive an active experimental drug (ie, placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than groups randomised to receive a placebo. 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.[169] Many of the data also had reporting concerns. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies. This led the team to propose a hierarchy for the outcome mechanical ventilation, as described in the methods.

The living nature of our systematic review and network meta-analysis 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 reduce this risk. Industry sponsored trials such as those for remdesivir and other patented drugs could be particularly at risk of publication bias, and positive results for these drugs might require more cautious interpretation than generic drugs tested in randomised controlled trials independent of industry influence. However, the inclusion of preprints in our network meta-analysis might introduce bias from simple errors and the 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. So far, there did not appear to be any major differences between preprints and peer-reviewed manuscripts.

It is possible that we did not detect important subgroup modification.[170] For example, the RECOVERY trial suggested that patients with more severe disease might obtain a greater benefit from dexamethasone than patients with less severe disease.[50] However, this subgroup effect only has moderate credibility. Users should carefully consider the characteristics of the patients included in the trials for each intervention.

Our living systematic review and network meta-analysis will continue to inform the development of the WHO living guidelines and *BMJ* Rapid Recommendations.[6 7] An important difference in the methods for assessing the certainty of the evidence does, however, exist between the two. In this living systematic review and network meta-analysis, we use a minimally contextualised approach for rating the certainty of the evidence, whereas the guideline panels use a fully contextualised approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.[25] The contextualisation explains 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 network meta-analysis and in the associated guidelines for remdesivir.[7]

To date, we are aware of two other similar efforts to ours.[171 172] We decided to proceed independently to ensure that the results fully inform clinical decision making for the associated living guidance.[6] We also include a more comprehensive search for the evidence and several differences in analytical 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 living systematic review and network meta-analysis. We from several new randomised trials that examined tocilizumab were published after our statistical analysis and trials on all drugs are being published at an increasingly faster rate. 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 living systematic review and network meta-analysis will also be accompanied by an interactive infographic and a website for users to access the most updated results in a user-friendly format (magicapp.org).

Conclusions

Evidence from this living systematic review and network meta-analysis suggests that corticosteroids probably reduce mortality, mechanical ventilation, and ventilator-free days in patients with severe covid-19. Whether or not remdesivir has any impact on any outcome remains uncertain. Hydroxychloroquine, lopinavir/ritonavir, and interferon beta may not reduce mortality or mechanical ventilation, and they seem unlikely to have any other benefits. The effects of most drug interventions are currently highly uncertain, and no definitive evidence exists that other interventions result in important benefits and harms for any outcomes.

What is already known on this topic

- Despite huge efforts to identify effective drug interventions for coronavirus disease 2019 (covid-19), evidence for effective treatment remains limited

What this study adds

- This living systematic review and network meta-analysis provides a comprehensive overview and assessment of the evidence published as of 21 October 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, mechanical ventilation. No other drug has compelling evidence of benefit.

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RACS 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.

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