



Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review

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ABSTRACT

OBJECTIVE To assess the trustworthiness (ie, complete and consistent reporting of key methods and results between preprint and published trial reports) and impact (ie, effects of preprints on meta-analytic estimates and the certainty of evidence) of preprint trial reports during the covid-19 pandemic.

DESIGN Retrospective review.

DATA SOURCES World Health Organization covid-19 database and the Living Overview of the Evidence (L-OVE) covid-19 platform by the Epistemonikos Foundation (up to 3 August 2021).

MAIN OUTCOME MEASURES Comparison of characteristics of covid-19 trials with and without preprints, estimates of time to publication of covid-19 preprints, and description of differences in reporting of key methods and results between preprints and their later publications. For the effects of eight treatments on mortality and mechanical

ventilation, the study comprised meta-analyses including preprints and excluding preprints at one, three, and six months after the first trial addressing the treatment became available either as a preprint or publication (120 meta-analyses in total, 60 of which included preprints and 60 of which excluded preprints) and assessed the certainty of evidence using the GRADE framework.

RESULTS Of 356 trials included in the study, 101 were only available as preprints, 181 as journal publications, and 74 as preprints first and subsequently published in journals. The median time to publication of preprints was about six months. Key methods and results showed few important differences between trial preprints and their subsequent published reports. Apart from two (3.3%) of 60 comparisons, point estimates were consistent between meta-analyses including preprints versus those excluding preprints as to whether they indicated benefit, no appreciable effect, or harm. For nine (15%) of 60 comparisons, the rating of the certainty of evidence was different when preprints were included versus being excluded—the certainty of evidence including preprints was higher in four comparisons and lower in five comparisons.

CONCLUSION No compelling evidence indicates that preprints provide results that are inconsistent with published papers. Preprints remain the only source of findings of many trials for several months—an unsuitable length of time in a health emergency that is not conducive to treating patients with timely evidence. The inclusion of preprints could affect the results of meta-analyses and the certainty of evidence. Evidence users should be encouraged to consider data from preprints.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Clinicians and decision makers need rapidly available, credible information on the comparative effectiveness of treatments and prophylaxis for covid-19
- ⇒ During the covid-19 pandemic, the scientific community adopted preprint servers, which allow the rapid dissemination of research findings before publication in peer reviewed journals
- ⇒ The medical community, however, has been cautious about adopting preprints owing to concerns that they could lead to the dissemination of erroneous provisional findings

WHAT THIS STUDY ADDS

- ⇒ After a review of covid-19 trial preprints and published reports, no compelling evidence indicated any important discrepancies between preprints and published reports
- ⇒ The inclusion of preprints could affect the results of meta-analyses and the certainty (quality) of evidence
- ⇒ Generalisability of these results is limited to covid-19; furthermore, preprints that are subsequently published in journals might be the most rigorous and might not represent all trial preprints—particularly those that remain unpublished

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- ⇒ Evidence users—including systematic reviewers, guideline developers, and clinicians—are encouraged to consider evidence from preprint trials in contexts in which decisions are being made rapidly and evidence is being produced faster than can be peer reviewed and published
- ⇒ Scepticism might still be warranted when suspicion arises regarding falsified data (for which criteria is provided in this article)

Introduction

During the covid-19 pandemic, the scientific community adopted preprint servers, which allow investigators to disseminate research findings before publication in peer reviewed journals. Authors of seminal covid-19 trials—for example, representing massive international collaborations such as RECOVERY¹⁻⁴ and SOLIDARITY⁵—reported their results in preprints before subsequent publication in journals.

Growing interest in preprints predates the covid-19 pandemic.^{6 7} Researchers and evidence users have raised concerns that the traditional publication model is slow, peer review might not always improve the quality of manuscripts, journals impede dissemination owing to paywalls and high publication fees and encourage publication bias by prioritising significant or anomalous findings—issues that preprints may avoid.⁸⁻¹⁴ Despite these concerns, and the potential of preprints to resolve them, preprints might result in the dissemination of provisional findings that contain important errors that, presumably, published papers do not—therefore, the medical community has been cautious regarding their adoption.^{15 16}

Authors of systematic reviews, guideline developers, and other decision makers face a trade-off when considering preprints: on the one hand, including preprints could reduce the credibility of evidence syntheses and risk serious errors if important differences appear in published reports; on the other, including preprints might increase the precision of estimates, allow timely dissemination of research, and minimise the effects of publication bias.

Knowledge of the extent to which preprints might accelerate the dissemination of findings, the frequency and nature of discrepancies between preprints and subsequent published reports, and the impact that preprints might have on meta-analytic estimates could inform the trade-off that evidence users face. Our study capitalises on our living systematic reviews and network meta-analyses (SRNMAs) of drug treatments, antiviral antibodies and cellular treatments, and prophylaxis for covid-19—an initiative launched in July 2020 that provides real time summaries of the comparative effectiveness of treatments and prophylaxis for covid-19.¹⁷⁻¹⁹ These living SRNMAs informed linked guidelines for covid-19 treatments and prophylaxis.²⁰ We use these reviews to assess the degree of discrepancies between covid-19 trial preprints and their later publications and to assess the effects of considering evidence from preprints on meta-analytic estimates, certainty (quality) of evidence, and decision making.

Methods

We submitted a protocol for this study for publication on 7 September 2021. Because the protocol was still under review at the time the study was completed, we withdrew the protocol for publication and present it in online supplement 1.

Search

Our study uses the search strategy of our living SRNMA that includes daily searches in the World Health Organization covid-19 database—a comprehensive multilingual source of global published and preprint literature on covid-19 (<https://search.bvsalud.org/global-literature-on-novel-corona-virus-2019-ncov/>). Before it was merged with the WHO covid-19 database on 9 October 2020, we searched the US Centres for Disease Control and Prevention's (CDC) covid-19 research articles downloadable database. A validated machine learning model facilitates efficient identification of randomised trials.²¹

Our search was supplemented by ongoing surveillance of living evidence retrieval services, including the Living Overview of the Evidence (L-OVE) covid-19 platform by the Epistemonikos Foundation (<https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d>) and the Systematic and Living Map on Covid-19 Evidence by the Norwegian Institute of Public Health (<https://www.fhi.no/en/qk/systematic-reviews-hta/map/>). Using the above sources, we monitor for retraction notices. Online supplement 2 includes additional details of our search strategy. This study included trials identified up to 3 August 2021.

Study selection

As part of the living SRNMA, pairs of reviewers, after calibration exercises to ensure sufficient agreement, worked independently and in duplicate to screen titles and abstracts of search records and subsequently the full texts of records determined as potentially eligible at the title and abstract screening stage. Reviewers also linked preprint reports with their subsequent publications based on trial registration numbers, the names of investigators, recruiting centres and countries, dates of recruitment, and baseline patient characteristics. When links between preprints and subsequent publications were unclear, we contacted trial authors for confirmation. Reviewers resolved discrepancies by discussion or, when necessary, by adjudication with a third party reviewer.

Eligible preprint and peer reviewed articles reported trials that randomised patients with suspected, probable, or confirmed covid-19 to drug treatments, antiviral antibodies and cellular treatments, placebo, or standard care, or reported trials that randomised healthy participants exposed or unexposed to covid-19 to prophylactic drugs, standard care, or placebo. We did not apply any restrictions on severity of illness, setting, or language of publication but excluded trials reporting on nutritional interventions, traditional Chinese herbal medicines without standardisation in formulations and dosing across batches, and non-drug supportive care interventions.

We did not perform a sample size calculation because we included all eligible trial reports identified through our living SRNMAs up to 3 August 2021. While the parallel living SRNMA performed ongoing daily searches, we pragmatically limited our search because it was no longer feasible to continue to collect additional data from preprints beyond this timepoint.

Data collection

As part of the living SRNMA, for each eligible trial, pairs of reviewers, after training and calibration exercises, independently extracted trial characteristics, methods, and results using a standardised, pilot tested data extraction form. To assess risk of bias, reviewers, after training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)²² (online supplement 3). Reviewers resolved discrepancies by discussion and, when necessary, by adjudication with a third party.

For the current study, pairs of trained and calibrated reviewers, working independently and in duplicate and using a pilot tested data collection form, collected data on differences in key methods and results between preprint and published trial reports. We prioritised collecting information on key methods and results that might affect the interpretation of trials and decision making by evidence users. For key methods, we focused on aspects of the methods that could affect risk-of-bias judgments, which included description of the randomisation process and allocation concealment, blinding of patients and healthcare providers, extent of and handling of missing outcome data, blinding of outcome assessors and adjudicators, and prespecification of outcomes and analyses. Key results included the number of participants analysed and number of events in each trial arm for dichotomous outcomes and number of participants analysed, means or medians and measures of variability for continuous outcomes. We focused on the same outcomes as our living SRNMA and linked guidelines that were identified as being important or critical for decision making by the review authors and authors of the parallel guidelines, including patient partners: mortality, mechanical ventilation, adverse events leading to discontinuation, admission to hospital, viral clearance, hospital length of stay, length of stay in intensive care, duration of mechanical ventilation, time to symptom resolution or clinical improvement, days free from mechanical ventilation, and time to viral clearance.^{17–20} For preprints with more than one version, we extracted data from the first version of the preprint, which is the least likely to have been modified in response to peer review.

Because risk of bias might vary across outcomes, for this analysis we presented risk-of-bias judgments corresponding to the following hierarchy of outcomes for therapy trials: mortality, mechanical ventilation, duration of hospital stay, time to symptom resolution or clinical improvement, and virological outcomes. For prophylaxis trials, we used the following hierarchy: mortality, laboratory confirmed and suspected covid-19 infection, and laboratory confirmed covid-19 infection. These hierarchies represent the relative importance of outcomes based on rankings made by the linked WHO guideline panel.²⁰

Data synthesis and analysis

We compared the characteristics and risk of bias of trials with preprints, trials with publications, and trials first posted as a preprint and subsequently published by calculating differences in proportions, associated confidence intervals, and z tests to test for differences in independent proportions. To compare the number of participants in trials with preprints, trials with publications, and trials first posted as a preprint and subsequently published, we performed Mann Whitney U tests.

We calculated the median time from a trial being posted on a preprint server to its eventual publication in a journal and used Kaplan-Meier curves and log-rank tests to assess whether the following factors were predictive of time to publication of trial preprints: source of funding, number of centres and participants, early termination for benefit, intensity of care (inpatient v outpatient), and severity (mild/moderate v severe/critical covid-19), significant primary or secondary outcomes (based on cut-off thresholds defined by the authors or, when no cut-off thresholds were defined, based on a cut-off threshold of $P<0.05$ or confidence intervals not including the null), and risk of bias (trials rated at low v high risk of bias).

Among trial preprints that were subsequently published in a peer reviewed journal, we described the number and types of discrepancies in key methods and results between preprint and published trial reports. For discrepancies in the reporting of key methods, we reported the number and percentage of the changes between preprints and publications that affected risk-of-bias judgments—changes that we considered to be critical. We also compared the number of preprint and published trials that have been retracted.

For trials that reported on interventions that have been addressed by the linked WHO living guideline²⁰ up to 3 August 2021 (ie, corticosteroids, remdesivir, lopinavir-ritonavir, hydroxychloroquine, ivermectin, interleukin 6 receptor blockers, and convalescent plasma for treatment and hydroxychloroquine for prophylaxis) and the two most commonly reported outcomes (ie, mortality, mechanical ventilation), we conducted pairwise frequentist random effects meta-analyses with the restricted maximum likelihood estimator including versus excluding evidence from preprints at one, three, and six months after the first trial of the drug of interest was made public, either via preprint or publication. The choice of timepoints was informed by timeframes within which guideline developers needed to issue recommendations.²⁰ We also conducted an analysis including versus excluding evidence from preprints at 3 August 2021—the longest timepoint at which we collected data. For hydroxychloroquine for prophylaxis, because mechanical ventilation was not an outcome of interest for prophylaxis trials, we reported only on mortality.

To facilitate interpretation, we calculated absolute effects. To calculate absolute effects, for drug treatments, we used mortality data from the CDC and data on ventilation from the International Severe Acute Respiratory and Emerging Infection covid-19 database.^{23–25} For prophylaxis, we used the event rate among all participants randomised to standard care or placebo to calculate the baseline risk.

We compared the direction of effect between meta-analyses including preprints and meta-analyses excluding preprints. We considered the direction of effect to be different if one point estimate suggested no effect and another suggested a benefit or harm or if one point estimate suggested benefit and another suggested harm. For treatment, we considered an effect to be beneficial if the point estimate indicated a reduction in risk of mortality of 1% or greater or a reduction in risk of mechanical ventilation of 2% or greater for treatment. For prophylaxis, we considered an effect to be beneficial if the point estimate indicated a reduction in risk of mortality of 0.5% or greater. For treatment, we considered an effect to be harmful if the point estimate indicated an increase in risk of mortality of 1% or greater or an increase in risk of mechanical ventilation of 2% or greater. For prophylaxis, we considered an effect to be harmful if the point estimate indicated an increase in risk of mortality of 0.5% or greater for prophylaxis. Otherwise, we inferred that there was no important effect. Our thresholds for beneficial and harmful effects were informed by surveys of the coauthors in the parallel living SRNMAs.^{17–19}

We used the GRADE approach to assess the certainty of evidence, considering risk of bias (limitations in trial design leading to systematic underestimation or over-estimation of treatment effects), inconsistency (heterogeneity in results reported across trials), indirectness (differences between the question asked in trials and the question of interest), imprecision (width of confidence intervals), and publication bias (propensity for studies with significant results, notable results, or results that support a particular hypothesis to be published, published faster, or published in journals with higher visibility). We also assessed whether meta-analyses including preprints versus excluding preprint reports led to differences in ratings of the overall certainty of evidence, judgments related to specific GRADE domains, and whether differences in ratings were likely to affect decision making (ie, evidence rated as high/moderate v low/very low).²⁶ We used a minimally contextualised approach to make judgments about imprecision.²⁷ This approach considers whether confidence intervals include the null effect and thus does not consider whether plausible effects, captured by confidence intervals, include both important and trivial effects. We considered any effect on mortality and mechanical ventilation to be important. Thresholds of 1% risk difference

for mortality and 2% risk difference for mechanical ventilation informed judgments of minimal or no treatment effect. For prophylaxis and mortality, we used a 0.5% risk difference.²⁷ We performed all statistical analyses in R (version 4.03, R Foundation for Statistical Computing), using the meta, forestplot, survival, and survminer packages.

Patient and public involvement

Patients were involved in outcome selection, interpretation of results, and the generation of parallel recommendations, as part of the parallel SRNMA and guidelines.²⁰ Patients were not involved in the present secondary study.

Results

Trial characteristics

As of 3 August 2021, we identified 356 eligible trials, of which 101 were only available as preprints, 181 only available as journal publications, and 74 first available as preprints and subsequently published as journal articles. Online supplement 4 presents additional details on the results of the search and table 1 presents trial characteristics.

Most trials were registered, completed at the time of reporting, addressed drug treatments, enrolled fewer than 250 participants, reported one or more outcomes that were statistically significant, and were funded by governments or institutions. Nearly two thirds of trials were at high risk of bias, primarily because of their open label design.

Compared with published trials without preprints, trials only available as preprints and trials first available as preprints and then subsequently published were more likely to be registered; trials only available as preprints were more likely to report on interim results, describe drug treatments compared with antiviral antibodies and cellular treatments or prophylaxis, and to have received industry funding; and trials first posted as preprints and subsequently published were more likely to have received government funding.

Predictors of publication and time to publication

During the 1.5 year span of this study, of 175 preprints, 74 (42.3%) were subsequently published in peer reviewed journals. Table 2 presents the proportion of preprints published up to one year. The median time to publication of preprints was 5.9 months. At one year, a third of preprints remained unpublished.

Table 3 presents predictors for the publication of preprints. Preprints that received government funding, reported on inpatients, or reported on patients with severe disease were published faster than preprints that did not receive government funding, reported on outpatients, or reported on patients with mild or moderate disease.

Table 1 | Trial characteristics. Data are number (%) of trials unless statement otherwise

Characteristic	All trials (n=556)	Published trials without preprints (n=8)	Trials only available as preprints (n=10)	Difference between trials only available as preprints and published trials without preprints (%; 95% CI)	P value	Trials first posted as preprints (n=74)	Difference between trials first posted as preprints and subsequently published and subsequently published and published trials without preprints (%; 95% CI)	P value
Trial registered	319 (89.6)	149 (82.3)	97 (96.0)	13.7 (7.0 to 20.5)	<0.001	73 (98.6)	16.3 (10.2 to 22.5)	<0.001
Study status								
Completed	268 (75.3)	142 (78.5)	75 (74.3)	-4.2 (-14.6 to 6.2)	0.44	51 (68.9)	-9.5 (-21.7 to 2.6)	0.12
Interim results	20 (5.6)	5 (2.8)	10 (9.9)	7.1 (0.8 to 13.4)	0.03	5 (6.8)	4.0 (-2.2 to 10.2)	0.21
Terminated early for benefit	2 (0.6)	0	2 (2.0)	2.0 (-0.7 to 4.7)	0.15	0	0 (0%)	1.00
Terminated early owing to feasibility	66 (18.5)	34 (18.8)	14 (13.9)	-4.9 (-13.7 to 3.9)	0.28	18 (24.3)	5.5 (-5.8 to 16.9)	0.34
Type of treatment								
Drug treatment	293 (82.3)	157 (86.7)	77 (76.2%)	-10.5 (-20.2 to -0.8)	0.03	59 (79.7)	-7.0 (-17.4 to 3.4)	0.19
Prophylaxis	17 (4.8)	7 (3.9)	8 (7.9)	4.0 (-1.9 to 10.0)	0.18	2 (2.7)	-1.2 (-5.8 to 3.5)	0.64
Antiviral antibodies and cellular treatments	46 (12.9)	17 (9.4)	16 (15.8)	6.5 (-1.8 to 14.7)	0.13	13 (17.6)	8.2 (-1.5 to 17.8)	0.10
Inpatient*	252 (74.3)	129 (72.3)	65 (69.9)	-4.3 (-15.6 to 7.1)	0.47	58 (80.6)	6.4 (-4.8 to 17.6)	0.27
Severe/critical disease*								
No of centres	88 (26.0)	46 (26.4)	26 (28.0)	1.5 (-9.7 to 12.8)	0.80	16 (22.2)	-4.2 (-15.8 to 7.4)	0.49
Single centre	151 (42.4)	86 (47.5)	39 (38.6)	-8.9 (-20.9 to 3.1)	0.15	26 (35.1)	-12.4 (-25.5 to 0.7)	0.06
Multicenter	177 (49.7)	85 (47.0)	48 (47.5)	0.6 (-12.0 to 12.7)	0.93	44 (59.5)	12.5 (-0.8 to 25.8)	0.07
Median (IQR) number of participants	106 (60-266)	101 (60-208)	163 (64-412)	—	0.01	100 (60 to 249)	—	0.54
Primary outcome—significant	151 (42.4)	74 (40.6)	49 (48.5)	7.6 (-4.5 to 19.7)	0.22	28 (37.8)	-3.1 (-16.2 to 10.1)	0.66
Any secondary outcome(s)—significant	186 (52.2)	90 (49.7)	53 (52.5)	2.8 (-9.4 to 14.9)	0.67	43 (58.1)	8.4 (-5.0 to 21.8)	0.22
Reasons for high risk of bias								
Randomisation	122 (34.3)	67 (37.0)	34 (33.7)	-3.4 (-15.0 to 8.2)	0.58	19 (25.7)	-11.3 (-23.5 to 0.6)	0.07
Deviations from intended intervention	214 (60.1)	111 (61.3)	56 (55.5)	-5.9 (-17.9 to 9.1)	0.34	47 (33.5)	2.2 (-10.9 to 15.3)	0.76
Missing outcome data	19 (5.3)	11 (6.1)	5 (5.0)	-1.1 (-6.6 to 4.4)	0.70	3 (4.1)	-2.0 (-7.1 to 3.7)	0.50
Measurement of the outcome	7 (2)	6 (3.3)	1 (1.0)	-2.3 (-5.6 to 0.9)	0.16	0	-3.3 (-5.9 to 0.7)	0.11
Selective reporting	22 (6.2)	9 (5.0)	8 (7.9)	3.0 (-3.2 to 9.1)	0.35	5 (6.8)	1.8 (-4.8 to 8.3)	0.60
Overall high risk of bias	228 (64)	117 (64.6)	61 (60.4)	-4.2 (-16.1 to 7.6)	0.49	50 (67.6)	2.9 (-9.8 to 15.7)	0.67
Funding†								
Industry	79 (22.2)	32 (17.7)	30 (29.7)	12.0 (1.5 to 22.5)	0.02	17 (23)	5.3 (-5.8 to 16.4)	0.35
Government	126 (35.4)	47 (26.0)	37 (36.6)	10.7 (-0.7 to 22.0)	0.07	47 (56.8)	30.8 (17.8 to 43.8)	<0.001
Institution	128 (36.0)	69 (38.1)	32 (31.7)	-6.4 (-17.9 to 5.1)	0.28	27 (36.5)	-1.6 (-14.7 to 11.4)	0.82
Not-for-profit	51 (14.3)	24 (13.3)	12 (11.9)	-1.4 (-9.4 to 6.6)	0.75	15 (20.3)	7.0 (-3.4 to 17.4)	0.19
Not reported	23 (6.5)	12 (6.6)	10 (9.9)	3.3 (-3.6 to 10.1)	0.36	1 (1.4)	-5.3 (-9.8 to -0.8)	0.02
No funding								
	49 (13.8)	33 (18.2)	10 (9.9)	-8.3 (-16.4 to 0.2)	0.04	6 (8.1)	-10.1 (-18.5 to -1.7)	0.02

CI=confidence interval; IQR=interquartile range.

*Estimates only include trials addressing treatment.

†Trials might not be classified in more than one category.

Table 2 | Time to publication of covid-19 trial preprints

Time	Proportion of preprints published (No/total No (%))	Cumulative proportion (%) of preprints published
0 to 2 weeks	3/174 (1.7)	1.70
2 weeks to 1 month	5/169 (3.0)	4.70
1 month to 2 months	12/162 (7.4)	12.10
2 months to 3 months	19/133 (14.3)	25.70
3 months to 6 months	27/98 (27.6)	50.10
6 months to 1 year	9/42 (21.4)	65.90
Median (95% CI) time to publication	5.9 months (5.1 to 10.3)	

CI=confidence interval.

Differences between preprint and published trial reports

Forty two (56.8%) trials had one or more discrepancies in the reporting of key methods and results between the preprint and the later published trial report. We identified a median of 1 (interquartile range 0-2) discrepancy per pair of preprint and publication reports. Online supplement 5 describes these discrepancies.

Thirty (40.5%) trials had one or more discrepancies in the reporting of key methods. The most common discrepancy in the reporting of key methods was the description of allocation concealment, which occurred in eight trials. For four of these eight trials, our judgment of risk of bias for the randomisation domain changed from "probably high" to "low" owing to additional details reported in the published report. **Box 1** presents an example.

Other differences in the reporting of key methods were the publication reporting one or more additional statistics important for meta-analysis (eg, interquartile ranges or standard deviations) that were not previously reported in the preprint (n=6; 8.1%), the preprint reporting on interim results and the publication on completed trial results (n=4; 5.4%), and the publication including a protocol or statistical analysis plan as a supplementary that was not previously included with the preprint (n=3; 4.1%). The overall trial rating of risk of bias, however, changed only for one trial based on additional information provided in the published report.

Thirty one (41.9%) trials had one or more differences in the reporting of key results between preprints and publications. The most common discrepancy in the reporting of key results were changes in outcome data between preprints and publications, which was seen in 20 (27.0%) trials—although most of these discrepancies might likely be attributed to events accumulating in trials from the time when the preprint was posted to when the trial was published. **Table 4** presents an example.

Despite discrepancies in outcome data being common, results were similar between preprints and publications both in magnitude and precision. **Figure 1** shows differences in results on

mortality and mechanical ventilation between preprints and publications. Among all preprints with differences in outcomes, differences in relative effects did not exceed 15%, except for one trial with very few events that included just one additional event in the publication.²⁸ Other differences between preprints and publications in key results included the publication reporting at least one additional key outcome that was not included in the preprint (n=11; 14.9%).

Retractions

We identified four retracted trials.²⁹⁻³⁶ Two trials reported on (hydroxy)chloroquine,²⁹⁻³² two on favipiravir,³¹⁻³⁴ and two on ivermectin.^{29 30 35 36} One of the trials was retracted when the authors noticed an error in their analysis^{35 36} and the remainder were retracted owing to concerns about data fabrication or falsification (eg, inconsistencies between the eligibility criteria and patients included in the trial, discrepancies between when the trial was reported to have been conducted and when patients were recruited, inconsistencies between the dataset and the results reported in the preprint, and inconsistencies between the distribution of baseline variables and the described randomisation procedure). We compared the number of retractions between preprints and journal publications. One of the retracted trials was posted as a preprint^{29 30} and the remainder were published in peer reviewed journals.

Meta-analyses including v excluding preprint reports

Tables 5 and 6 presents results of meta-analyses including and excluding data from unpublished preprints for the comparison of placebo or standard care with several treatments for covid-19, with the outcomes of mortality and mechanical ventilation. Treatments included corticosteroids, remdesivir, lopinavir-ritonavir, hydroxychloroquine, ivermectin, interleukin 6 receptor blockers, and convalescent plasma. Results were recorded at one, three, and six months after the first trial addressing the intervention was made public, either as a preprint or a publication, and at the longest point of follow-up of the trials (up to 3 August 2021). Online supplement 6 presents a more detailed table.

In total, we performed and assessed the certainty of evidence of 120 meta-analyses, 60 of which included preprints and 60 of which excluded preprints. Online supplement 7 presents forest plots for meta-analyses.

Because of insufficient data, we could not perform meta-analyses for six comparisons without preprints: mortality and mechanical ventilation, at one month, for ivermectin versus placebo or standard care and for interleukin 6 receptor blockers versus placebo or standard care; and mortality and mechanical ventilation, at three months, for ivermectin versus placebo or standard care.

Table 3 | Predictors of time to publication of covid-19 trial preprints

	Median (95% CI) time to publication (days)	P value
Funding		
Industry funding (n=47)	171 (145 to NA)	0.72
No industry funding (n=127)	219 (177 to NA)	
Government funding (n=78)	155 (120 to 192)	0.02
No government funding (n=96)	309 (183 to NA)	
Institutional funding (n=58)	136 (90 to NA)	0.14
No institutional funding (n=116)	192 (166 to NA)	
Not-for-profit funding (n=26)	110 (79 to NA)	0.07
No not-for-profit funding (n=148)	188 (161 to NA)	
No of centres		
Single centre (n=65)	Undefined (130 to undefined)	0.13
Multicentre (n=90)	161 (136 to 219)	
No of participants		
More than median (n=88)	142 (120 to NA)	0.14
Less than median (n=85)	219 (171 to NA)	
Intensity of care		
Inpatient (n=122)	110 (95 to 144)	<0.00001
Outpatient (n=38)	Undefined	
Severity		
Mild or moderate disease (n=79)	182 (159 to 263)	0.00001
Severe or critical disease (n=42) ³⁷	101 (89 to 128)	
Early termination for benefit	NA	NA
Primary outcome significance		
Significant (n=77)	243 (155 to undefined)	0.12
Not significant (n=91)	161 (127 to 219)	
Any secondary outcomes statistically significant		
Significant (n=96)	187 (120 to NA)	0.66
Not significant (n=64)	152 (120 to NA)	
Risk of bias		
Low (n=52)	155 (124 to 187)	0.17
High (n=102)	122 (98 to 161)	

CI= confidence interval; NA=not available. Upper bounds of confidence intervals could often not be estimated owing to insufficient follow-up of preprints.

Differences in estimates from meta-analyses including v excluding preprints

Except for two (3.3%) cases, all meta-analyses including and excluding results from unpublished preprints produced point estimates that were consistent as to whether they indicated benefit, no appreciable effect, or harm. The meta-analysis of corticosteroids at one month suggested a reduction in risk of mechanical ventilation when preprints were excluded (43 fewer per 1000 people (95% confidence interval 59.24 fewer to 22.12 fewer); moderate

BOX 1 | EXAMPLE OF TRIAL REPORTING ADDITIONAL INFORMATION ON ALLOCATION CONCEALMENT IN ITS PUBLISHED REPORT

The PANAMO trial, which was initially available as a preprint on the Social Science Research Network and later published in *Lancet Rheumatology*, provided additional details on allocation concealment in the publication. The publication described central randomisation with an online tool and the development of the randomisation list by a third party—all of which were not reported in the preprint.^{49 50} This addition resulted in a change in the rating of the risk of bias owing to randomisation, from "probably high risk of bias" to "definitely low risk of bias."

PREPRINT

"Patients were randomly assigned in a 1:1 ratio to receive IFX-1, at a dose of 800 mg intravenously, for a maximum of seven doses, plus best supportive care, or best supportive care only ... Randomisation was performed with an online tool within the eCRF (electronic case report form) and was stratified by study site."

PUBLICATION

"Patients were randomly assigned in a 1:1 ratio to IFX-1 plus best supportive care (the IFX-1 group) or to best supportive care only (the control group). Randomisation was done by investigators centrally with an online tool within the electronic case report form and was stratified by study site. The tool used a randomised variable block length of either two or four. The randomisation list was only available to contract research organisation (Metronomia) staff involved in the production of the randomisation list and set-up of the online randomisation tool."

certainty) and no appreciable effect when preprints were included (1.2 more per 1000 people (60.3 fewer to 131.1 more); very low certainty). The meta-analysis without preprints included one trial with 5418 participants and the meta-analysis with preprints included two trials with 5472 participants.

The meta-analysis of ivermectin at six months suggested no appreciable effect on risk of mechanical ventilation when preprints were excluded (2.3 fewer per 1000 people (95% confidence interval 52.2 fewer to 83.5 more); low certainty) and a reduction in risk of mechanical ventilation when preprints were included (26.7 fewer per 1000 people (74.2 fewer to 75.4 more); very low certainty). The meta-analysis without preprints included seven trials with 1826 participants and the meta-analysis with preprints included nine trials with 4000 participants. Four of 60 meta-analyses had results that were significant with preprints and not significant without preprints, or vice versa.

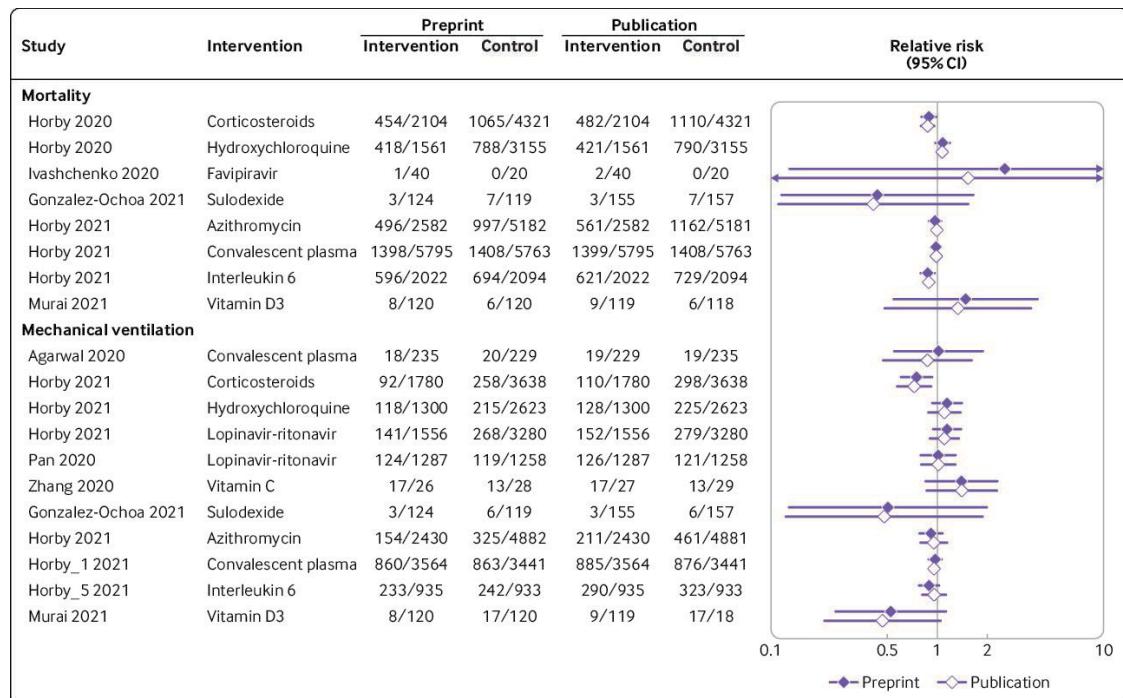


Figure 1 | Differences in results on mortality and mechanical ventilation between preprints and publications of covid-19 trials. ^{1–5 28} Data are events/total number of participants

Differences in ratings of certainty of evidence from meta-analyses including v excluding preprints

We judged nine (15%) of 60 meta-analyses to have different ratings of the certainty of evidence when preprints were included versus when preprints were excluded. For four of these nine cases, we rated the certainty of evidence for the meta-analyses including preprints to be higher than the evidence excluding preprints. For five of these nine cases, we rated the certainty of meta-analyses excluding preprints to be higher than the meta-analyses including preprints. In six of these cases, differences in ratings of the certainty of evidence could have affected decision making (ie, evidence including preprints is rated as high or moderate whereas evidence excluding preprints is rated as low or very low, or vice versa).

Differences in ratings of GRADE domains from meta-analyses including v excluding preprints

Risk of bias

Between meta-analyses including preprints and meta-analyses excluding preprints, judgments

related to the GRADE risk-of-bias domain differed only for one meta-analysis (remdesivir v standard care or placebo for mechanical ventilation at six months). We judged the meta-analysis excluding preprints to not have any concerns related to risk of bias and downgraded the meta-analysis including preprints due to serious risk of bias.

Imprecision

Between meta-analyses including preprints and meta-analyses excluding preprints, judgments related to the GRADE imprecision domain differed for 13 of 60 meta-analyses. We judged nine meta-analyses excluding preprints to have more serious concerns related to imprecision than their counterparts including preprints (ie, additional data from preprints narrowed confidence intervals). Furthermore, we judged four meta-analyses excluding preprints to have less serious concerns related to imprecision than meta-analyses including preprints (ie, additional data from preprints increased statistical heterogeneity and hence imprecision).

Table 4 | Example of trial* reporting different outcome data between preprint⁵¹ and publication,² by outcome and treatment group

Outcome	Preprint ⁵¹	Publication ²
Mortality	Corticosteroids: 454/2104 (21.6) Standard care: 1065/4321 (24.6)	Corticosteroids: 482/2104 (22.9) Standard care: 1110/4321 (25.7)
Mechanical ventilation	Corticosteroids: 92/1780 (5.2) Standard care: 258/3638 (7.1)	Corticosteroids: 110/1780 (6.2) Standard care: 298/3638 (8.2)

Data are events/total number (%) of participants in each treatment group.

*The RECOVERY publication on dexamethasone treatment for covid-19 reported different results for mortality and mechanical ventilation—likely not because of an error in the preprint but because of events accumulating in the trial from when the preprint was posted to when it was published.^{2 51}

Table 5 | Results of meta-analyses excluding and including results from preprints, by mortality outcome

Drug treatment duration	Meta-analyses excluding unpublished preprints			Meta-analyses including all preprints		
	No of studies (participants)	Risk difference with standard care/ placebo (95% CI; per 1000 people)	GRADE assessment for certainty of evidence	No of studies (participants)	Risk difference with standard care/ placebo (95% CI; per 1000 people)	GRADE assessment for certainty of evidence
Mortality						
Corticosteroids						
1 month	1 (6425)	14.3 fewer (24.7 fewer to 2.6 fewer)	Moderate	2 (6489)	14.3 fewer (24.7 fewer to 2.6 fewer)	Moderate
3 months	5 (7667)	13 fewer (22.1 fewer to 3.9 fewer)	Moderate	6 (7731)	13 fewer (22.1 fewer to 3.9 fewer)	Moderate
6 months	5 (7667)	13 fewer (22.1 fewer to 3.9 fewer)	Moderate	6 (7731)	13 fewer (22.1 fewer to 3.9 fewer)	Moderate
Current	10 (7959)	13 fewer (22.1 fewer to 3.9 fewer)	Moderate	10 (7959)	13 fewer (22.1 fewer to 3.9 fewer)	Moderate
Remdesivir						
1 month	2 (1298)	27.3 fewer (53.3 fewer to 6.5 more)	Moderate	2 (1298)	27.3 fewer (53.3 fewer to 6.5 more)	Moderate
3 months	2 (1298)	27.3 fewer (53.3 fewer to 6.5 more)	Moderate	2 (1298)	27.3 fewer (53.3 fewer to 6.5 more)	Moderate
6 months	3 (1882)	28.6 fewer (53.3 fewer to 5.2 more)	Moderate	4 (7333)	13 fewer (35.1 fewer to 14.3 more)	Low
Current	5 (7415)	11.7 fewer (32.5 fewer to 14.3 more)	Low	6 (8247)	10.4 fewer (27.3 fewer to 9.1 more)	Moderate
Lopinavir-ritonavir						
1 month	1 (199)	29.9 fewer (71.5 fewer to 39 more)	Very low	2 (250)	29.9 fewer (71.5 fewer to 39 more)	Very low
3 months	2 (250)	29.9 fewer (71.5 fewer to 39 more)	Very low	2 (250)	29.9 fewer (71.5 fewer to 39 more)	Very low
6 months	2 (250)	29.9 fewer (71.5 fewer to 39 more)	Very low	2 (250)	29.9 fewer (71.5 fewer to 39 more)	Very low
Current	7 (9427)	5.20 more (6.5 fewer to 18.2 more)	Very low	7 (9427)	5.20 more (6.5 fewer to 18.2 more)	Very low
(Hydroxy)chloroquine						
1 month	1 (30)	NA	NA	1 (30)	NA	NA
3 months	1 (30)	NA	NA	2 (180)	NA	NA
6 months	5 (1287)	20.8 more (54.6 fewer to 174.2 more)	Very low	9 (6135)	10.4 more (2.60 fewer to 24.7 more)	Low
Current	19 (10634)	11.7 more (0 fewer to 24.7 more)	Low	23 (10997)	9.10 more (2.60 fewer to 22.1 more)	Low
Ivermectin						
1 month	0 (0)	NA	NA	1 (180)	106.6 fewer (122.2 fewer to 65 fewer)	Very low
3 months	0 (0)	NA	NA	4 (517)	87.1 fewer (118.3 fewer to 22.1 more)	Very low
6 months	1 (398)	87.1 fewer (128.7 fewer to 916.5 more)	Very low	6 (1169)	85.8 fewer (115.7 fewer to 0 fewer)	Low
Current	5 (1220)	36.4 fewer (93.6 fewer to 110.5 more)	Very low	9 (1879)	63.7 fewer (100.1 fewer to 16.9 more)	Very low
Interleukin 6 receptor blockers						
1 month	0 (0)	NA	NA	1 (97)	20.8 fewer (70.2 fewer to 66.3 more)	Very low
3 months	2 (26)	91 fewer (124.8 fewer to 165.1 more)	Very low	4 (435)	15.6 fewer (54.6 fewer to 41.6 more)	Very low
6 months	6 (1292)	23.4 fewer (42.9 fewer to 0 fewer)	Low	7 (5408)	22.1 fewer (31.2 fewer to 13 fewer)	Moderate
Current	8 (5457)	22.1 fewer (31.2 fewer to 13 fewer)	Moderate	11 (6303)	22.1 fewer (31.2 fewer to 13 fewer)	Moderate
Convalescent plasma						
1 month	1 (101)	45.5 fewer (92.3 fewer to 59.8 more)	Very low	2 (187)	52 fewer (87.1 fewer to 13 more)	Very low
3 months	1 (101)	45.5 fewer (92.3 fewer to 59.8 more)	Very low	4 (428)	57.2 fewer (88.4 fewer to 3.90 fewer)	Very low
6 months	3 (898)	6.5 fewer (41.6 fewer to 42.9 more)	Very low	7 (1185)	22.1 fewer (48.1 fewer to 14.3 more)	Very low
Current	9 (12962)	2.60 fewer (10.4 fewer to 6.5 more)	Moderate	14 (16073)	2.60 fewer (9.10 fewer to 3.90 more)	Moderate
(Hydroxy)chloroquine (prophylaxis)						
1 month	1 (744)	NA	NA	1 (744)	NA	NA
3 months	1 (744)	NA	NA	2 (3151)	0.8 fewer (2.3 fewer to 3.7 more)	High
6 months	4 (8569)	0.8 fewer (2 fewer to 3.7 more)	High	4 (8569)	0.8 fewer (2 fewer to 3.7 more)	High
Current	4 (8569)	0.8 fewer (2 fewer to 3.7 more)	High	4 (8569)	0.8 fewer (2 fewer to 3.7 more)	High

GRADE=grading of recommendations assessment, development, and evaluation; NA=not available.

Discussion

Main findings

Our study presents a detailed assessment of the degree of discrepancies between covid-19 trial preprints and their later publications and the impact of trial preprints meta-analytic estimates, the certainty of evidence, and decision making. We show that preprints remain the only source of findings of many trials for several months. Half of all preprints, for example, remain unpublished at six months and a third at one year—a length of time that might be unacceptable in a health

emergency or to patients who might expect that their care is guided by the most recent and best available evidence. Preprints can importantly accelerate the time to dissemination of trial findings.

We did not find compelling evidence of important differences between preprint and published reports of trials—although preprint reports of trials that are subsequently published in journals might not be representative of all trial preprints. Further, we found retractions to occur for both preprints and publications, suggesting that publication in a peer reviewed

Table 6 | Results of meta-analyses excluding and including results from preprints, by mechanical ventilation outcome

Drug treatment duration	Meta-analyses excluding unpublished preprints			Meta-analyses including all preprints		
	No of studies (participants)	Risk difference with standard care/ placebo (95% CI; per 1000 people)	GRADE assessment for certainty of evidence	No of studies (participants)	Risk difference with standard care/ placebo (95% CI; per 1000 people)	GRADE assessment for certainty of evidence
Mechanical Ventilation						
Corticosteroids						
1 month	1 (5418)	43 fewer (59.24 fewer to 22.12 fewer)	Moderate	2 (5472)	1.2 more (60.3 fewer to 131.1 more)	Very low
3 months	5 (6324)	32.56 fewer (44.16 fewer to 19.8 fewer)	Moderate	6 (6378)	17.4 fewer (29 fewer to 3.5 fewer)	Moderate
6 months	5 (6324)	32.56 fewer (44.16 fewer to 19.8 fewer)	Moderate	6 (6378)	17.4 fewer (29 fewer to 3.5 fewer)	Moderate
Current	9 (6576)	27.92 fewer (39.52 fewer to 15.16 fewer)	Moderate	9 (6576)	13.9 fewer (25.5 fewer to 1.2 fewer)	Moderate
Remdesivir						
1 month	2 (1001)	47.6 fewer (65 fewer to 24.4 fewer)	High	2 (1001)	47.6 fewer (65 fewer to 24.4 fewer)	High
3 months	2 (1001)	47.6 fewer (65 fewer to 24.4 fewer)	High	2 (1001)	47.6 fewer (65 fewer to 24.4 fewer)	High
6 months	3 (1585)	51 fewer (67.3 fewer to 30.2 fewer)	High	4 (6549)	39.4 fewer (68.4 fewer to 8.1 more)	Low
Current	5 (6619)	32.5 fewer (62.6 fewer to 13.9 more)	Low	6 (7451)	27.8 fewer (52.2 fewer to 4.6 more)	Low
Lopinavir-ritonavir						
1 month	1 (198)	30.2 fewer (71.9 fewer to 48.7 more)	Very low	1 (198)	30.2 fewer (71.9 fewer to 48.7 more)	Very low
3 months	1 (198)	30.2 fewer (71.9 fewer to 48.7 more)	Very low	1 (198)	30.2 fewer (71.9 fewer to 48.7 more)	Very low
6 months	1 (198)	30.2 fewer (71.9 fewer to 48.7 more)	Very low	1 (198)	30.2 fewer (71.9 fewer to 48.7 more)	Very low
Current	5 (8474)	16.2 more (2.3 fewer to 30.2 more)	Low	5 (8474)	16.2 more (2.3 fewer to 30.2 more)	Low
(Hydroxy)chloroquine (treatment)						
1 month	2 (642)	16.2 more (45.2 fewer to 129.9 more)	Very low	4 (4616)	17.4 more (7.0 fewer to 45.2 more)	Low
3 months	4 (4693)	19.7 more (4.6 fewer to 46.4 more)	Low	6 (6430)	17.4 more (3.5 fewer to 40.6 more)	Low
6 months	7 (6877)	15.1 more (4.6 fewer to 37.1 more)	Low	9 (7417)	12.8 more (4.6 fewer to 33.6 more)	Low
Current	12 (8053)	26.7 more (5.8 more to 53.4 more)	Moderate	12 (8053)	26.7 more (5.8 more to 53.4 more)	Moderate
Ivermectin						
1 month	1 (45)	NA	NA	2 (90)	60.3 more (107.9 fewer to 496.5 more)	Very low
3 months	1 (45)	NA	NA	4 (354)	69.6 fewer (109 fewer to 169.4 more)	Very low
6 months	4 (642)	2.3 fewer (52.2 fewer to 83.5 more)	Low	7 (951)	26.7 fewer (74.2 fewer to 75.4 more)	Very low
Current	8 (1464)	7.0 fewer (48.7 fewer to 61.5 more)	Low	9 (1616)	7.0 fewer (48.7 fewer to 61.5 more)	Low
Interleukin six receptor blockers						
1 month	0 (0)	NA	NA	1 (273)	27.8 fewer (54.5 fewer to 10.4 more)	Low
3 months	3 (495)	37.1 fewer (66.1 fewer to 10.4 more)	Low	5 (1145)	33.6 fewer (52.2 fewer to 8.1 fewer)	Moderate
6 months	7 (1826)	30.2 fewer (42.9 fewer to 16.2 fewer)	Moderate	9 (4000)	20.9 fewer (31.3 fewer to 8.1 fewer)	Moderate
Current	10 (4170)	19.7 fewer (30.2 fewer to 8.1 fewer)	Moderate	12 (4560)	19.7 fewer (30.2 fewer to 9.3 fewer)	Moderate
Convalescent plasma						
1 month	1 (464)	9.3 more (47.6 fewer to 104.4 more)	Very low	3 (705)	19.7 fewer (70.8 fewer to 90.5 more)	Very low
3 months	3 (827)	16.2 more (22 fewer to 70.8 more)	Very low	6 (1108)	4.6 more (29 fewer to 48.7 more)	Very low
6 months	4 (987)	12.8 more (24.4 fewer to 62.6 more)	Very low	6 (1108)	4.6 more (29 fewer to 48.7 more)	Very low
Current	8 (8252)	2.3 fewer (11.6 fewer to seven more)	Moderate	9 (8333)	2.3 fewer (11.6 fewer to 5.8 more)	Moderate

GRADE=grading of recommendations assessment, development, and evaluation; NA=not available.

journal alone does not indicate the trustworthiness of a trial report.

We also found that in most cases, meta-analyses including versus excluding evidence from preprints yielded consistent results. In a minority of circumstances, however, including preprints improved the certainty (quality) of evidence. At six months after trial data first became available, when preprints were excluded, we found low certainty evidence indicating that interleukin 6 receptor blockers might reduce mortality—downgraded because of risk of bias and imprecision. But when preprints were included, we found moderate certainty evidence indicating that interleukin 6 receptor blockers probably reduce mortality—downgraded because of risk of bias. For interleukin 6 receptor blockers, consideration of evidence from preprints could have importantly

accelerated the time to incorporation of this treatment as part of standard care.²⁰

In a minority of circumstances, meta-analyses including preprints also reduced the certainty of evidence. At one month after trial data first became available, for example, when preprints were excluded, we found moderate certainty evidence that corticosteroids probably reduce mechanical ventilation, downgraded because of serious risk of bias; we also found very low certainty evidence when we included preprints, downgraded because of serious risk of bias and very serious imprecision. For corticosteroids, including preprints increased imprecision.

Implications

Our findings have implications for evidence users, such as clinicians, who are concerned with the

quality of preprints and for systematic reviewers and guideline developers deciding whether to consider preprint reports in systematic reviews and guideline recommendations. Our results support the overall usefulness of preprints, and preprints as a venue through which the dissemination of trial findings might be accelerated. While we found that preprints could both increase or reduce the certainty of evidence, we encourage systematic reviewers and guideline developers to consider evidence from preprints, appraise preprint reports, and only consider excluding preprints in situations where there are data fabrication or integrity issues.

Because at the point of submission to peer reviewed journals trials have already been completed and major methodological decisions (such as whether to collect data on an outcome or whether to blind investigators) cannot be changed, peer review probably looks at only the transparency of trial reports and interpretation of results. We encourage systematic reviewers and guideline developers to consider trial evidence from preprints, especially in circumstances in which decisions are being made rapidly and evidence is being produced faster than can be peer reviewed and published.

We caution, however, that preprints (and publications) might describe untrustworthy trials with fabricated or falsified data. Evidence users might consider scrutinising both preprint and published trials for anomalies that suggest fabrication and falsification (examples of which are reported in box 2).^{37 38} While such methods require subjective judgments and cannot be used to definitively identify untrustworthy trials, they could be useful to identify trials that are at high risk of such issues. Evidence users might subsequently investigate such trials further or systematic reviewers might consider sensitivity analyses excluding such trials from meta-analyses. We direct readers to other sources that describe these methods.³⁹ These methods could also be useful to journal editors and peer reviewers to apply when considering trials for publication.

Review authors who are concerned about publication bias or are wanting to make decisions within timeframes that might not be conducive to peer review and publication might also consider conducting prospective meta-analyses—meta-analyses that are conducted using an inception cohort of registered trials and incorporate unpublished data from investigators.⁴⁰ During the covid-19 pandemic, investigators have conducted such prospective meta-analyses to review the effectiveness of corticosteroids and interleukin 6 receptor blockers for covid-19.^{41 42}

Relation of study's findings to previous work

Our study presents data on the contribution of preprints to the body of evidence of covid-19 treatments and prophylaxis. Three studies have reported on differences between covid-19 preprint and

BOX 2 | METHODS TO ASSESS FOR FABRICATION AND FALSIFICATION IN CLINICAL TRIALS³⁹

- ⇒ Judge whether the reported recruitment speed is feasible given local disease patterns, trial eligibility criteria, and capacity of the recruiting centres^{52 53}
- ⇒ Review the trial registration or protocol and assess the consistency between the registration and the manuscript in aspects of the trial that cannot be modified after completion (eg, blinding status)
- ⇒ Review profiles of the investigators or institutions involved, for a history of research misconduct
- ⇒ Review baseline patient characteristics and test whether reported distributions are consistent with randomisation^{37 38 54}
- ⇒ Review primary data, when available, for duplicate records or inconsistencies between the data and reported statistics in the trial manuscript
- ⇒ Review primary data, when available, and assess whether correlations between variables are plausible⁵²

published study reports and citations and Altmetric attention metrics.^{43–45} One study looked at publication characteristics and dissemination of covid-19 preprints, another looked at outcome reporting and spin in interpretation of results, and another looked at risk of bias and spin. These studies were, however, restricted to only publications up to August and October 2020—which is not representative of the current landscape of covid-19 research and which does not include the majority of evidence being currently used to guide covid-19 care, including critical trials of the effects of corticosteroids and interleukin 6 receptor blockers.^{1 2} These studies did not compare the effects of including preprints on meta-analytic estimates and the certainty of the body of evidence, which is particularly important because evidence users use the totality of the body of evidence, rather than single studies, to make treatment decisions and recommendations.⁴³ One study has reviewed publication rates and citations for covid-19 research but it primarily deals with basic science research and so its findings might not apply to covid-19 clinical trials.⁴⁶

The covid-19 pandemic highlighted the need for rapid dissemination of research and incited increased interest in preprint servers, which yielded an substantial amount of research that was published on preprint servers and which made this study possible. We are not aware of studies looking at the trustworthiness or impact of preprints in other areas—although such research in other areas would

also be useful. Our results are also aligned with previous assessments before covid-19 that study interpretations and other study details do not change importantly between preprints and their later publications in high impact journals.⁴⁷

Strengths and limitations of the study

The strengths of this study include the comprehensive search for and inclusion of preprint and published covid-19 trial reports and rigorous data collection. The generalisability of our results is, however, limited to covid-19. Journals have expedited the publication of covid-19 research and have been publishing more prolifically on covid-19 than on other areas, which could reduce opportunity for revisions between preprints and their subsequent publications and might mean that time to and predictors of publication might differ than in other research areas. For these reasons, our estimated time to publication of covid-19 preprints is different from estimates made from before covid-19.⁴⁸

Although the WHO covid-19 database is a comprehensive source of published and preprint literature, it does not include all preprint servers—but preprint servers not covered by our search strategy include other subjects and are unlikely to include covid-19 trials.

Preprints of trials that are subsequently published in journals could represent the most rigorous or transparently reported preprints, which are not representative of all trial preprints. To minimise this limitation, we compared the characteristics of published and unpublished trial preprints and we did not identify any important differences. This comparison suggested that published and unpublished trial reports in our sample are comparable.

Furthermore, published trial reports might still contain errors, posting trial reports as preprints could allow more errors to be identified before final publication, and even trials without discrepancies between the preprint and later published report might have important limitations that reduce their trustworthiness.

Our assessment of differences in key results between preprints and publications was limited to the outcomes that were included in our living SRNMA. While these outcomes were identified as being important or critical to decision making by coauthors of the living SRNMA and the parallel guideline, they do not include adverse events. Differences in such outcomes could exist between preprints and publications.⁴⁴ Further, other aspects of the reporting of results (eg, baseline characteristics of patients) could be different between preprints and publications.

We report on the number of publications and preprints that were retracted. Preprints, however, could be less likely to be retracted because they might draw less attention and because preprint

servers could be less likely than journals to have formal policies on research integrity. Further, we found too few retractions to be able to draw confident conclusions.

Our assessment of the impact of preprints focused only on the impact of preprints on meta-analytic estimates, the certainty of evidence, and decision making and did not consider other aspects of impact, such as number of citations or Altmetrics.

We used the GRADE approach to assess the certainty of evidence.²⁶ While the GRADE framework provides a transparent and systematic framework of all factors that might bear on the certainty of evidence, its application is subjective.

Our assessment of the contribution of trial preprint reports to meta-analytic estimates and their effect on the certainty of evidence was undertaken in the context of pairwise meta-analysis and the minimally contextualised approach for assessing the certainty of evidence, whereas parallel guideline recommendations have been based on network meta-analyses and the fully contextualised approach.^{20 27} Despite no compelling reasons that our results will not be generalisable to network meta-analyses, more differences in judgments will be related to the certainty of evidence in a fully contextualised framework where judgments are more dependent on the magnitude and precision of estimates.

We limited our assessment of the impact of meta-analyses including versus excluding preprint reports on meta-analytic estimates to only interventions that have been addressed by the WHO living guideline at the time of analysis.²⁰ While the effects of including or excluding preprints in meta-analyses might vary across interventions, our analysis looks at the interventions that have had sufficient interest and research to instigate guideline recommendations. Interventions informed by fewer trials may be more sensitive to including or excluding evidence from preprints.

Our estimate of the time to publication of preprint reports might have been over-estimated if some preprint authors did not attempt to subsequently publish in peer reviewed journals—although evidence shows that most authors of covid-19 preprints intend to publish their findings.⁴³ Time to publication might also be under-estimated if preprints are made public later in the submission process.

Where discrepancies exist between preprints and publications, systematic reviewers and guideline developers will also need to consider whether the results of preprints or publications are more trustworthy and should be incorporated in the meta-analysis. In such situations, systematic reviewers and guideline developers might assume that changes between preprints and publications are due to errors or inaccuracies in the reporting of the preprint that were later corrected during peer review. Future research should investigate whether including

results from preprints or final publications affects overall findings and decisions.

Finally, although we describe discrepancies in the reporting of key methods and results, we did not assess differences in the discussion or conclusion sections of trial reports.

Conclusions

We found no compelling evidence indicating important discrepancies between preprint and published trial reports. We show that including preprints might affect the results of meta-analyses and the certainty of evidence, and might encourage evidence users to consider data from preprints in contexts in which decisions are being made rapidly and evidence is being produced faster than can be peer reviewed and published. Scepticism might still be warranted when suspicion arises regarding falsified data (for which we provide criteria).

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Contributors DZ, RACS, and RB-P conceptualised the study. JJB, FV-P, GR, and AQ screened studies for eligibility. TP, GL, EC, AA, FK, ZE, MAC, MG, YW, EK, JJB, and AQ collected data. DZ drafted the first version of the manuscript. All authors reviewed the manuscript and provided important intellectual input. DZ is study guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author affirms that the 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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COVID-19 Trial Preprints: Consistency with later publications and impact for decision-making

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Supplement 1 – Study protocol**The credibility and utility of trial preprints during the COVID-19 pandemic: A protocol for a methodological study*****Background***

Clinicians and other decision makers need rapidly available and credible data addressing the comparative effectiveness of potential treatments and prophylaxis for the coronavirus disease 2019 (COVID-19). During the COVID-19 pandemic, the scientific community has adopted preprint servers, which allow investigators to disseminate research findings before publication in peer-reviewed journals.

Growing interest in preprints predates the COVID-19 pandemic (1, 2). Researchers and evidence users have raised concerns that the traditional publication model is slow, peer review may not always improve the quality of manuscripts, journals impede dissemination due to paywalls and high publication fees and encourage publication bias by prioritizing statistically significant or anomalous findings—issues preprints may avoid (3-9). Despite these concerns, and the potential of preprints to address them, because preprints may result in the dissemination of provisional findings that contain important errors, the medical community has been cautious about their adoption (10, 11). Authors of systematic reviews, guideline developers, and other decision makers face a trade-off when considering preprints: on the one hand inclusion could reduce the credibility of evidence syntheses and risk serious errors if important differences appear in later published reports; on the other, including preprints may increase the precision of estimates, allow timely dissemination, and minimize the effects of publication bias.

Knowledge of the extent to which preprints may accelerate the dissemination of findings, the frequency and nature of discrepancies between pre-prints and subsequent reports, and their impact on meta-analytic estimates could inform the trade-off that evidence users face. Our study will capitalize on the methods and data of our living systematic review and network meta-analysis (SRNMA) of drug treatments, antiviral antibodies and cellular therapies, and prophylaxis for COVID-19—an initiative launched in July 2020 that provides real-time summaries addressing the comparative effectiveness of potential treatments and prophylaxis for COVID-19—to report on the characteristics, credibility, and utility of COVID-19 trial preprint reports (12). We define credibility as complete and consistent reporting of key aspects of the methods and results between preprint and published trial reports and utility as the contribution of preprint reports to narrow confidence intervals and produce higher certainty evidence.

Methods*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.

Search

Our study will use the search strategy of our living SRNMA that includes daily searches of the World Health Organization (WHO) COVID-19 database—a comprehensive multilingual source of global published and preprint literature on COVID-19 (<https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/>). Prior to its merge with the WHO COVID-19 database on 9 October 2020, we searched the US Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database. We use a validated machine learning model to identify randomized controlled trials (13). We also search six Chinese databases monthly: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints).

Our search is supplemented by ongoing surveillance of living evidence retrieval services, including the Living Overview of the Evidence (L-OVE) COVID-19 platform by the Epistemonikos Foundation (<https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d>) and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health (<https://www.fhi.no/en/qk/systematic-reviews-hta/map/>).

Supplementary 1 includes additional details of our search strategy.

Study selection

As part of the living SRNMA, pairs of reviewers, following calibration exercises, work independently and in duplicate to screen titles and abstracts of search records and subsequently the full texts of records determined potentially eligible at the title and abstract screening stage. Reviewers also link preprint reports with their subsequent publications based on trial registration numbers, authors, and other trial characteristics. Reviewers resolve discrepancies by discussion or, when necessary, by adjudication with a third-party reviewer.

We include preprint and peer reviewed reports of trials that randomize patients with suspected, probable, or confirmed COVID-19 to drug treatments, antiviral antibodies and cellular therapies, placebo, or standard care or trials that randomize healthy participants exposed or unexposed to COVID-19 to prophylactic drugs, standard care, or placebo. We do not apply any restrictions based on severity of illness, setting, or language of

publication. We exclude trials that report on nutritional interventions, traditional Chinese herbal medicines without standardization in formulations and dosing across batches, and non-drug supportive care interventions.

For this project, we will include all eligible trial reports identified through our living SRNMA.

Data collection

As part of the living SRNMA, for each eligible trial, pairs of reviewers, following training and calibration exercises, independently extract trial characteristics, methods, and results using a standardized, pilot tested data extraction form. To assess risk of bias, reviewers, following training and calibration exercises, use a revision of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) (14) (Supplementary 2). Reviewers resolve discrepancies by discussion and, when necessary, by adjudication with a third party.

For the current study, pairs of trained and calibrated reviewers, working independently and in duplicate and using a pilot-tested form, will collect data on differences between preprint and published trial reports in key methods and results. Key methods include description of the randomization process and allocation concealment, blinding of patients and healthcare providers, extent of and handling of missing outcome data, blinding of outcome assessors and adjudicators, and prespecification of outcomes and analyses. For key methods, we will consider discrepancies that may affect the rating of risk of bias. Key results include number of participants analyzed and means or medians and measures of variability for continuous outcomes and the number of events for dichotomous outcomes. We will focus on the same outcomes as our living SRNMA: mortality, mechanical ventilation, adverse events leading to discontinuation, viral clearance, admission to hospital, viral clearance, hospital length of stay, ICU length of stay, duration of mechanical ventilation, time to symptom resolution or clinical improvement, time to viral clearance, days free from mechanical ventilation, and time to viral clearance. For preprints with more than one version, we will extract data from the first version of the preprint, which is the least likely to have been modified in response to peer review.

Data synthesis and analysis

We will compare the characteristics of trials with versus without preprints, including country of recruitment, registration, study status, type of interventions studied (drug therapy, antiviral antibodies and cellular therapies, or prophylaxis), severity of disease (inpatient/outpatient and whether patients were severe/critical), number of centers, number of participants, statistical significance of primary and secondary outcomes (based on cut-offs defined by the authors or, when no cut-offs are defined, based on a cut-off of $p<0.05$ or confidence intervals not including the null), risk of bias, and source of funding, by calculating differences in proportions and

associated 95% confidence intervals. Because risk of bias may vary across outcomes, we will present risk of bias ratings corresponding to the following hierarchy which represents the relative importance of outcomes for clinical decisions and recommendations: mortality, mechanical ventilation, duration of hospitalization, time to symptom resolution or clinical improvement, and virologic outcomes. For prophylaxis trials, we will use the following hierarchy: mortality, laboratory confirmed and suspected COVID-19 infection, and laboratory confirmed COVID-19 infection.

We will calculate the median time from a trial being posted on a preprint server to its eventual publication in a journal and will assess whether source of funding, number of centers and participants, intensity of care (inpatient versus outpatient), early termination for benefit, statistically significant primary or secondary outcomes (based on cut-offs defined by the authors or, when no cut-offs were defined, based on a cut-off of $p<0.05$ or confidence intervals not including the null), and risk of bias are predictive of time to publication using Kaplan-Meier curves with log-rank tests. We anticipate large, multicenter trials, industry-funded trials, trials that are terminated early for benefit, trials that report on inpatients, trials with statistically significant results, and trials at low risk of bias to be published faster.

We will describe the number and types of discrepancies in the reporting and presentation of key methods and results between preprint and published trial reports. For discrepancies in the reporting of methods, we will assess whether the differences changed risk of bias ratings.

To investigate differences in meta-analyses that include versus exclude evidence from preprints, we will focus on interventions that have been addressed by the WHO living guideline (15), IL-6 receptor blockers, ivermectin, hydroxychloroquine, lopinavir-ritonavir, remdesivir, and corticosteroids, and the two most commonly reported outcomes in trials (i.e., mortality, mechanical ventilation). For these interventions and outcomes, we will conduct pairwise frequentist random-effects meta-analyses with the restricted maximum likelihood estimator that include and exclude evidence from available preprints at one, three, and six months after the first trial preprint or published report addressing the intervention of interest became publicly available.

To facilitate interpretation, we will use baseline risks from the CDC and International Severe Acute Respiratory and Emerging Infection COVID-19 database to calculate absolute effects (16-18). We will assess the certainty of evidence using GRADE approach and report whether including versus excluding preprint reports leads to important differences in the effect estimates, ratings of the overall certainty of evidence, judgments related to

specific domains of GRADE, and whether differences in ratings are likely to impact decision making (i.e., evidence rated as high/moderate is downgraded to low/very low or vice versa) (19).

We will consider differences in effect estimates important if a meta-analysis including preprints suggests benefit and a meta-analysis excluding preprints suggests harm, or vice versa, or if a meta-analysis including preprints suggests no effect and a meta-analysis excluding preprints suggests benefit or harm, or vice versa. Judgments of imprecision will be made using a minimally contextualized approach. The minimally contextualized approach considers only whether confidence intervals include the null effect and thus does not consider whether confidence intervals include both important and trivial effects. To evaluate certainty of no effect, we will use a 1% risk difference threshold for mortality and a 2% risk difference for mechanical ventilation (20).

Discussion

Clinicians and decision-makers need rapidly available and credible data on the comparative effectiveness of potential treatments and prophylaxis for COVID-19. Preprints have become central venues through which trial authors can quickly disseminate their findings (1-4, 21-23). Authors of seminal COVID-19 trials, for example, representing massive international collaborations, such as RECOVERY (24-27) and SOLIDARITY (28, 29), chose to report their results in preprints before subsequent publication in journals. Evidence users have, however, expressed concerns about the credibility of trial preprints (10, 11).

Our study will present a detailed assessment of the credibility and utility of COVID-19 trial preprint reports. We will show the extent to which preprints accelerate time to dissemination of trial findings, differences between preprints and their subsequent published reports in key methods and results, and test whether including preprints in meta-analyses improves the precision and overall certainty of evidence.

Implications

Our findings will have implications for evidence users and decision makers who are concerned with the credibility of preprint reports and for systematic reviewers and guideline developers deciding whether to consider preprint reports in systematic reviews and guideline recommendations. Evidence that preprints accelerate dissemination of findings, do not report results which are inconsistent with published trial reports, and that including preprint reports in systematic reviews results in higher certainty evidence will lend further support to the credibility and utility of preprints for consideration in systematic reviews and guidelines. Opposite results will mandate consideration of excluding preprints. Future health emergencies will also

necessitate rapid dissemination of research and our study will inform whether evidence-users can confidently rely on preprint trial reports during health emergencies.

Relation to previous work

Our study will be the first to present data addressing the relative contribution of preprint reports to the evidence regarding the comparative effectiveness of COVID-19 therapies and prophylaxis, and to test the robustness of meta-analyses and conclusions that include versus exclude preprint reports.

Two studies have reported on differences between preprint and published study reports and citations and Altmetric attention metrics (30, 31). One study additionally addressed publication characteristics and dissemination of COVID-19 preprints and the other spin in interpretation of results. Both studies were, however, restricted to publications up to August and October 2020—which is not representative of the current landscape of COVID-19 research and which does not include the majority of evidence being currently used to guide COVID-19 care, including critical trials addressing the effects of corticosteroids (24, 25). These studies also included all study designs rather than focusing only on randomized trials that are primarily used to guide clinical decisions and recommendations (15, 32), and did not compare the effects of including preprints on meta-analytic estimates and the certainty of the body of evidence (30). The latter issue is particularly important because evidence users use the totality of the body of evidence, rather than single studies, to make treatment decisions and recommendations.

Strengths and limitations

The strengths of this study include the comprehensive search for and inclusion of preprint and published COVID-19 trial reports and rigorous data collection. We also focus on the implications of preprints for evidence users and decision-makers rather than only on only discrepancies between preprints and publications that may not matter importantly. The generalizability of our results is, however, limited to COVID-19. Journals have been expediting publication of COVID-19 research and have been publishing more prolifically on COVID-19 than in other areas, which may reduce opportunity for revisions between preprints and their subsequent publications and may mean time to publication and predictors of publication may be different than in other research areas.

Although the WHO COVID-19 database is a comprehensive source of published and preprint literature, it does not include all preprint servers—though preprint servers not covered by our search address other subjects and are unlikely to include COVID-19 trials.

We will limit our assessment of the effects of including versus excluding preprint reports on meta-analytic estimates and the certainty of evidence to only interventions that have been addressed by the WHO living

guideline. It is possible that preprint reports of trials that are subsequently published in journals represent the most rigorous or transparently reported preprints and that they are not representative of all trial preprints. Our estimate of the time to publication of preprint reports may be overestimated if some preprint authors did not attempt to subsequently publish in peer-reviewed journals—although evidence shows that most preprint authors of COVID-19 studies intend to publish their findings (30). Finally, although we will describe discrepancies in the reporting of key methods and results between preprint and published trial reports, we will not assess differences in the discussion or conclusion sections of trial reports and the interpretation of findings. It is possible that preprint reports may contain more spin and positive interpretation of results compared to published trial reports (31).

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Supplement 2 – Search Strategy

Search purpose: Systematic search of the COVID-19 literature performed Monday through Friday for the WHO Database. Searches performed by Tomas Allen, Kavita Kothari, and Martha Knuth.

Use following commands to pull daily new entries:

- Entry_date:[20210101 TO 20210120]
- Entry_date:[20210105]

Duplicates: Duplicates are found in EndNote and Distillr using the Wicher method. Further screening is done by expert reviewers but some duplicates may still be in the database.

Daily Search Strategy:

Database	Search Strategy
Medline (Ovid) 1946-	(coronavir* OR corona virus* OR corona pandemic* OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR wuhan virus*).mp. OR (sars AND cov).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR Coronavirus Infections/ OR Coronavirus/ OR betacoronavirus/ Limits: 2020-
CAB Abstracts(Ovid) 1910-	(coronavir* OR corona virus* OR corona pandemic* OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR wuhan virus*).mp. OR (sars AND cov).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR exp Betacoronavirus/
Global Health (Ovid) 1910-	(coronavir* OR corona virus* OR corona pandemic* OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR wuhan virus*).mp. OR (sars AND cov).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR exp Betacoronavirus/
PsycInfo (Ovid) 1806-	(coronavir* OR corona virus* OR corona pandemic* OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR wuhan virus*).mp. OR (sars AND cov).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. Limits: 2020-
Scopus 1960-	TITLE-ABS-KEY (coronavir* OR "corona virus" OR "corona pandemic" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR TITLE-ABS-KEY(sars AND cov) OR (TITLE-ABS-KEY (wuhan OR hubei OR huanan) AND TITLE-ABS-KEY ("severe acute respiratory" OR pneumonia*) AND TITLE-ABS-KEY (outbreak*)) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO

	(PUBYEAR , 2020))
Academic Search Complete (Ebsco)	TI,AB,SU((coronavir* OR "corona virus" OR "corona pandemic" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR (sars AND cov) OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) OR ((MH "Coronavirus") OR (MH "Coronavirus Infections")) Limits: Dec. 2019-, peer-reviewed
Africa Wide Information (Ebsco)	TI,AB,SU((coronavir* OR "corona virus" OR "corona pandemic" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR (sars AND cov) OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) Limits: 2019-,
CINAHL (Ebsco)	TI,AB,SU((coronavir* OR "corona virus" OR "corona pandemic" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR (sars AND cov) OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) OR ((MH "Coronavirus") OR (MH "Coronavirus Infections")) Limits: Dec. 2019-, peer-reviewed
ProQuest Central (Proquest) 1952-	TI,AB,SU((coronavir* OR "corona virus" OR "corona pandemic" OR betacoronavir* OR covid19 OR covid OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR (sars AND cov) OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) Limits: Dec. 2019-, peer-reviewed
China CDC MMWR	Covid OR cov2 OR coronavirus OR "sars cov" OR ncov
CDC Reports	Covid OR cov2 OR coronavirus OR "sars cov" OR ncov
bioRxiv medRxiv chemRxiv (preprints)	Covid OR cov2 OR coronavirus OR "sars cov" OR ncov
Embase (Ovid)	ncov OR ('coronavirus'/exp OR coronavirus) AND ('wuhan'/exp OR wuhan)) OR 'novel coronavirus' OR ('pneumonia'/exp OR pneumonia) AND wuhan:ti,ab) OR 'covid' OR 2019ncov OR 'sars-cov'/exp OR 'sars-cov' OR covid OR ('coronavirus'/exp OR coronavirus) AND novel) OR ('corona virus':ti,ab OR 'coronavirus':ti,ab) AND (outbreak:ti,ab OR epidemic*:ti,ab OR pandemic*:ti,ab OR quaran*:ti,ab OR lockdown*:ti,ab OR syndemic*:ti,ab)) OR hcov OR 'sars virus'/exp OR 'sars virus' OR 'coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR 'novel coronavirus pneumonia' OR 'covid 19 virus' OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2' OR 'coronavirinae'/exp OR 'coronavirinae' OR 'coronavirus infection'/exp OR 'coronavirus infection' OR 'covid19'/exp OR covid19 OR covid2019 OR 'corona pandemic' OR 'sarscov 2' OR 'sarscov-2' OR 'sars co v 2' OR 'social distancing'/exp OR 'social distancing' OR coivid OR 'flatten the curve' OR 'flattening the curve' OR pandoeconom*

	OR twindemic* OR 'sars voc'
Global Index Medicus	(nCov OR (coronavirus AND wuhan) OR "novel coronavirus" OR (pneumonia AND wuhan) OR covid OR 2019ncov OR "sars-cov" OR covid OR (coronavirus AND novel) OR ("corona virus" OR coronavirus) AND (ti:outbreak OR ti:epidemic* OR ti:pandemic* OR ti:quaran* OR ti:syndem* OR hcov OR "sars virus")) OR "coronavirus disease 2019" OR " novel coronavirus pneumonia" OR "COVID 19 virus" OR "severe acute respiratory syndrome coronavirus 2" OR Coronavirinae OR "Coronavirus infection" OR covid19 OR covid2019 OR lockdown* OR "social distancing" OR "physical distancing" OR "corona pandemic" OR "sarscov 2" OR "sarscov-2" OR "sars co v 2" OR coivd OR "flatten the curve" OR "flattening the curve" OR "sars voc")
Web of Science	TI=coronavirus OR TI=covid OR TI=Covid19 OR TI=ncov OR TI=(SARS NEAR/3 COV) OR TI="novel coron*virus" OR TI=2019*ncov OR TI=2019ncov OR TI=(CORON*VIRUS NEAR/3 (OUTBREAK OR pandemic OR 2019 OR new OR novel)) OR TI=coronavirinae OR TI=coronaviridae OR TI=betacoronavirus OR TI=Sars2 OR TI=COV2 OR TI="corona pandemic" OR ((TI=wuhan OR TI=hubei OR TI=huanan) AND (TI="severe acute respiratory" OR TI=pneumonia) AND (TI=outbreak))
PubMed Central	coronavirus[Title] OR "corona virus" [Title] OR "corona pandemic"[Title] OR coronavirinae[Title] OR coronaviridae[Title] OR betacoronavirus[Title] OR covid19[Title] OR covid[Title] OR nCoV[Title] OR "CoV 2"[Title] OR CoV2[Title] OR sars2[Title] OR sarscov2[Title] OR 2019nCoV[Title] OR "novel CoV"[Title] OR "wuhan virus"[Title] OR coronavirus[Abstract] OR "corona virus" [Abstract] OR "corona pandemic"[Abstract] OR coronavirinae[Abstract] OR coronaviridae[Abstract] OR betacoronavirus[Abstract] OR covid19[Abstract] OR covid[Abstract] OR nCoV[Abstract] OR "CoV 2"[Abstract] OR CoV2[Abstract] OR sars2[Abstract] OR sarscov2[Abstract] OR 2019nCoV[Abstract] OR "novel CoV"[Abstract] OR "wuhan virus"[Abstract] OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR ((wuhan[Title] OR hubei[Title] OR huanan[Title]) OR (wuhan[Abstract] OR hubei[Abstract] OR huanan[Abstract])) AND ("severe acute respiratory"[Title] OR pneumonia[Title])) OR (("severe acute respiratory"[Abstract] OR pneumonia[Abstract]) AND (outbreak[Title]) OR outbreak[Abstract]))
Science Direct	COVID OR COVID19 OR 2019Ncov OR Ncov OR Coronavirus OR "corona virus" OR (SARS AND Cov)
Wiley Online	COVID-19 OR nCov OR 2019ncov OR (pneumonia AND wuhan) OR (sars AND cov) OR COVID OR Covid19 OR "corona virus" OR coronavirus OR COV2 OR SARS2 OR coronavirinae OR coronaviridae OR betacoronavirus OR "corona pandemic" OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia) AND (outbreak)))

Supplement 3 – Risk of Bias Guidance

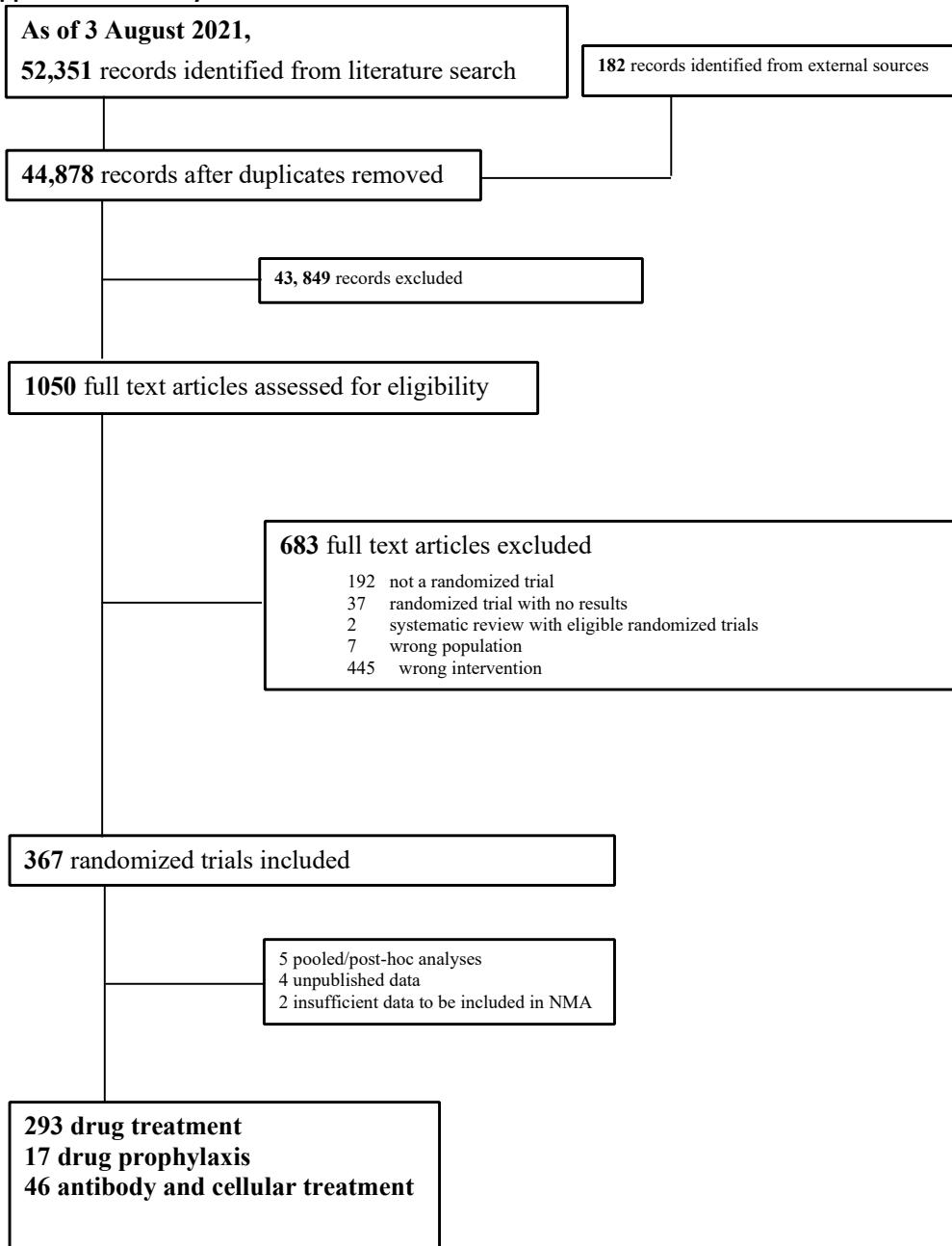
Bias from the randomization process	
Issues to consider:	
Definitely low risk of bias	<p>Trials that assign participants to alternative interventions using a randomly generated sequence and maintain allocation concealment.</p> <p>Examples of methods for developing a randomly generated allocation sequence include a random number generator, random number table, coin tossing, shuffling cards or envelopes, and throwing dice. If a trial is described as 'randomized' without any additional details related to how the allocation sequence was developed, we will assume that the allocation sequence was appropriately developed.</p> <p>Examples of methods for maintaining allocation concealment include using central allocation via a computer or phone system, pharmacy-controlled allocation, opaque sealed envelopes, and sequentially numbered drug containers.</p> <p><i>Note that an explicit description of random sequence generation is not necessary for a rating of low risk of bias.</i></p>
Probably low risk of bias	<p>Trials in which healthcare providers were blind to the intervention but which provide no information on allocation concealment and in which there are no major baseline imbalances.</p> <p><i>Note that an explicit description of random sequence generation is not necessary for a rating of probably low risk of bias.</i></p>
Probably high risk of bias	<p>Trials in which healthcare providers were not blind to the intervention and which provide no information on allocation concealment.</p> <p>Trials in which there are substantial baseline differences between trial arms that suggest a problem with the randomization process but there are no other limitations related to randomization.</p>
Definitely high risk of bias	<p>Trials in which allocation is by judgment of the clinician, by preference of the participant, by availability of the intervention, based on the results of a laboratory test, or other non-random rules (e.g., birthdate, etc.).</p> <p>Trials in which investigators enrolling participants could possibly foresee the arm to which each subsequent patient would be randomized, such as allocation using an open allocation schedule (e.g. a list of random numbers), assignment envelopes used without appropriate safeguards (e.g. use of unsealed, non-opaque or not sequentially numbered envelopes), alternation between arms, case record number, or any other</p>

	explicitly unconcealed procedure, rate as high risk.
Bias due to deviations from the intended intervention	
Issues to consider:	
Blinding of healthcare providers/clinicians and participants	
Imbalances in cointerventions or behaviors	
Definitely low risk of bias	<p>Therapy trials in which healthcare providers are blind to the intervention administered and in which there are no significant differences in administered co-interventions.</p> <p>Therapy trials that are described as double or triple blind.</p> <p>Prophylaxis trials in which participants are blind to the intervention that they have been randomized.</p> <p>Prophylaxis trials that are described as double or triple blind.</p>
Probably low risk of bias	
Probably high risk of bias	<p>Therapy trials in which healthcare providers are not blind to the intervention administered.</p> <p>Therapy trials in which healthcare providers are blind to the intervention administered but there are significant differences in administered co-interventions that suggests that blinding may have been compromised.</p> <p>Therapy trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate.</p> <p>Prophylaxis trials in which participants are not blind to the intervention that they have been randomized.</p> <p>Prophylaxis trials in which participants are blind to the intervention to which they have been randomized but there are significant differences in social distancing and risk-taking behaviors that suggest that blinding may have been compromised.</p> <p>Prophylaxis trials in which healthcare providers are not blind to the intervention and in which healthcare providers were very involved and counselled patients on social distancing, risk-taking behaviors, or testing for COVID-19.</p>
Definitely high risk of bias	<p>Therapy trials in which healthcare providers are not blind to the intervention and in which there are significant differences in administered co-interventions.</p> <p>Prophylaxis trials in which participants are not blind to the intervention and in which there are significant differences in social distancing and risk-taking behaviors.</p>

Bias due to missing data	
Issues to consider:	
Missing outcome measures	
Loss to follow-up	
Definitely low risk of bias	<p>Trials in which missing outcome data (including outcome data that has been imputed) < 10%.</p> <p>For in-patient trials, we will assume low risk of bias due to missing data unless otherwise specified.</p>
Probably low risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is unlikely to be related to the true outcome and there is no imbalance in numbers of or reasons for missing data across intervention groups.
Probably high risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is likely to be related to the true outcome or there are imbalances in numbers of or reasons for missing data across intervention groups.
Definitely high risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) > 15%.
Bias due to measurement of the outcome	
Issues to consider:	
Blinding of outcome adjudicators	
Objectivity of outcome	
<i>Note that the judgments may differ across outcomes.</i>	
Definitely low risk of bias	<p>Trials in which patients are blind to the intervention and in which outcomes are patient-reported.</p> <p>Trials in which outcomes are measured by a third-party (investigator or clinician) and in which the third-party is blind to the intervention.</p> <p>Trials in which the outcomes are objective (e.g., mortality, infection with COVID-19 confirmed by a positive RT-PCR swab, mechanical ventilation, admission to hospital, duration of hospital stay, ICU length of stay, ventilator free days, duration of mechanical ventilation, time to clinical improvement if clinical improvement is measured via objective criteria, viral clearance, time to viral clearance).</p> <p>Trials that are described as double or triple blind.</p>
Probably low risk of bias	
Probably high risk of bias	
Definitely high risk of bias	Trials in which patients are not blind and in which outcomes are patient-reported (e.g., time to symptom resolution).

	Trials in which outcome adjudicators are not blind and the outcomes are not objective (e.g., adverse effects leading to discontinuation, transfusion-related acute lung injury, transfusion-associated circulatory overload, allergic reactions, infection with suspected/symptomatic COVID-19, venous thromboembolism, time to symptom resolution including fever, time to clinical improvement if the criteria for clinical improvement are not objective).
Bias in selection of the reported results	
Issues to consider:	
Selective reporting of timepoints	
Selective reporting of outcome measures	
<p><i>Note that we are only interested in selective reporting for the outcomes for which we are extracting data.</i></p> <p><i>Note that the judgments may differ across outcomes.</i></p>	
Definitely low risk of bias	Results for outcomes that were analyzed and reported according to a pre-specified statistical analysis plan or protocol (including the timepoint for the measurement of the outcome).
Probably low risk of bias	<p>Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is consistent with the timepoint for other outcomes in the trial report or there is little reason to believe the outcome was selectively reported.</p> <p>Please note that outcomes that were not prespecified in a protocol or statistical analysis plan and that are reported in the trial preprint or publication should be rated at probably low risk of bias unless there are other important reasons to suspect that results for those outcomes were selectively reported (e.g., results are presented at timepoints that don't match the timepoints reported for other outcomes).</p>
Probably high risk of bias	Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is not consistent with the timepoint for other outcomes in the trial report or there are other reasons to believe that the outcome is selectively reported.
Definitely high risk of bias	Results for outcomes that were analyzed and reported for which there are inconsistencies with the statistical analysis plan or protocol. These inconsistencies may include outcome measures of interest or the timepoints for the measurement of outcomes.
Bias due to competing risks	
Issues to consider:	
Competing risks due to early termination (<u>only for continuous outcomes</u>)	
Definitely low risk of bias	Results are very unlikely to have been affected by competing risk due to death.

	For example, the intervention arm increased the risk of death but the duration of hospitalization is shorter in the control arm.
Probably low risk of bias	<p>Results are unlikely to have been affected by competing risk due to death.</p> <p>For example, the intervention arm increased the risk of death but the duration of hospitalization is slightly shorter in the control arm or there is no appreciable difference between arms.</p>
Probably high risk of bias	<p>Results are likely to have been affected by competing risk due to death.</p> <p>For example, the intervention increased the risk of death and the duration of hospitalization is appreciably lower in the intervention arm.</p> <p>Note that for outcomes such as ICU length of stay and duration of ventilation in which only patients admitted to the ICU or patients are ventilated may be included in analyses, even small imbalances in deaths across trial arms may lead to bias due to competing risks because patients who die are also likely the ones who were admitted to the ICU or ventilated. While patients who die may make up only a small proportion of the total patients included in the trial, they may make up an appreciable proportion of patients who are admitted to the ICU and who are ventilated.</p>
Definitely high risk of bias	<p>Results are very likely to have been affected by competing risk due to death.</p> <p>For example, the intervention arm increased the risk of death and the duration of hospitalization is much lower in the intervention arm.</p>

Supplement 4 – Study flow

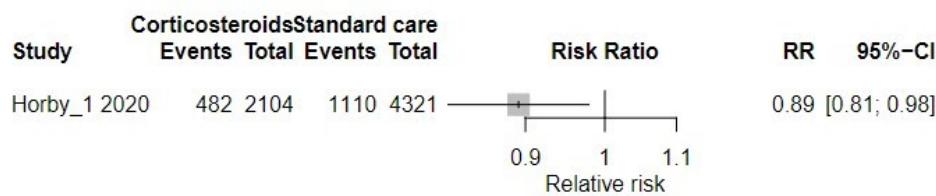
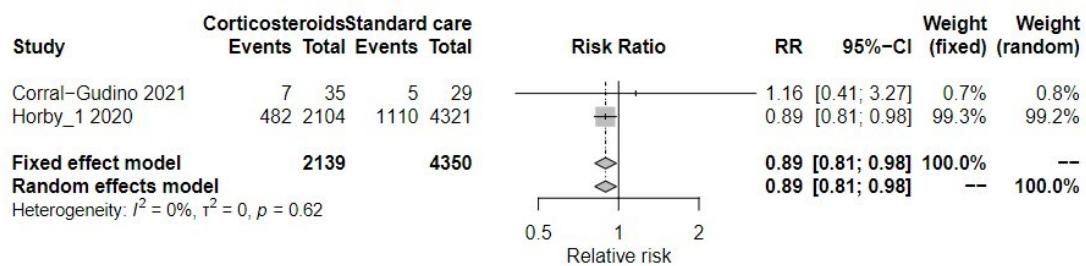
Supplement 5 – Differences between preprint and published trial reports

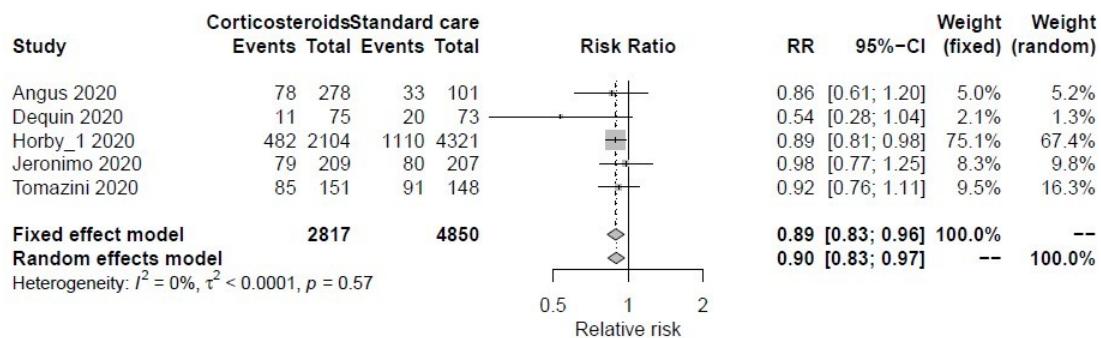
Methods	Number (%)
The publication reports additional information on allocation concealment.	8 (10.8%)
Resulted in change in RoB (randomization)	4 (5.4%)
The publication reports additional statistic(s) important for meta-analysis	6 (8.1%)
The preprint reports interim results and publication reports complete results	4 (5.4%)
The publication lists one or more additional funding sources	4 (5.4%)
The publication includes SAP/protocol	3 (4.1%)
Resulted in change in RoB (selective reporting)	1 (1.4%)
The publication reports additional information on trial status	2 (2.7%)
Publication and preprint report different types of analyses (i.e., ITT vs. PP)	2 (2.7%)
Resulted in change in RoB (missing outcome data)	1 (1.4%)
The preprint reports outcome for an unspecified subgroup whereas the publication reports outcome data for the full randomized population	1 (1.4%)
Resulted in change in RoB (selective reporting)	1 (1.4%)
The publication reports additional information on missing outcome data	1 (1.4%)
Resulted in change in RoB (missing outcome data)	1 (1.4%)
The publication reports a trial name	1 (1.4%)
The preprint reported an incorrect trial registration	1 (1.4%)
The publication lists an additional country	1 (1.4%)
The number of participants randomized changed between preprint and publication	1 (1.4%)
The publication reports stratified results based on allocation by randomization versus preference whereas the preprint reports results for all patients	1 (1.4%)
The publication reports additional details about the intervention	1 (1.4%)
Results	Number (%)
Change in outcome data	20 (27%)
The publication reports one or more additional outcome(s)	11 (14.9%)
The preprint reports one or more additional outcome(s)	6 (8.1%)
The preprint excluded patients from analysis that discontinued treatment but the publication included them	1 (1.4%)
The preprint and publication report one or more outcomes at different timepoints	1 (1.4%)
The proportion of data that was missing changed	1 (1.4%)

Supplement 6 – Differences between meta-analyses including and excluding meta-analyses

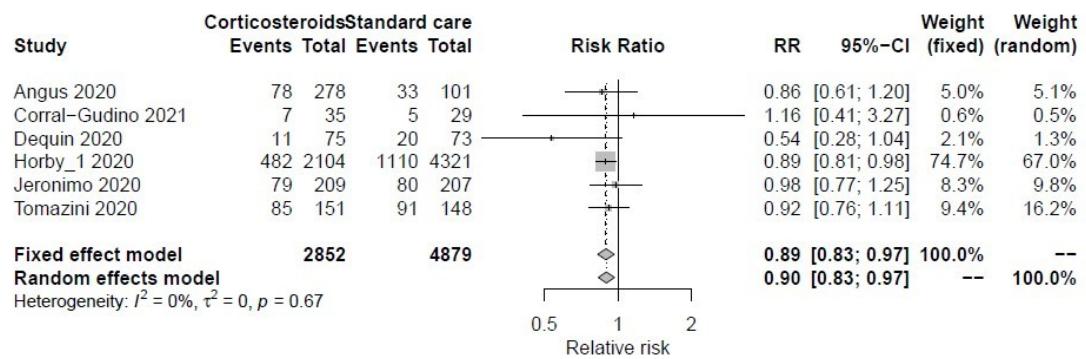
Drug	Excluding unpublished preprints							Including all preprints						
	Number of studies	Number of participants	MA estimate	Risk with standard care /placebo (/1000)	Risk difference (/1000 people)	GRADE	Number of studies	Number of participants	MA estimate	Risk with standard care /placebo (/1000)	Risk difference (/1000 people)	GRADE		
Mortality														
Corticosteroids														
1 month	1	6425	0.89 [0.81 to 0.98]	130	14.3 fewer (24.7 fewer to 2.6 fewer)	Moderate due to risk of bias	2	6489	0.89 [0.81 to 0.98]	130	14.3 fewer (24.7 fewer to 2.6 fewer)	Moderate due to risk of bias		
3 months	5	7667	0.90 [0.83 to 0.97]	130	13 fewer (22.1 fewer to 3.9 fewer)	Moderate due to risk of bias	6	7731	0.90 [0.83 to 0.97]	130	13 fewer (22.1 fewer to 3.9 fewer)	Moderate due to risk of bias		
6 months	5	7667	0.90 [0.83 to 0.97]	130	13 fewer (22.1 fewer to 3.9 fewer)	Moderate due to risk of bias	6	7731	0.90 [0.83 to 0.97]	130	13 fewer (22.1 fewer to 3.9 fewer)	Moderate due to risk of bias		
Current	10	7959	0.90 [0.83 to 0.97]	130	13 fewer (22.1 fewer to 3.9 fewer)	Moderate due to risk of bias	10	7959	0.90 [0.83 to 0.97]	130	13 fewer (22.1 fewer to 3.9 fewer)	Moderate due to risk of bias		
Remdesivir														
1 month	2	1298	0.79 [0.59 to 1.05]	130	27.3 fewer (53.3 fewer to 6.5 more)	Moderate due to imprecision	2	1298	0.79 [0.59 to 1.05]	130	27.3 fewer (53.3 fewer to 6.5 more)	Moderate due to imprecision		
3 months	2	1298	0.79 [0.59 to 1.05]	130	27.3 fewer (53.3 fewer to 6.5 more)	Moderate due to imprecision	2	1298	0.79 [0.59 to 1.05]	130	27.3 fewer (53.3 fewer to 6.5 more)	Moderate due to imprecision		
6 months	3	1882	0.78 [0.59 to 1.04]	130	28.6 fewer (53.3 fewer to 5.2 more)	Moderate due to imprecision	4	7333	0.90 [0.73 to 1.11]	130	13 fewer (35.1 fewer to 14.3 more)	Low due to imprecision (x2)		
Current	5	7415	0.91 [0.75 to 1.11]	130	11.7 fewer (32.5 fewer to 14.3 more)	Low due to imprecision (x2)	6	8247	0.92 [0.79 to 1.07]	130	10.4 fewer (27.3 fewer to 9.1 more)	Moderate due to imprecision		
Lopinavir-ritonavir														
1 month	1	199	0.77 [0.45 to 1.30]	130	29.9 fewer (71.5 fewer to 39 more)	Very low due to risk of bias, imprecision (x2)	2	250	0.77 [0.45 to 1.30]	130	29.9 fewer (71.5 fewer to 39 more)	Very low due to risk of bias, imprecision (x2)		
3 months	2	250	0.77 [0.45 to 1.30]	130	29.9 fewer (71.5 fewer to 39 more)	Very low due to risk of bias, imprecision (x2)	2	250	0.77 [0.45 to 1.30]	130	29.9 fewer (71.5 fewer to 39 more)	Very low due to risk of bias, imprecision (x2)		
6 months	2	250	0.77 [0.45 to 1.30]	130	29.9 fewer (71.5 fewer to 39 more)	Very low due to risk of bias, imprecision (x2)	2	250	0.77 [0.45 to 1.30]	130	29.9 fewer (71.5 fewer to 39 more)	Very low due to risk of bias, imprecision (x2)		
Current	7	9427	1.04 [0.95 to 1.14]	130	5.20 more (6.5 fewer to 18.2 more)	Very low due to risk of bias, imprecision (x2)	7	9427	1.04 [0.95 to 1.14]	130	5.20 more (6.5 fewer to 18.2 more)	Very low due to risk of bias, imprecision (x2)		
(Hydroxy)chloroquine (treatment)														
1 month	1	30	NA (0 events)	130	NA	NA NA	1	30	NA (0 events)	130	NA	NA NA		
3 months	1	30	NA (0 events)	130	NA	NA NA	2	180	NA (0 events)	130	NA	NA NA		
6 months	5	1287	1.16 [0.58 to 2.34]	130	20.8 more (54.6 fewer to 174.2 more)	Very low due to risk of bias, imprecision (x3)	9	6135	1.08 [0.98 to 1.19]	130	10.4 more (2.60 fewer to 24.7 more)	Low due to risk of bias, imprecision		
Current	19	10634	1.09 [1.00 to 1.19]	130	11.7 more (0 fewer to 24.7 more)	Low due to risk of bias, imprecision	23	10997	1.07 [0.98 to 1.17]	130	9.10 more (2.60 fewer to 22.1 more)	Low due to risk of bias, imprecision		
Ivermectin														
1 month	0	0	NA	130	NA	NA NA	1	180	0.18 [0.06 to 0.55]	130	106.6 fewer (122.2 fewer to 65 fewer)	Very low due to risk of bias, imprecision (x2)		
3 months	0	0	NA	130	NA	NA NA	4	517	0.33 [0.09 to 1.17]	130	87.1 fewer (118.3 fewer to 22.1 more)	Very low due to risk of bias, imprecision (x2)		
6 months	1	398	0.33 [0.01 to 8.05]	130	87.1 fewer (128.7 fewer to 916.5 more)	Very low due to risk of bias, imprecision (x3)	6	1169	0.34 [0.11 to 1.00]	130	85.8 fewer (115.7 fewer to 0 fewer)	Low due to risk of bias, imprecision		
Current	5	1220	0.72 [0.28 to 1.85]	130	36.4 fewer (93.6 fewer to 110.5 more)	Very low due to risk of bias, imprecision (x3)	9	1879	0.51 [0.23 to 1.13]	130	63.7 fewer (100.1 fewer to 16.9 more)	Very low due to risk of bias, imprecision (x2)		
IL-6 receptor blockers														
1 month	0	0	NA	130	NA	NA NA	1	97	0.84 [0.46 to 1.51]	130	20.8 fewer (70.2 fewer to 66.3 more)	Very low due to risk of bias, imprecision (x3)		
3 months	2	26	0.30 [0.04 to 2.27]	130	91 fewer (124.8 fewer to 165.1 more)	Very low due to risk of bias, imprecision (x2)	4	435	0.88 [0.58 to 1.32]	130	15.6 fewer (54.6 fewer to 41.6 more)	Very low due to risk of bias, imprecision (x3)		
6 months	6	1292	0.82 [0.67 to 1.00]	130	23.4 fewer (42.9 fewer to 0 fewer)	Low due to risk of bias, imprecision	7	5408	0.87 [0.80 to 0.94]	130	22.1 fewer (31.2 fewer to 13 fewer)	Moderate due to risk of bias		
Current	8	5457	0.87 [0.80 to 0.94]	130	22.1 fewer (31.2 fewer to 13 fewer)	Moderate due to risk of bias	11	6303	0.86 [0.80 to 0.93]	130	22.1 fewer (31.2 fewer to 13 fewer)	Moderate due to risk of bias		
Convalescent plasma														
1 month	1	101	0.65 [0.29 to 1.46]	130	45.5 fewer (92.3 fewer to 59.8 more)	Very low due to risk of bias, imprecision (x3)	2	187	0.60 [0.33 to 1.10]	130	52 fewer (87.1 fewer to 13 more)	Very low due to risk of bias, imprecision (x3)		
3 months	1	101	0.65 [0.29 to 1.46]	130	45.5 fewer (92.3 fewer to 59.8 more)	Very low due to risk of bias, imprecision (x3)	4	428	0.56 [0.32 to 0.97]	130	57.2 fewer (88.4 fewer to 3.90 fewer)	Very low due to risk of bias, imprecision (x2)		
6 months	3	898	0.95 [0.68 to 1.33]	130	6.5 fewer (41.6 fewer to 42.9 more)	Very low due to risk of bias, imprecision (x2)	7	1185	0.83 [0.63 to 1.11]	130	22.1 fewer (48.1 fewer to 14.3 more)	Very low due to risk of bias, imprecision (x2)		
Current	9	12962	0.98 [0.92 to 1.05]	130	2.60 fewer (10.4 fewer to 6.5 more)	Moderate due to risk of bias	14	16073	0.98 [0.93 to 1.03]	130	2.60 fewer (9.10 fewer to 3.90 more)	Moderate due to risk of bias		
(Hydroxy)chloroquine (prophylaxis)														
1 month	1	744	NA (0 events)	3	NA	NA NA	1	744	NA (0 events)	3	NA	NA NA		

3 months	1	744	NA (0 events)	3	NA	NA	NA	2	3151	0.73 [0.24 to 2.24]	3	0.8 fewer (2.3 fewer to 3.7 more)	High	NA
6 months	4	8569	0.73 [0.24 to 2.24]	3	0.8 fewer (2 fewer to 3.7 more)	High	NA	4	8569	0.73 [0.24 to 2.24]	3	0.8 fewer (2 fewer to 3.7 more)	High	NA
Current	4	8569	0.73 [0.24 to 2.24]	3	0.8 fewer (2 fewer to 3.7 more)	High	NA	4	8569	0.73 [0.24 to 2.24]	3	0.8 fewer (2 fewer to 3.7 more)	High	NA
Mechanical Ventilation														
Corticosteroids														
1 month	1	5418	0.75 [0.61 to 0.93]	116	43 fewer (59.24 fewer to 22.12 fewer)	Moderate	due to risk of bias	2	5472	1.01 [0.48 to 2.13]	116	1.2 more (60.3 fewer to 131.1 more)	Very low	due to risk of bias, imprecision (x2)
3 months	5	6324	0.84 [0.74 to 0.95]	116	32.56 fewer (44.16 fewer to 19.8 fewer)	Moderate	due to risk of bias	6	6378	0.85 [0.75 to 0.97]	116	17.4 fewer (29 fewer to 3.5 fewer)	Moderate	due to risk of bias
6 months	5	6324	0.84 [0.74 to 0.95]	116	32.56 fewer (44.16 fewer to 19.8 fewer)	Moderate	due to risk of bias	6	6378	0.85 [0.75 to 0.97]	116	17.4 fewer (29 fewer to 3.5 fewer)	Moderate	due to risk of bias
Current	9	6576	0.88 [0.78 to 0.99]	116	27.92 fewer (39.52 fewer to 15.16 fewer)	Moderate	due to risk of bias	9	6576	0.88 [0.78 to 0.99]	116	13.9 fewer (25.5 fewer to 1.2 fewer)	Moderate	due to risk of bias
Remdesivir														
1 month	2	1001	0.59 [0.44 to 0.79]	116	47.6 fewer (65 fewer to 24.4 fewer)	High	NA	2	1001	0.59 [0.44 to 0.79]	116	47.6 fewer (65 fewer to 24.4 fewer)	High	NA
3 months	2	1001	0.59 [0.44 to 0.79]	116	47.6 fewer (65 fewer to 24.4 fewer)	High	NA	2	1001	0.59 [0.44 to 0.79]	116	47.6 fewer (65 fewer to 24.4 fewer)	High	NA
6 months	3	1585	0.56 [0.42 to 0.74]	116	51 fewer (67.3 fewer to 30.2 fewer)	High	NA	4	6549	0.66 [0.41 to 1.07]	116	39.4 fewer (68.4 fewer to 8.1 more)	Low	due to risk of bias, imprecision
Current	5	6619	0.72 [0.46 to 1.12]	116	32.5 fewer (62.6 fewer to 13.9 more)	Low	due to risk of bias, imprecision	6	7451	0.76 [0.55 to 1.04]	116	27.8 fewer (52.2 fewer to 4.6 more)	Low	due to risk of bias, imprecision
Lopinavir-ritonavir														
1 month	1	198	0.74 [0.38 to 1.42]	116	30.2 fewer (71.9 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)	1	198	0.74 [0.38 to 1.42]	116	30.2 fewer (71.9 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)
3 months	1	198	0.74 [0.38 to 1.42]	116	30.2 fewer (71.9 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)	1	198	0.74 [0.38 to 1.42]	116	30.2 fewer (71.9 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)
6 months	1	198	0.74 [0.38 to 1.42]	116	30.2 fewer (71.9 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)	1	198	0.74 [0.38 to 1.42]	116	30.2 fewer (71.9 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)
Current	5	8474	1.14 [1.02 to 1.26]	116	16.2 more (2.3 fewer to 30.2 more)	Low	due to risk of bias, imprecision	5	8474	1.14 [1.02 to 1.26]	116	16.2 more (2.3 fewer to 30.2 more)	Low	due to risk of bias, imprecision
(Hydroxy)chloroquine (Treatment)														
1 month	2	642	1.14 [0.61 to 2.12]	116	16.2 more (45.2 fewer to 129.9 more)	Very low	due to risk of bias, imprecision (x3)	4	4616	1.15 [0.94 to 1.39]	116	17.4 more (7.0 fewer to 45.2 more)	Low	due to risk of bias, imprecision
3 months	4	4693	1.17 [0.96 to 1.42]	116	19.7 more (4.6 fewer to 46.4 more)	Low	due to risk of bias, imprecision	6	6430	1.15 [0.97 to 1.35]	116	17.4 more (3.5 fewer to 40.6 more)	Low	due to risk of bias, imprecision
6 months	7	6877	1.13 [0.96 to 1.32]	116	15.1 more (4.6 fewer to 37.1 more)	Low	due to risk of bias, imprecision	9	7417	1.11 [0.96 to 1.29]	116	12.8 more (4.6 fewer to 33.6 more)	Low	due to risk of bias, imprecision
Current	12	8053	1.23 [1.05 to 1.46]	116	26.7 more (5.8 more to 53.4 more)	Moderate	due to risk of bias	12	8053	1.23 [1.05 to 1.46]	116	26.7 more (5.8 more to 53.4 more)	Moderate	due to risk of bias
Ivermectin														
1 month	1	45	NA (0 events)	116	NA	NA	NA	2	90	1.52 [0.07 to 35.28]	116	60.3 more (107.9 fewer to 496.5 more)	Very low	due to risk of bias, imprecision (x3)
3 months	1	45	NA (0 events)	116	NA	NA	NA	4	354	0.40 [0.06 to 2.46]	116	69.6 fewer (109 fewer to 169.4 more)	Very low	due to risk of bias, imprecision (x3)
6 months	4	642	0.98 [0.55 to 1.72]	116	2.3 fewer (52.2 fewer to 83.5 more)	Low	due to imprecision (x2)	7	951	0.77 [0.36 to 1.65]	116	26.7 fewer (74.2 fewer to 75.4 more)	Very low	due to imprecision (x3)
Current	8	1464	0.94 [0.58 to 1.53]	116	7.0 fewer (48.7 fewer to 61.5 more)	Low	due to imprecision (x2)	9	1616	0.94 [0.58 to 1.53]	116	7.0 fewer (48.7 fewer to 61.5 more)	Low	due to imprecision (x2)
IL-6 receptor blockers														
1 month	0	0	NA	116	NA	NA	NA	1	273	0.76 [0.53 to 1.09]	116	27.8 fewer (54.5 fewer to 10.4 more)	Low	due to risk of bias, imprecision
3 months	3	495	0.68 [0.43 to 1.09]	116	37.1 fewer (66.1 fewer to 10.4 more)	Low	due to risk of bias, imprecision	5	1145	0.71 [0.55 to 0.93]	116	33.6 fewer (52.2 fewer to 8.1 fewer)	Moderate	due to risk of bias
6 months	7	1826	0.74 [0.63 to 0.86]	116	30.2 fewer (42.9 fewer to 16.2 fewer)	Moderate	due to risk of bias	9	4000	0.82 [0.73 to 0.93]	116	20.9 fewer (31.3 fewer to 8.1 fewer)	Moderate	due to risk of bias
Current	10	4170	0.83 [0.74 to 0.93]	116	19.7 fewer (30.2 fewer to 8.1 fewer)	Moderate	due to risk of bias	12	4560	0.83 [0.74 to 0.92]	116	19.7 fewer (30.2 fewer to 9.3 fewer)	Moderate	due to risk of bias
Convalescent plasma														
1 month	1	464	1.08 [0.59 to 1.99]	116	9.3 more (47.6 fewer to 104.4 more)	Very low	due to risk of bias, imprecision (x2)	3	705	0.83 [0.39 to 1.78]	116	19.7 fewer (70.8 fewer to 90.5 more)	Very low	due to risk of bias, imprecision (x2)
3 months	3	827	1.14 [0.81 to 1.61]	116	16.2 more (22 fewer to 70.8 more)	Very low	due to risk of bias, imprecision (x2)	6	1108	1.04 [0.75 to 1.42]	116	4.6 more (29 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)
6 months	4	987	1.11 [0.79 to 1.54]	116	12.8 more (24.4 fewer to 62.6 more)	Very low	due to risk of bias, imprecision (x2)	6	1108	1.04 [0.75 to 1.42]	116	4.6 more (29 fewer to 48.7 more)	Very low	due to risk of bias, imprecision (x2)
Current	8	8252	0.98 [0.90 to 1.06]	116	2.3 fewer (11.6 fewer to 7 more)	Moderate	due to risk of bias	9	8333	0.98 [0.90 to 1.05]	116	2.3 fewer (11.6 fewer to 5.8 more)	Moderate	due to risk of bias

Supplement 7 – Forest plots for meta-analyses including and excluding preprints**Corticosteroids for mortality****1 month***Without preprints**With preprints***3 months***Without pre-prints*

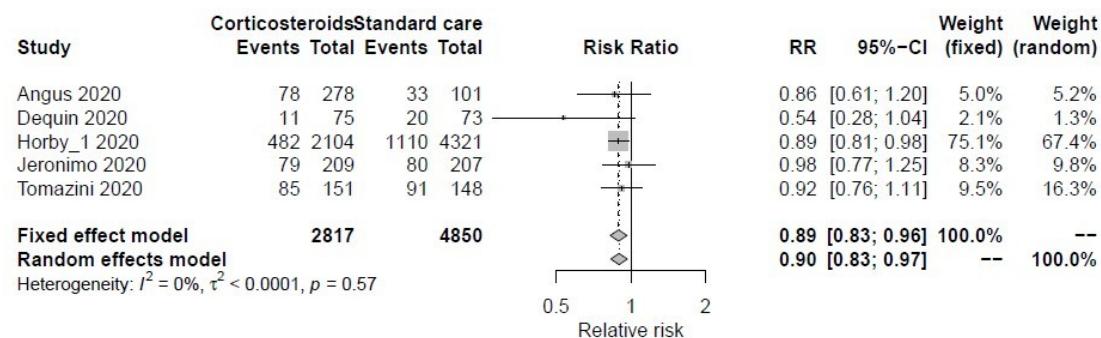


With pre-prints

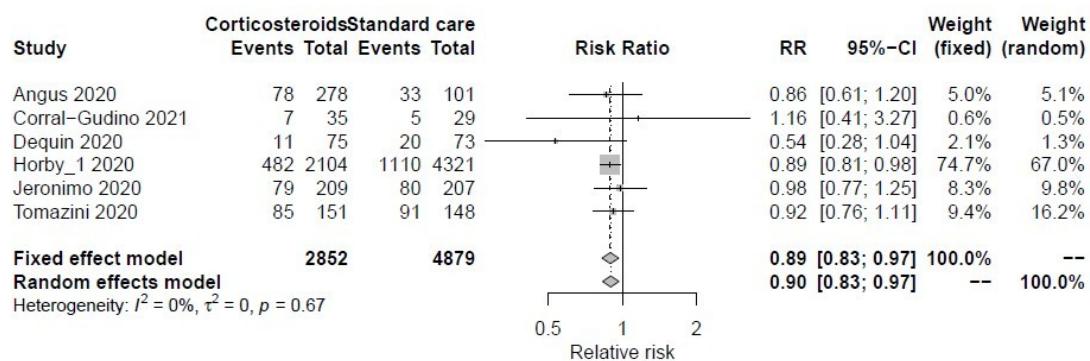


6 months

Without pre-prints

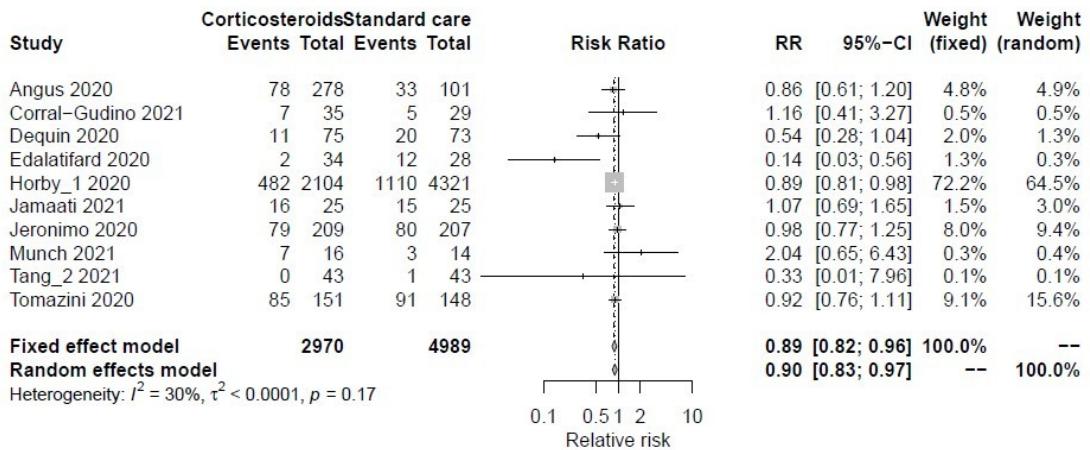


With pre-prints

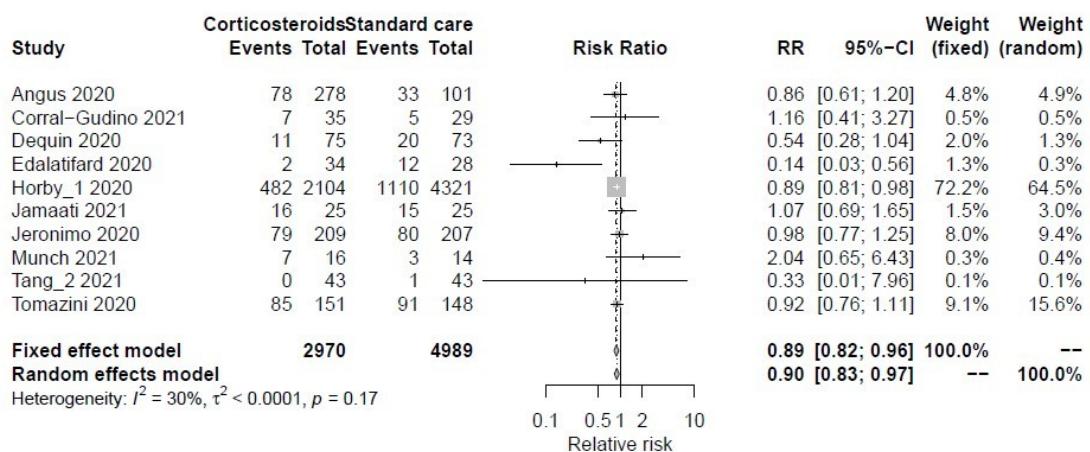


Current

Without pre-prints



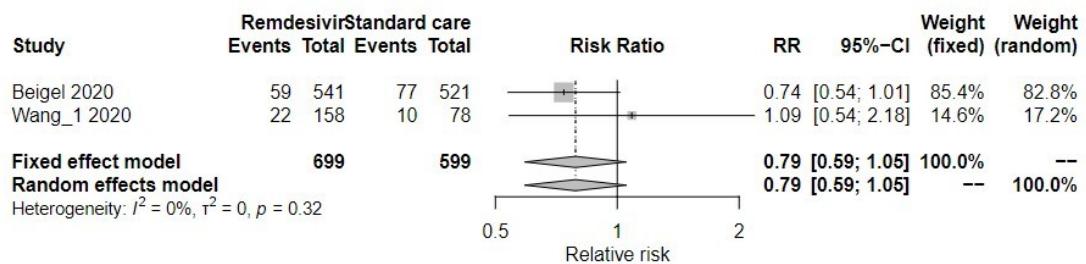
With pre-prints



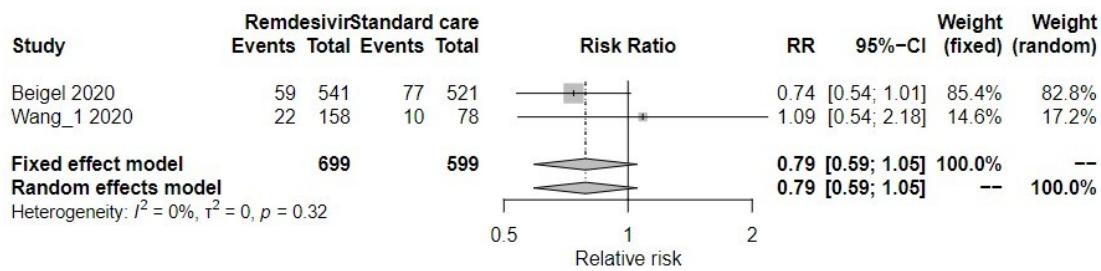
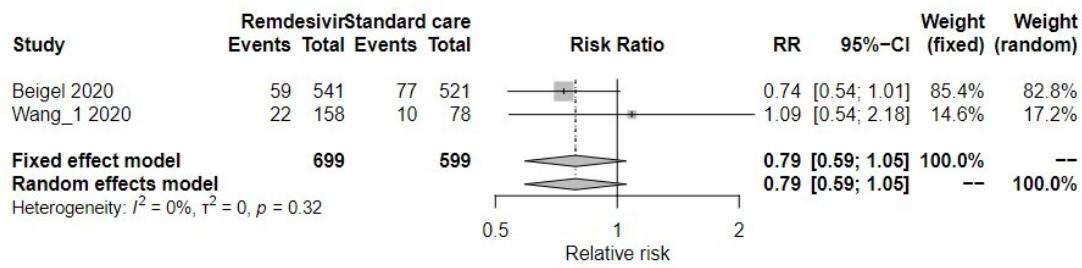
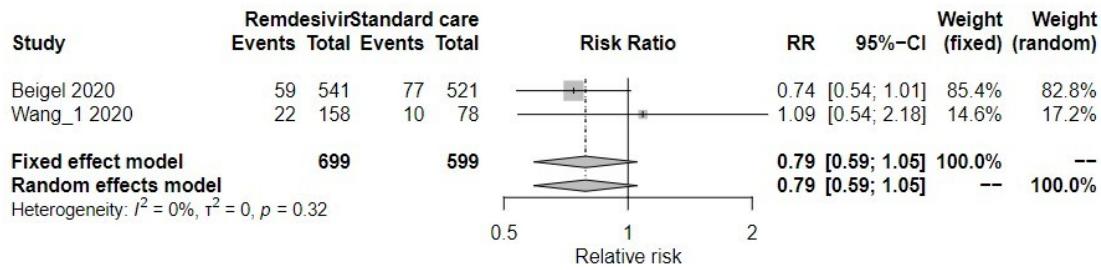
Remdesivir for mortality

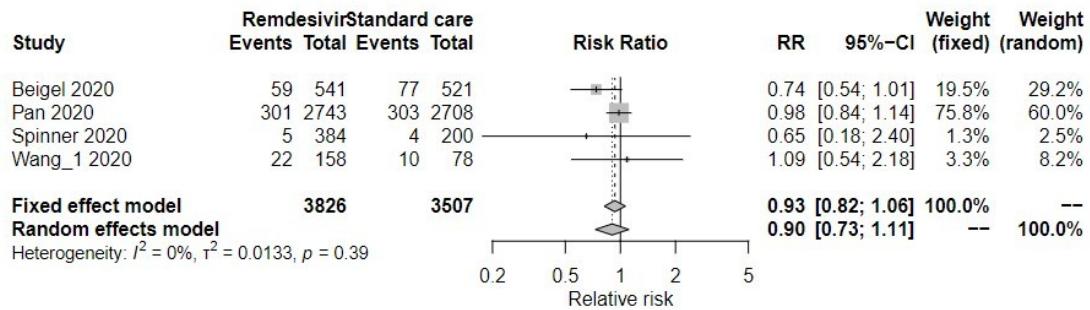
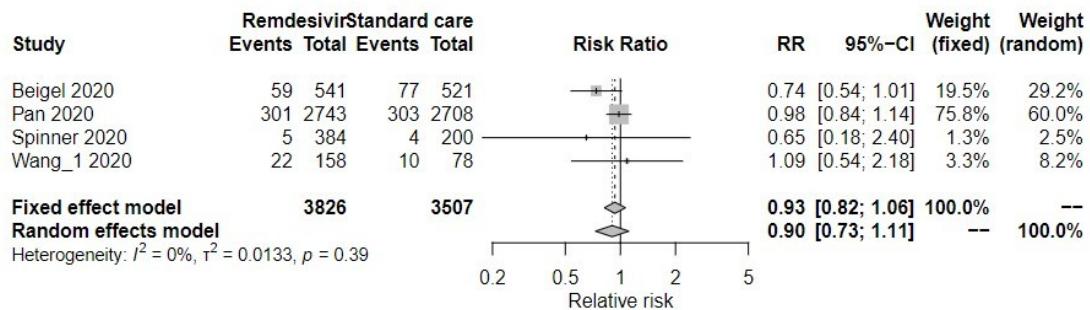
1 month

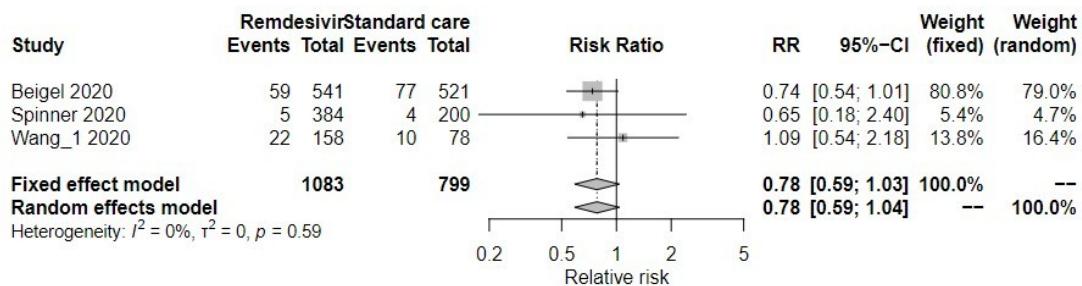
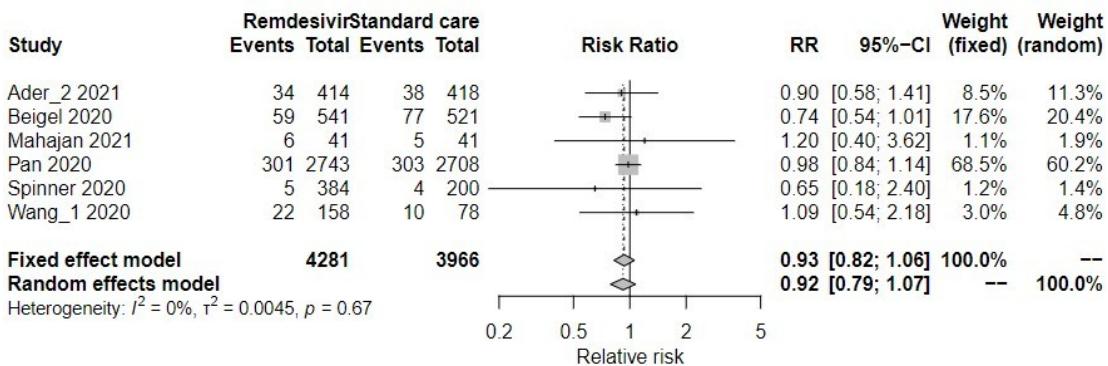
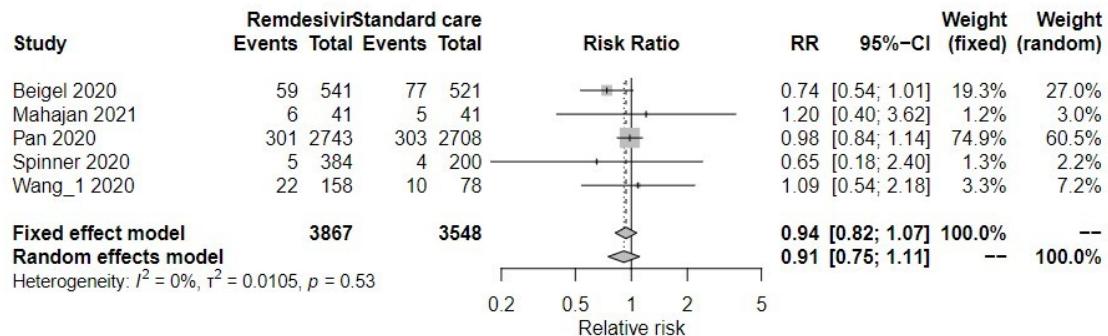
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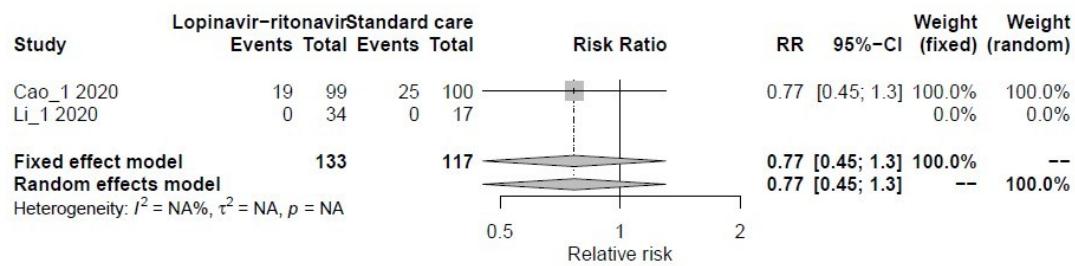
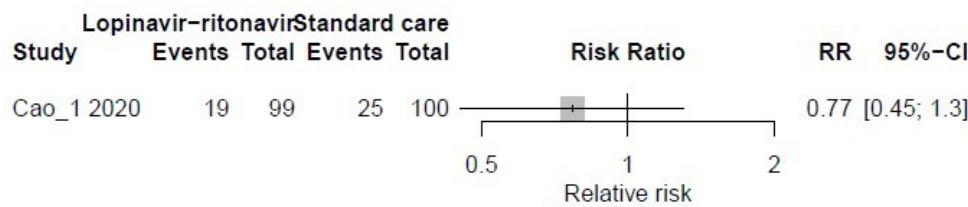
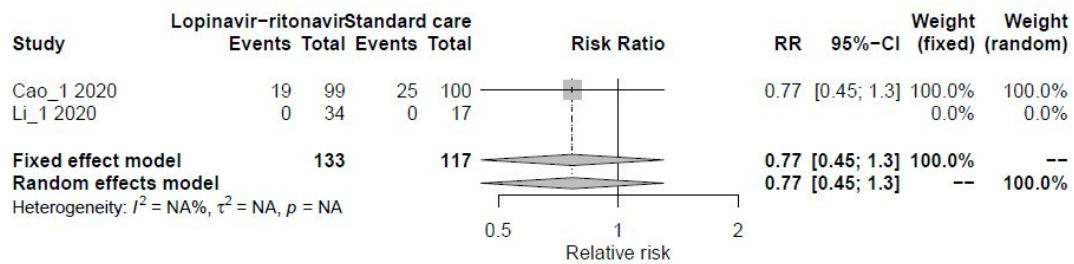


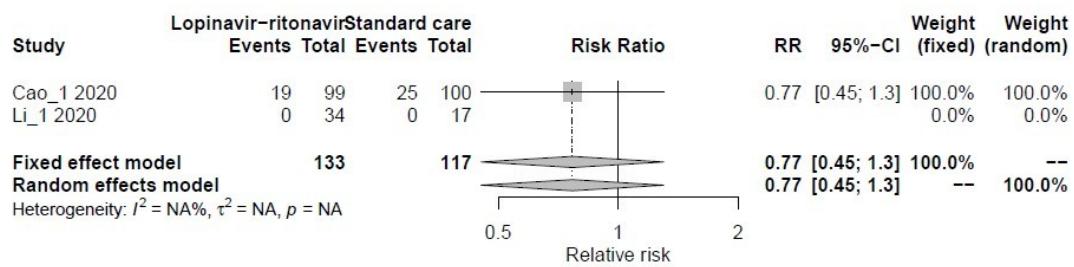
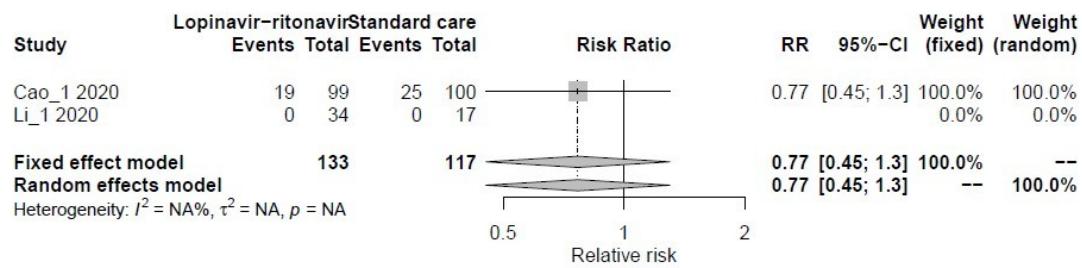
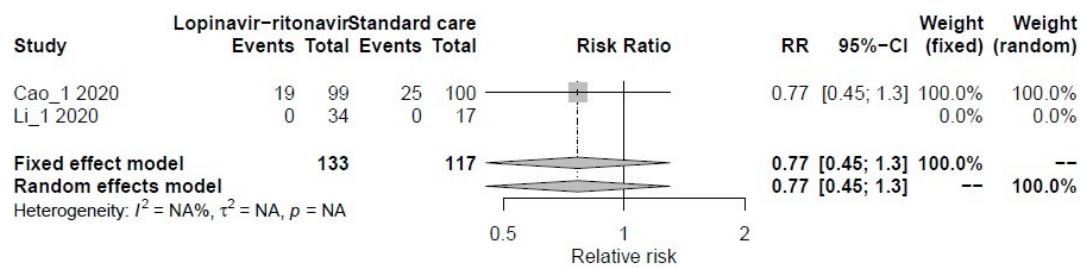
With pre-prints

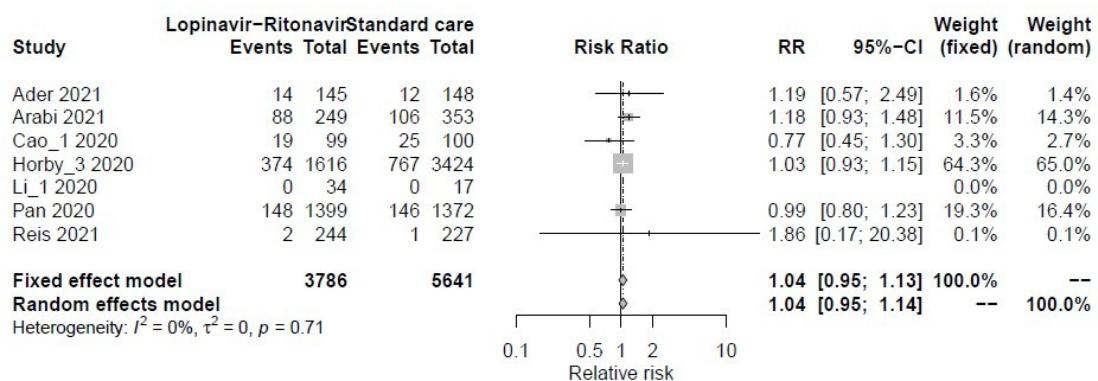
**3 months***Without pre-prints**With pre-prints***6 months**

Without pre-prints*With pre-prints**Without pre-prints*

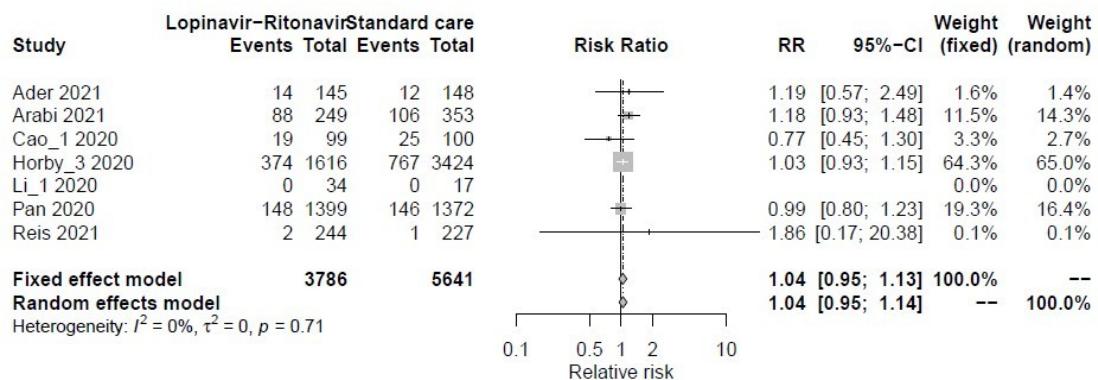
**Current:***With pre-prints**Without pre-prints***Lopinavir-ritonavir for mortality**

1 month*With pre-prints**Without pre-prints***3 months***With pre-prints**Without pre-prints*

**6 months***With pre-prints**Without pre-prints***Current***With pre-prints*



Without pre-prints



(Hydroxy)chloroquine (treatment) for mortality

1 month

With pre-prints

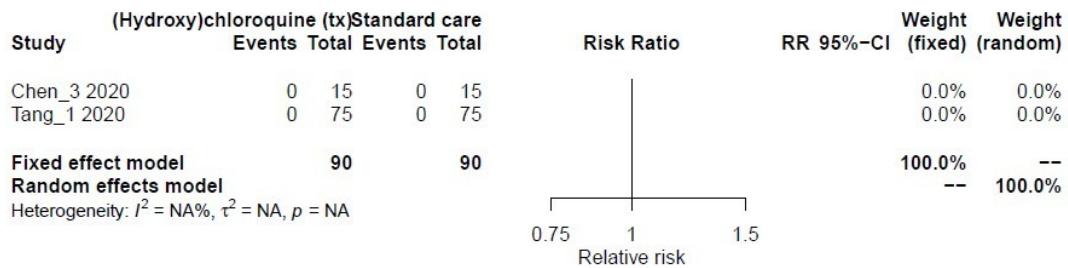


Without pre-prints

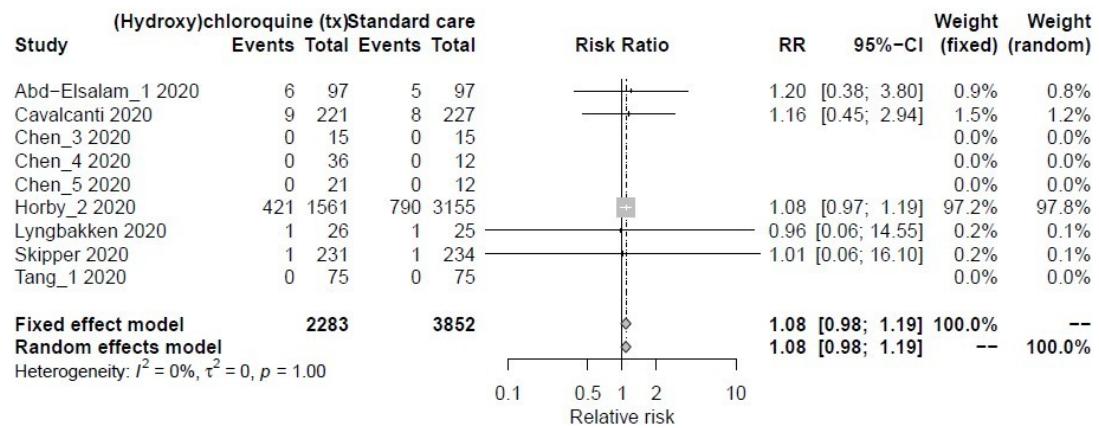


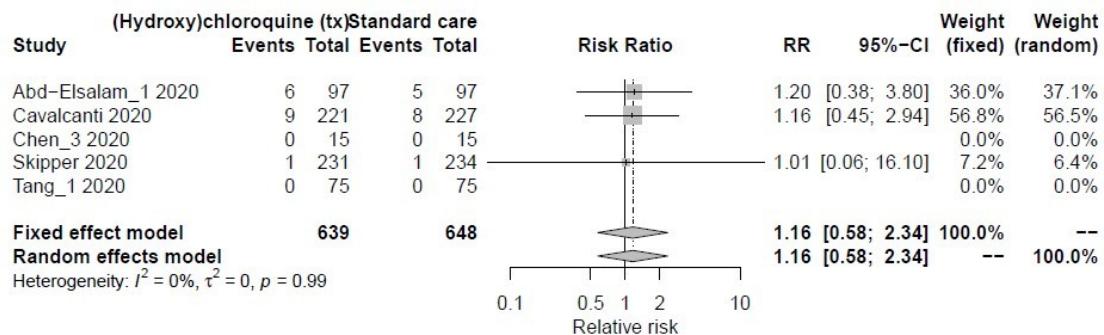
3 months

With pre-prints



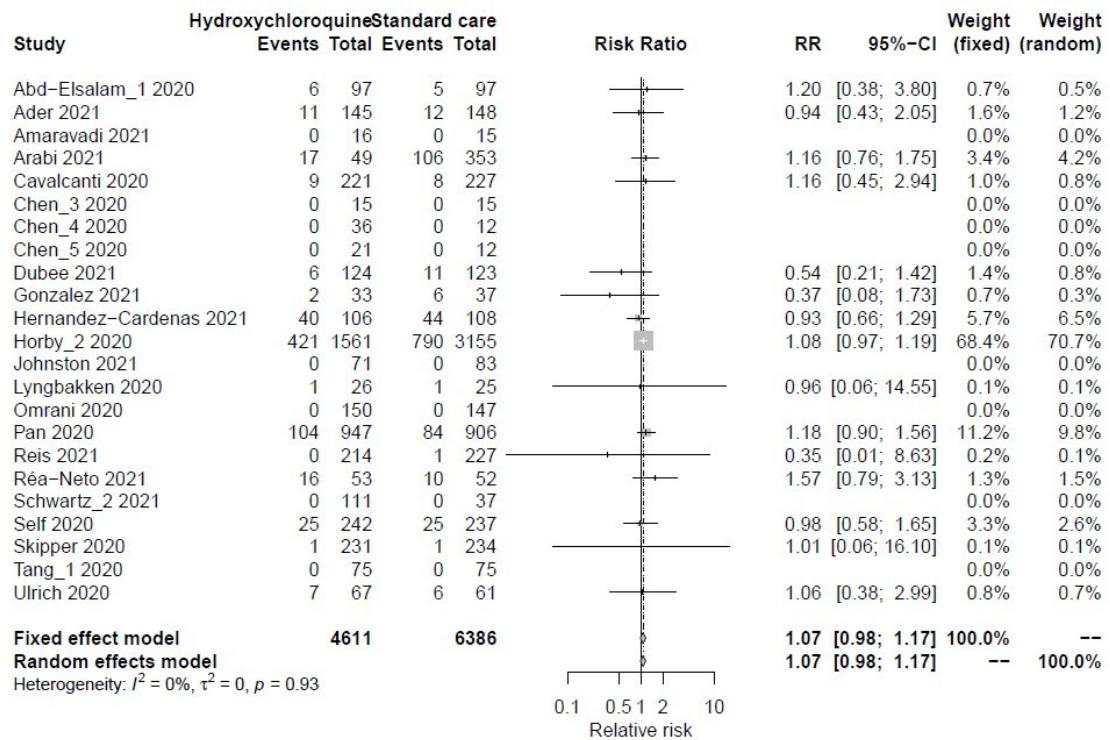
Without pre-prints

**6 months***With pre-prints**Without pre-prints*

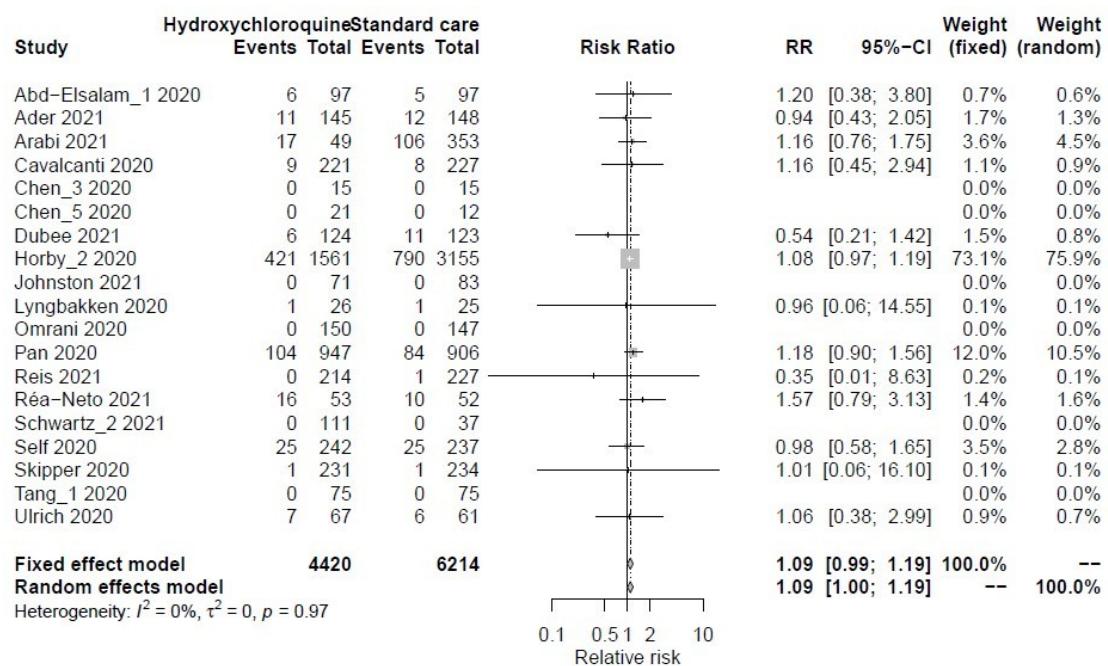


Current

With pre-prints



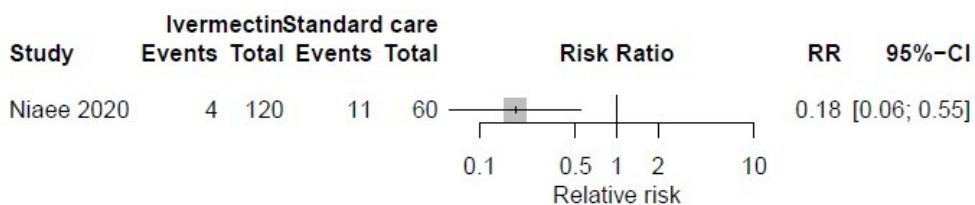
Without pre-prints



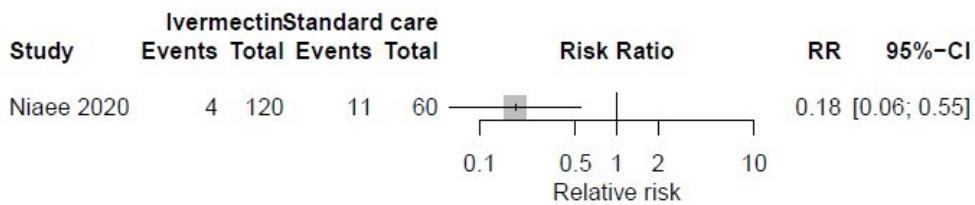
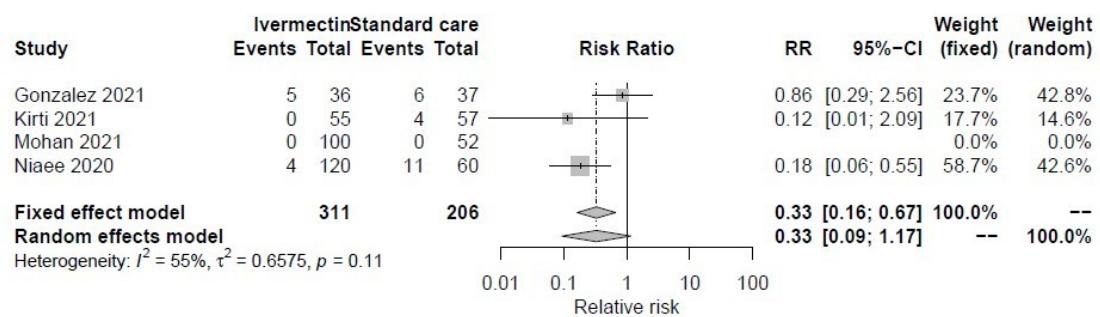
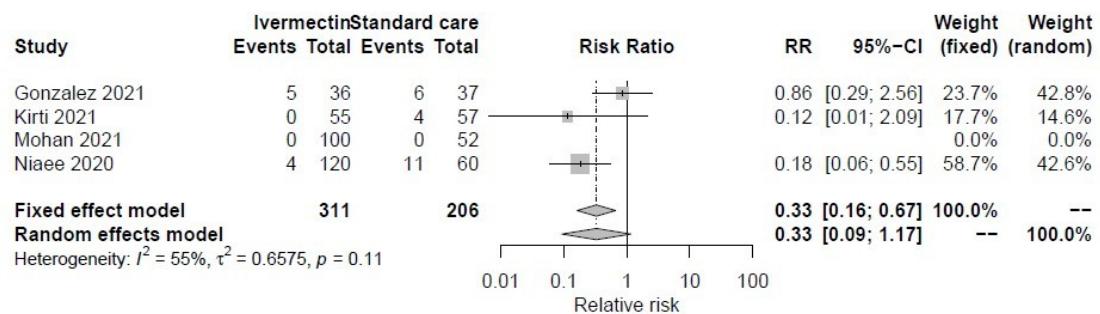
Ivermectin for mortality

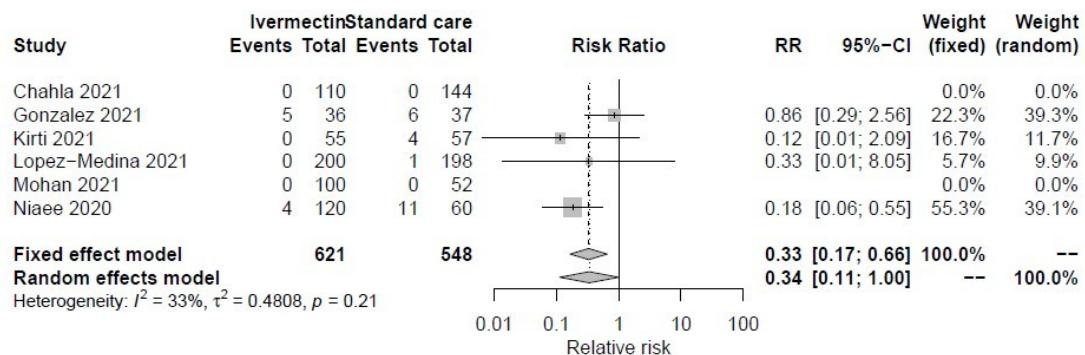
1 month

With pre-prints

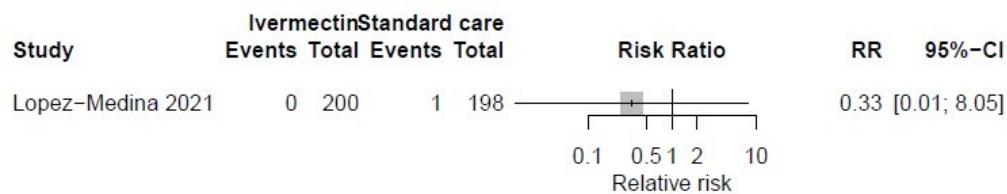


Without pre-prints

**3 months***With pre-prints**Without pre-prints***6 months***With pre-prints*

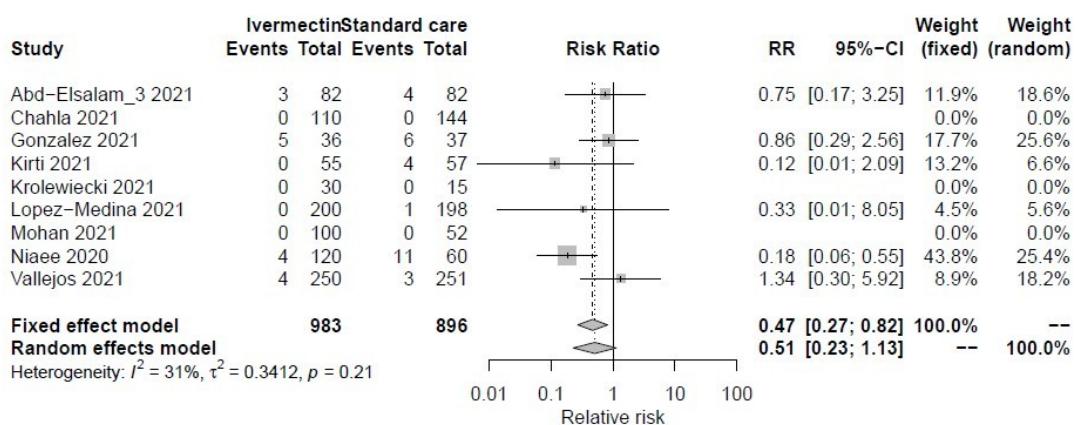


Without pre-prints

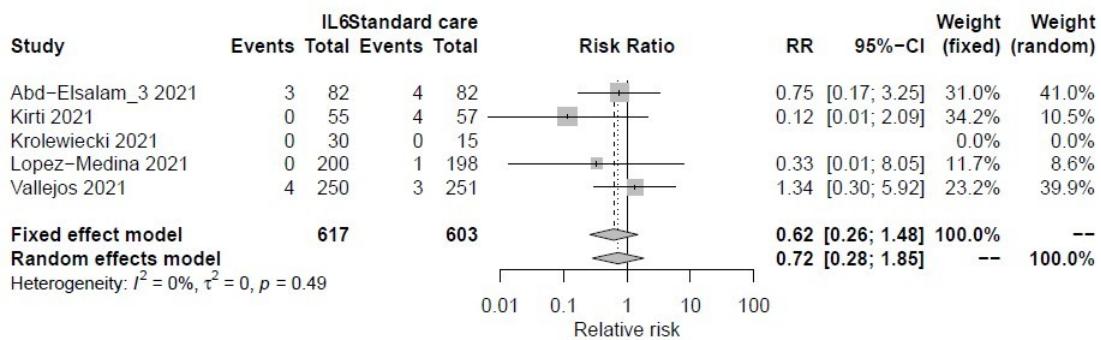


Current

With pre-prints



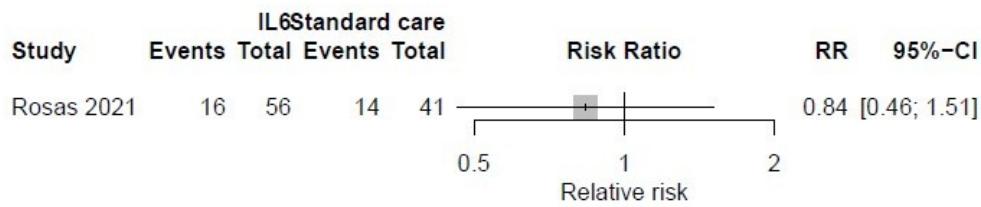
Without pre-prints



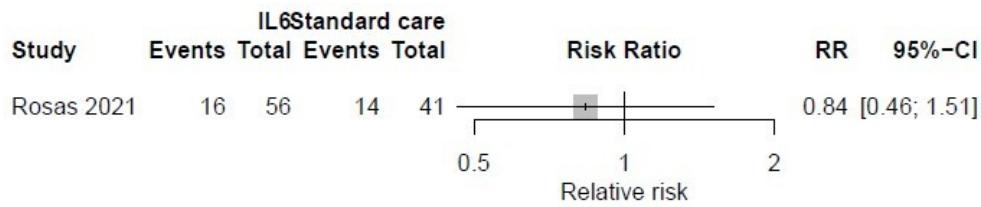
IL-6 receptor blockers for mortality

1 month

With pre-prints

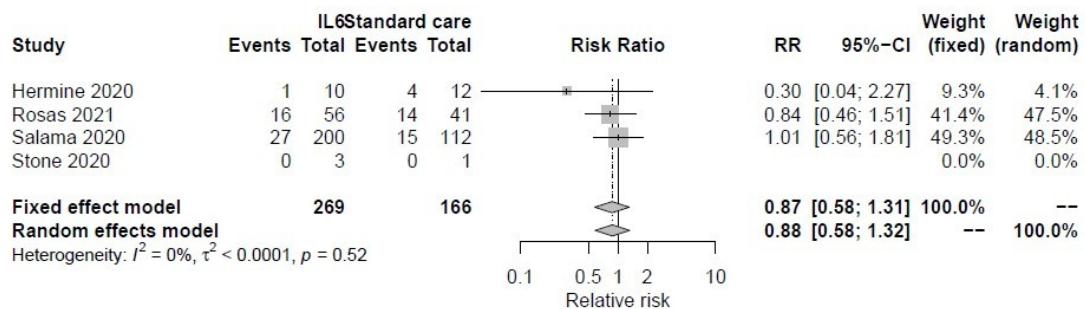


Without pre-prints

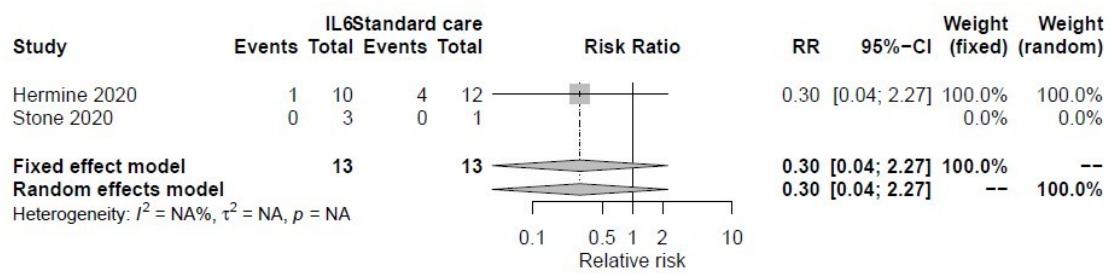


3 months

With pre-prints

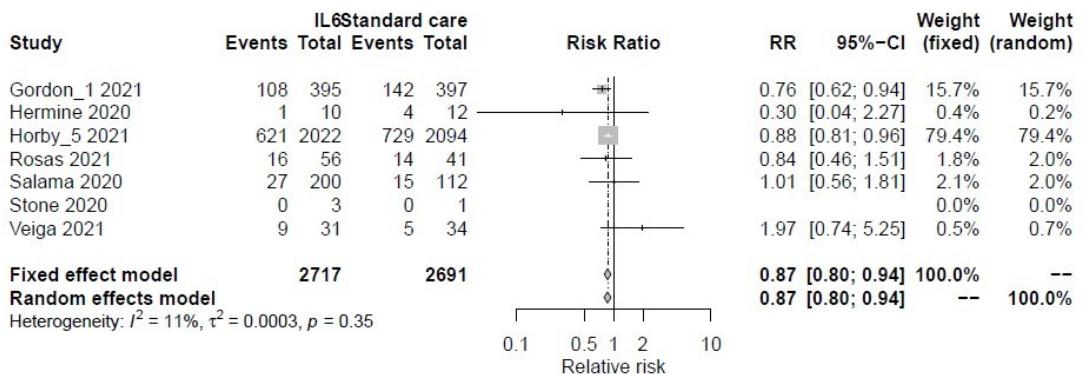


Without pre-prints

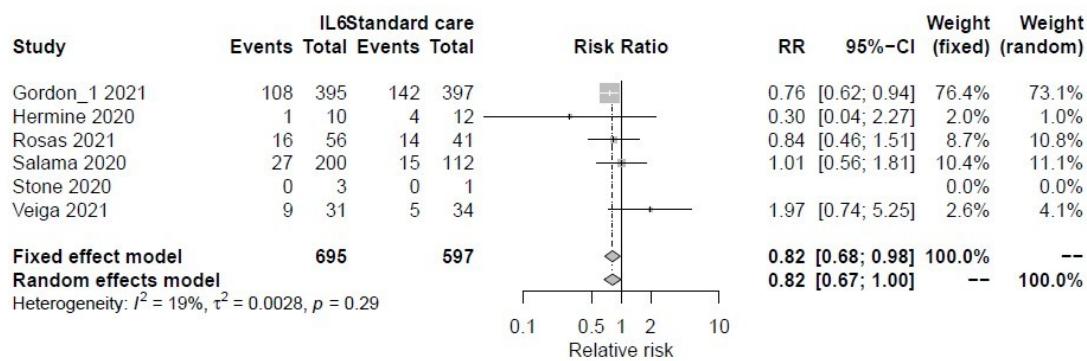


6 months

With pre-prints

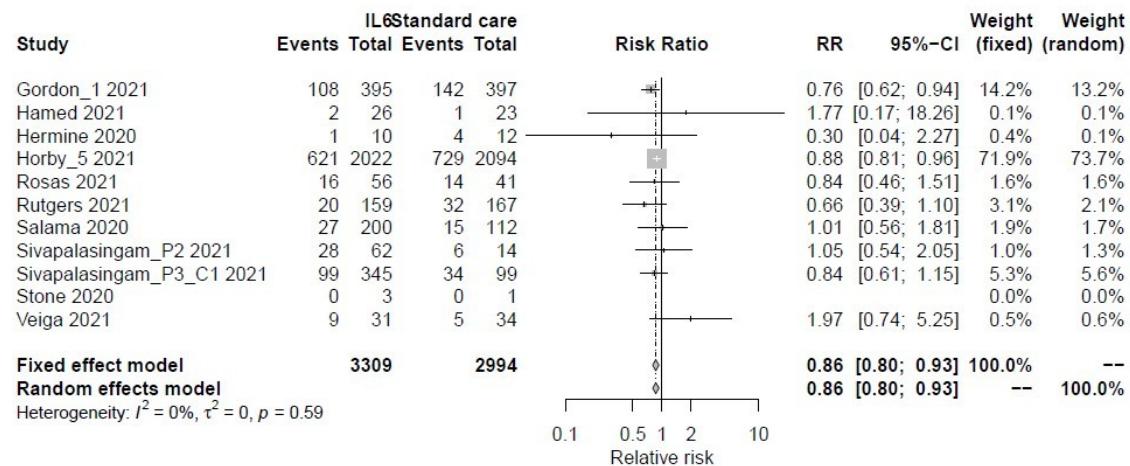


Without pre-prints

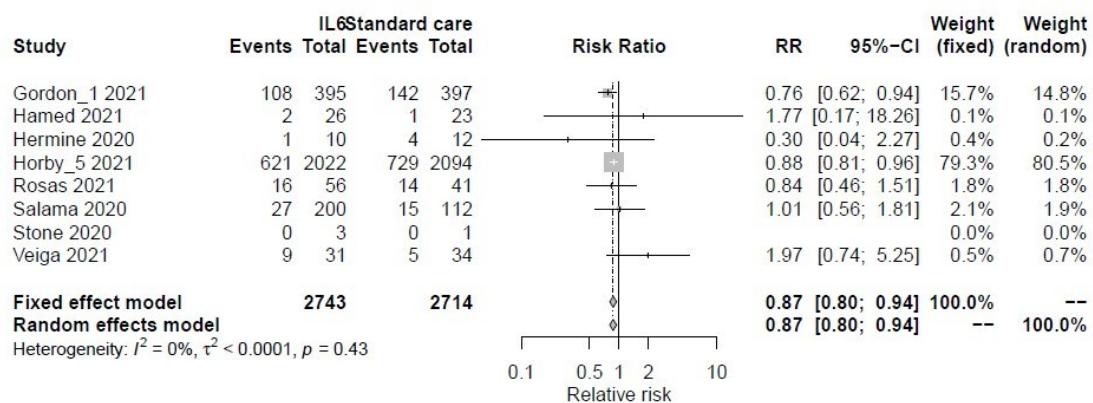


Current

With pre-prints



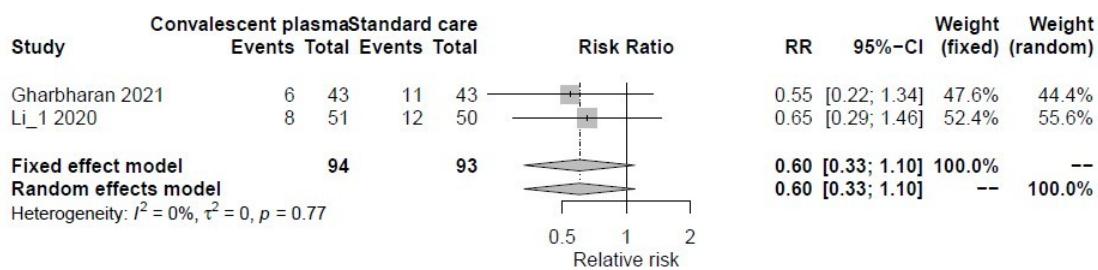
Without pre-prints



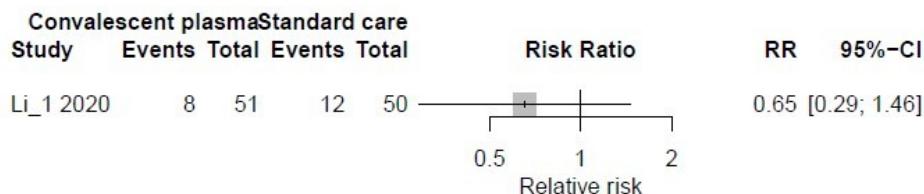
Convalescent plasma for mortality

1 month

With pre-prints

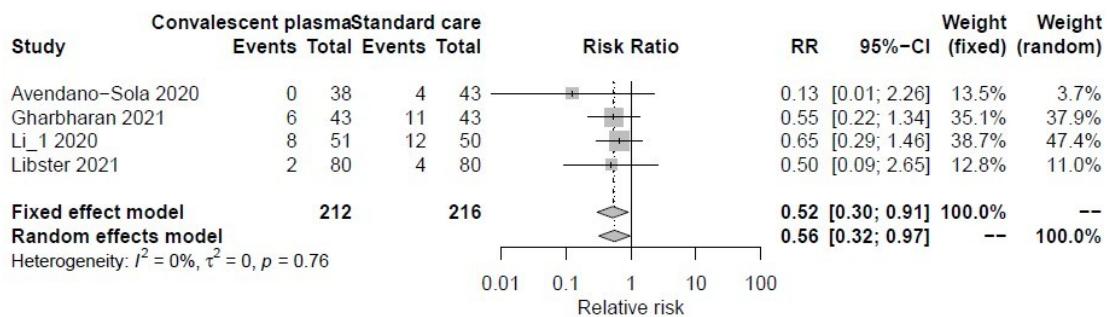


Without pre-prints

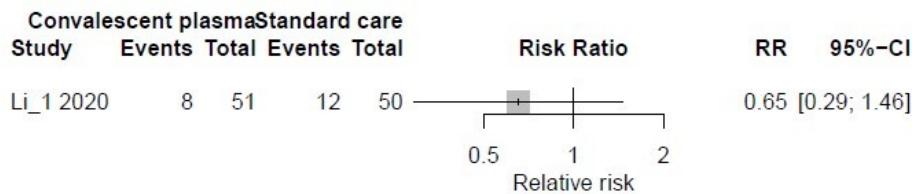


3 months

With pre-prints

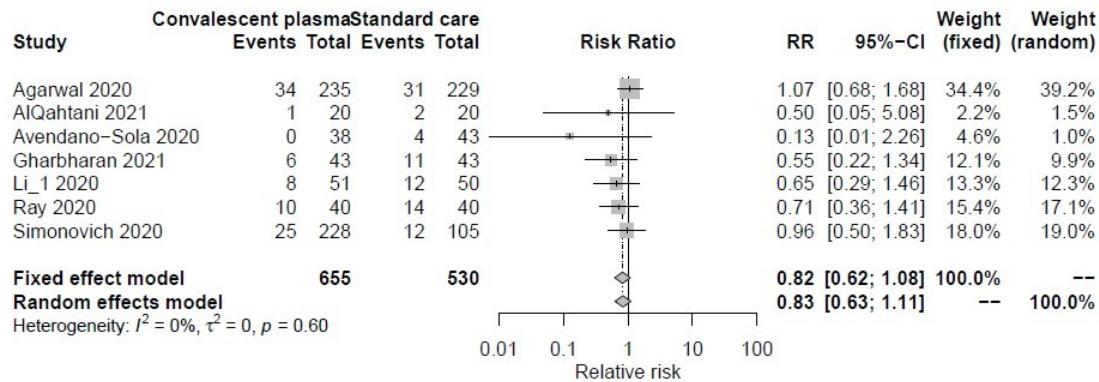


Without pre-prints

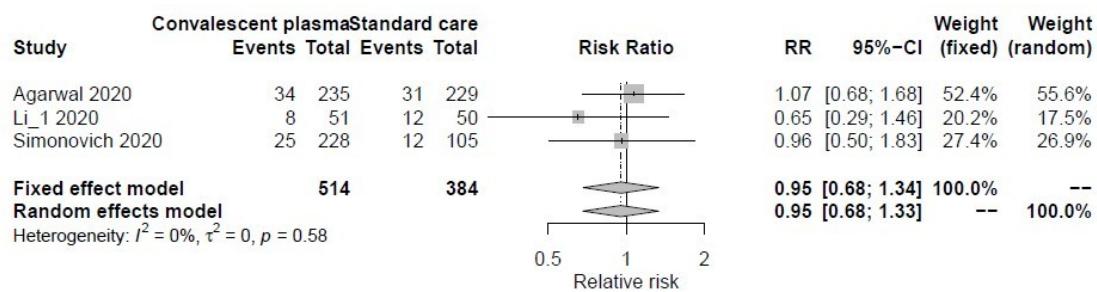


6 months

With pre-prints

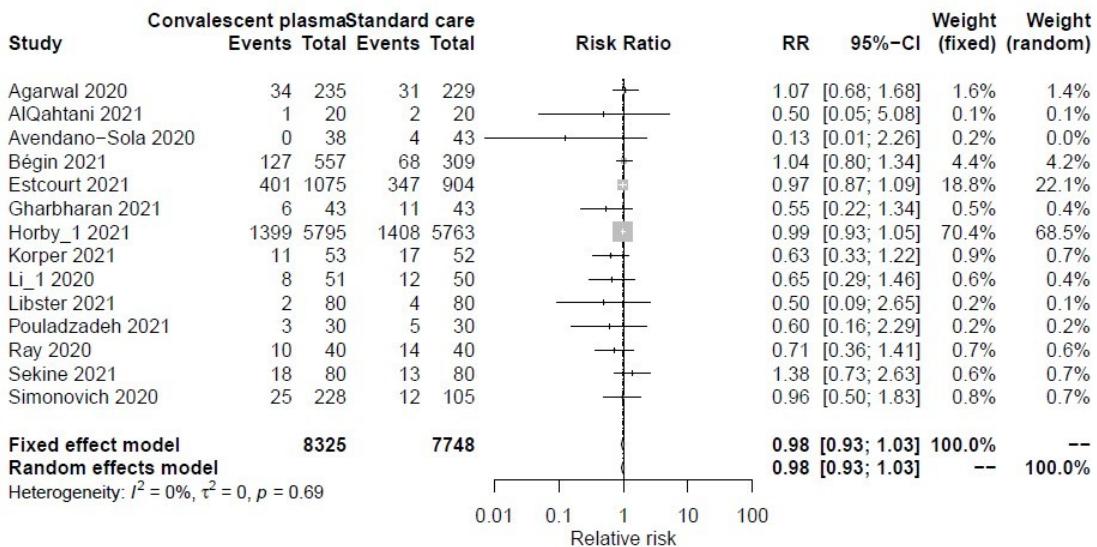


Without pre-prints

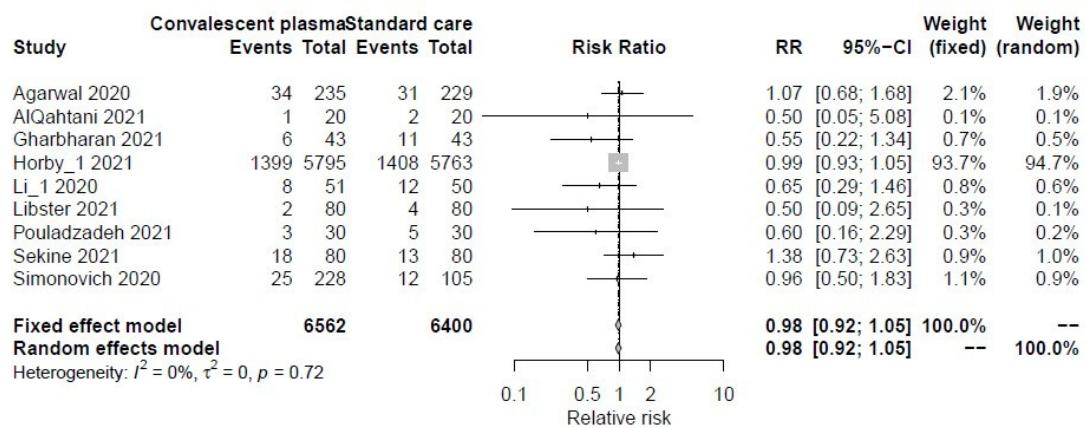


Current

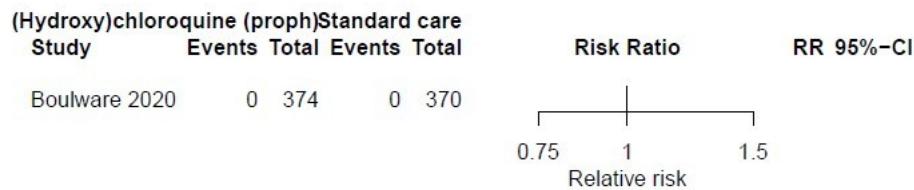
With pre-prints



Without pre-prints

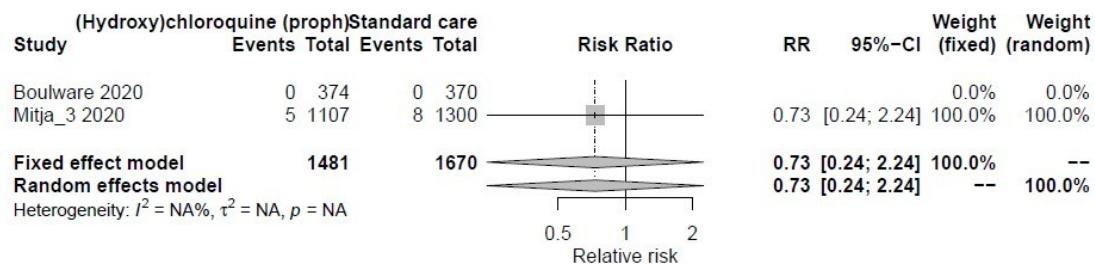
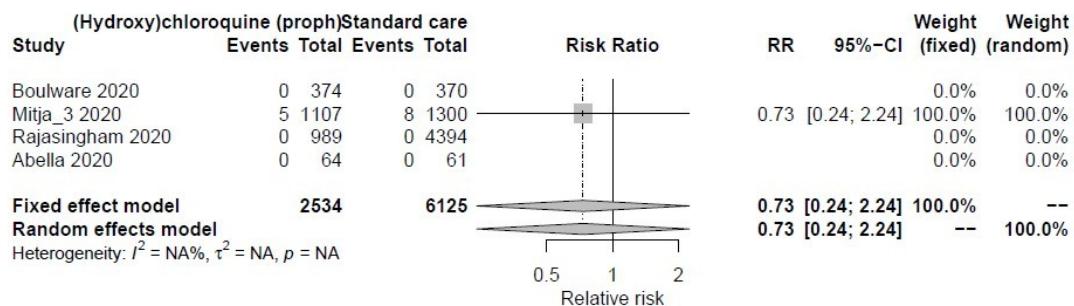
**(Hydroxy)chloroquine (prophylaxis) for mortality****1 month**

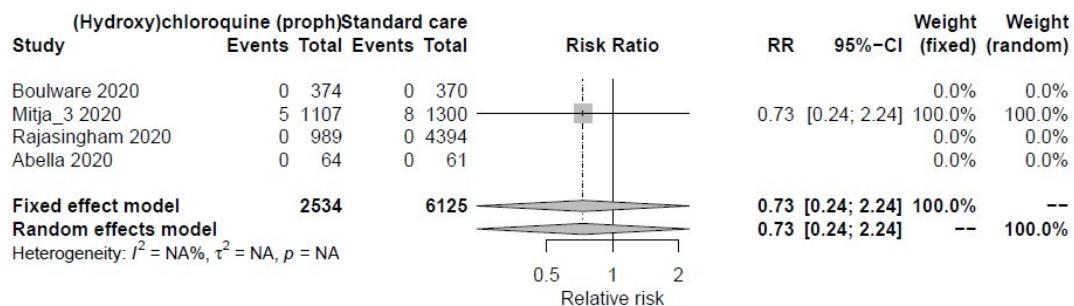
With pre-prints



Without pre-prints

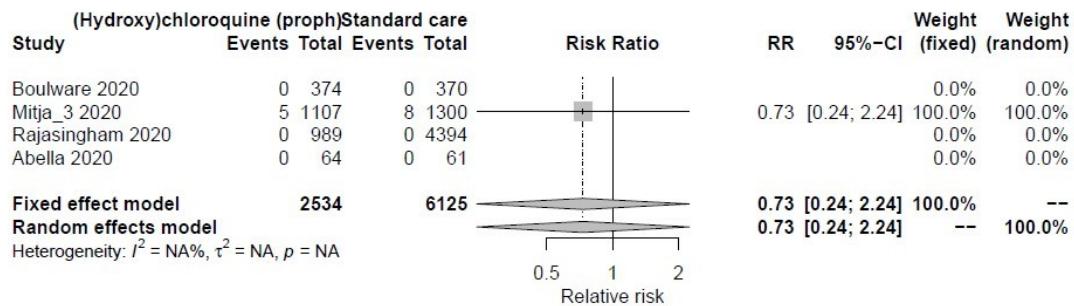


3 months*With pre-prints**Without pre-prints***6 months***With pre-prints**Without pre-prints*

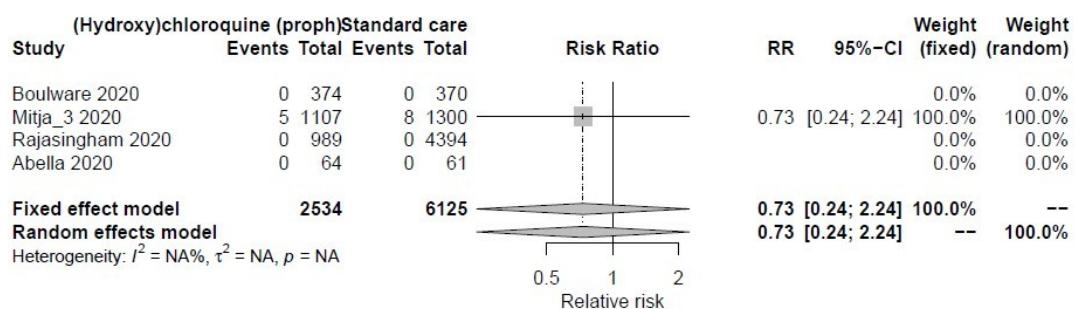


Current

With pre-prints



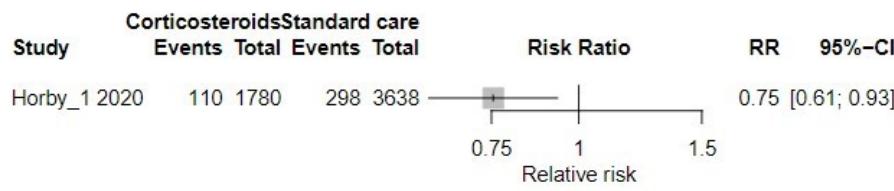
Without pre-prints



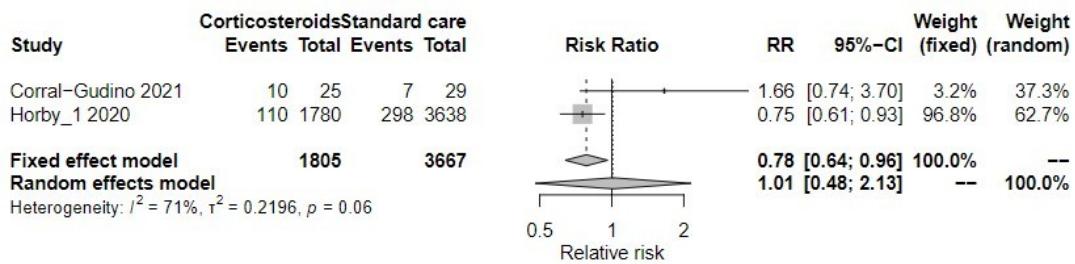
Corticosteroids for mechanical ventilation

1 month

Without preprints

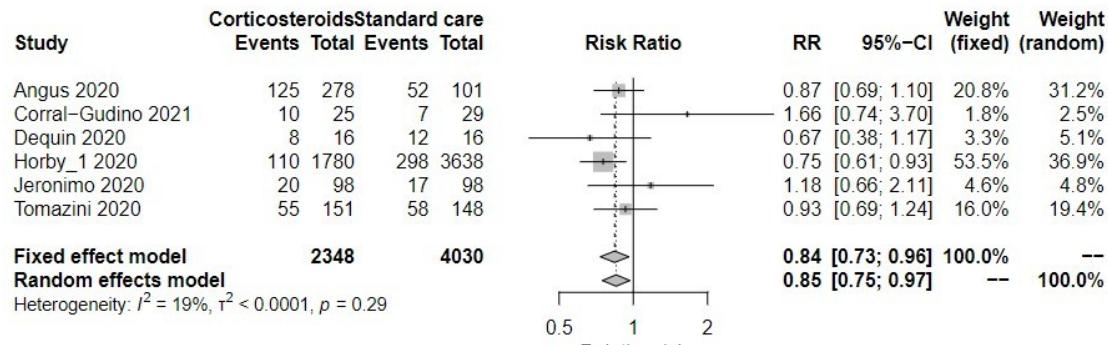


With preprints

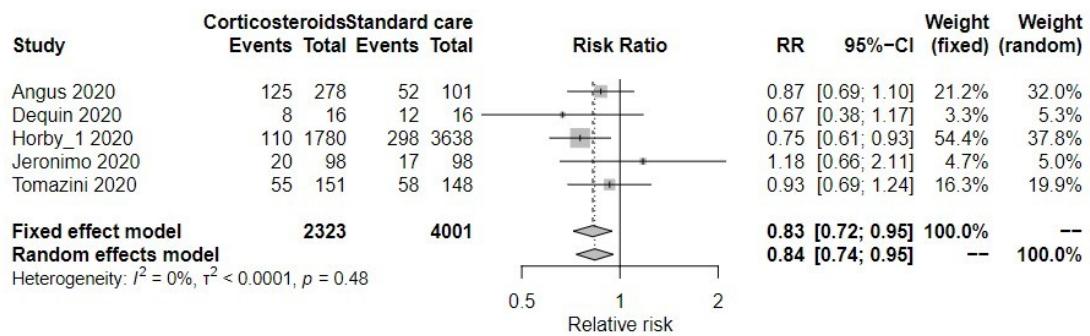


3 months

Without preprints

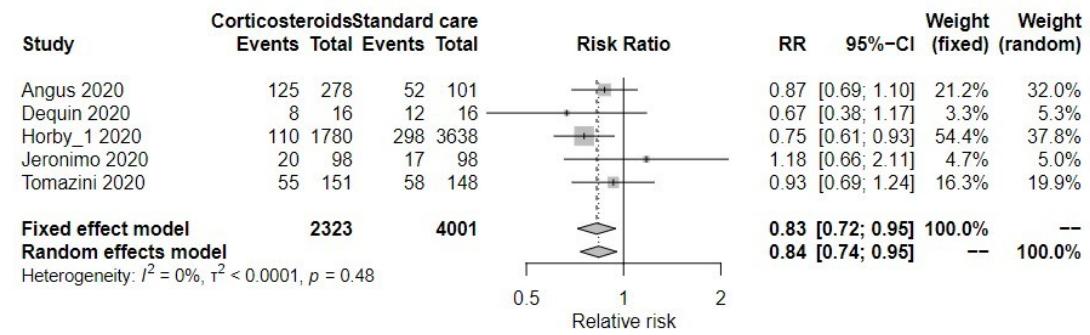


With preprints

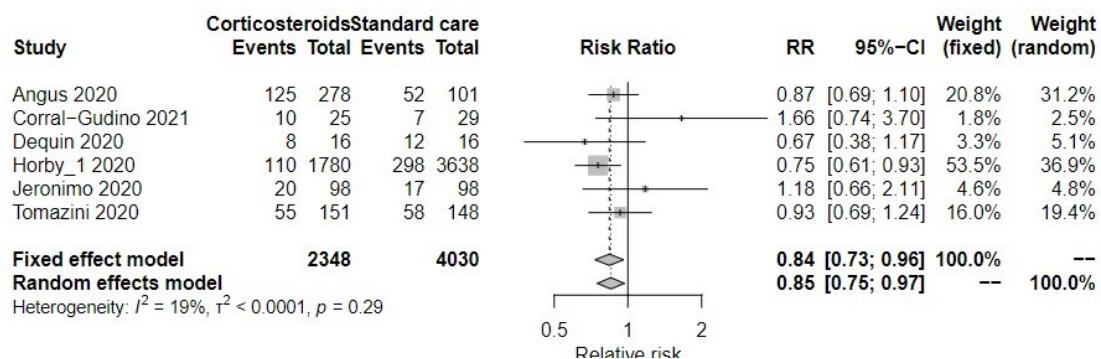


6 months

Without preprints

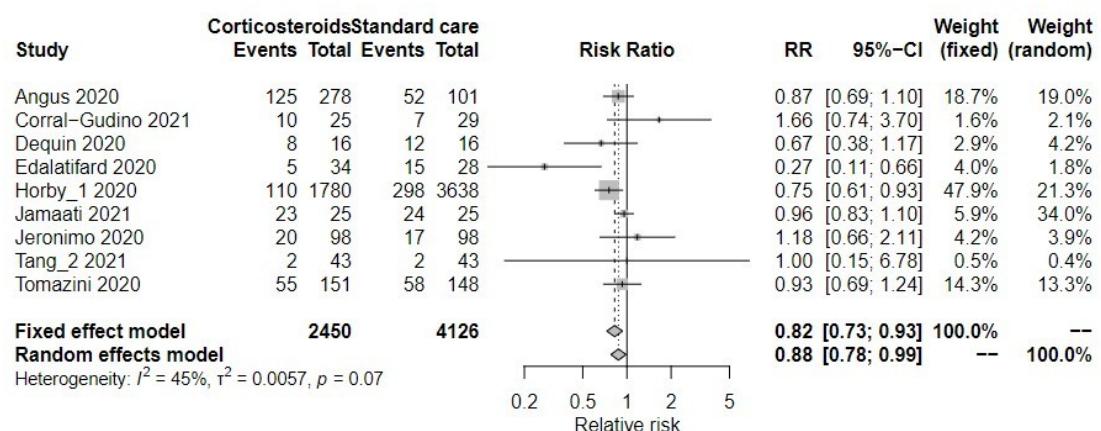


With preprints

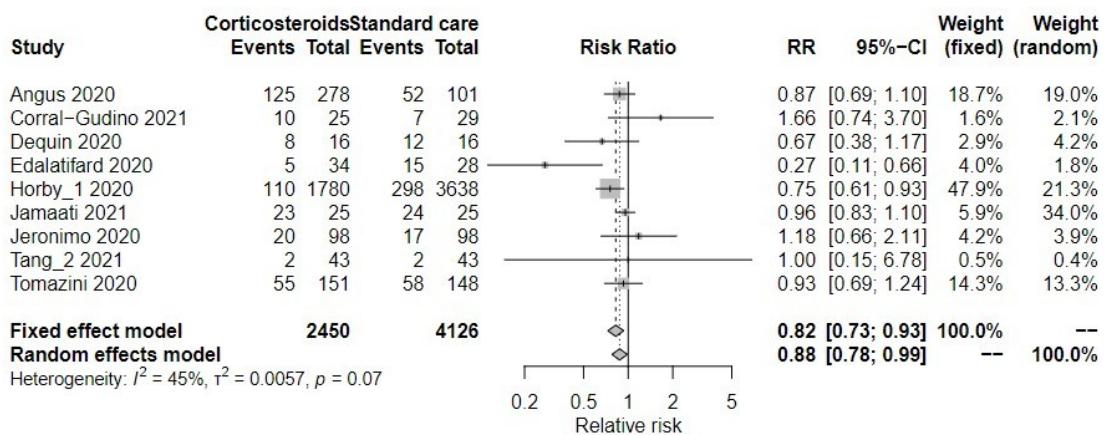


Current

Without preprints



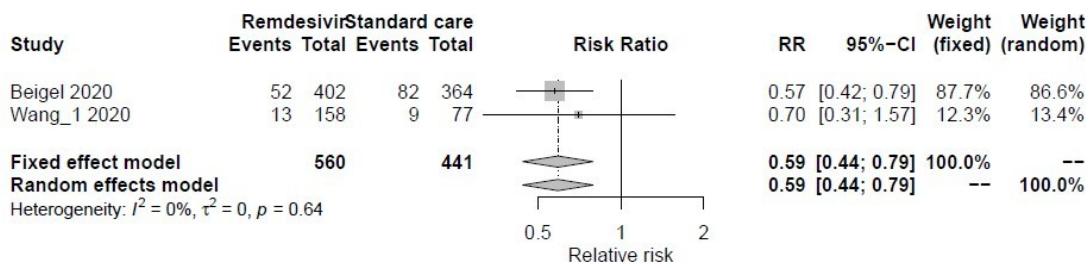
With preprints



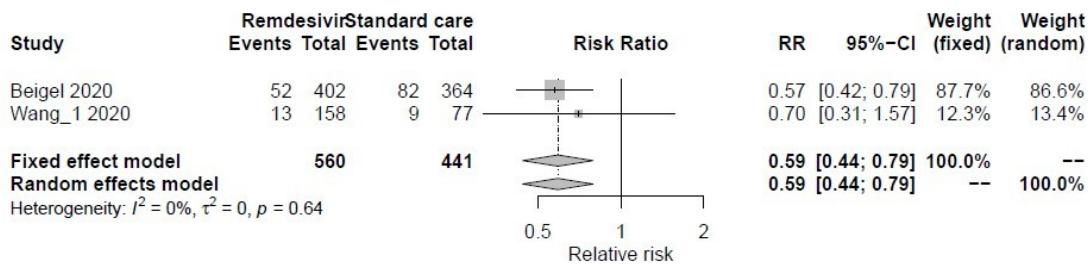
Remdesivir for mechanical ventilation

1 month

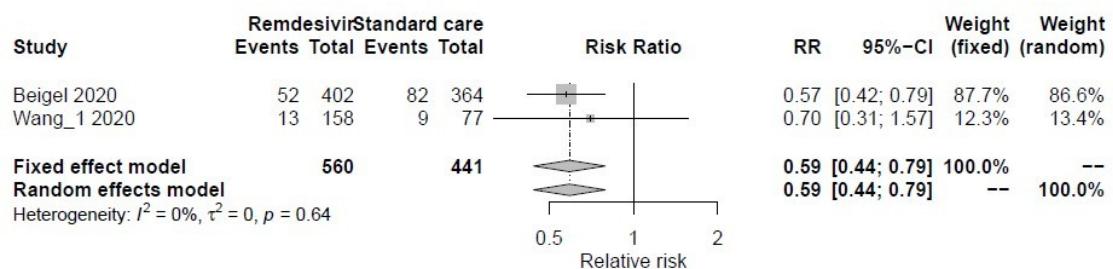
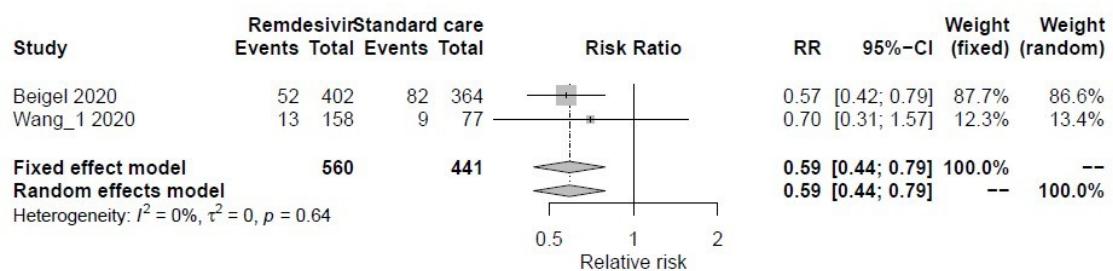
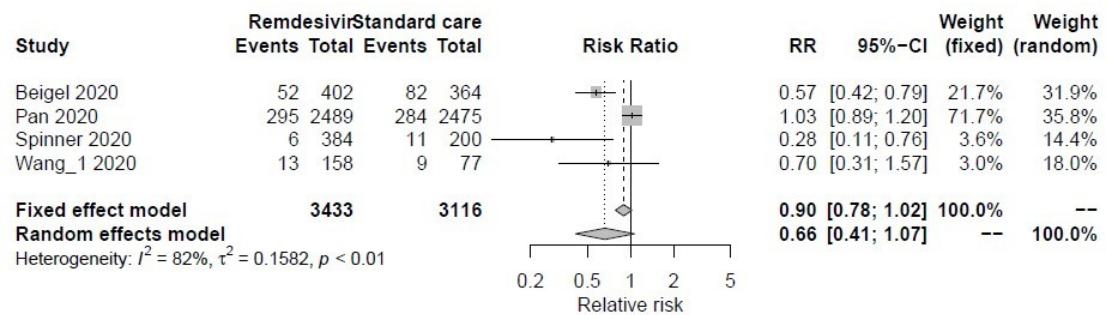
With preprints

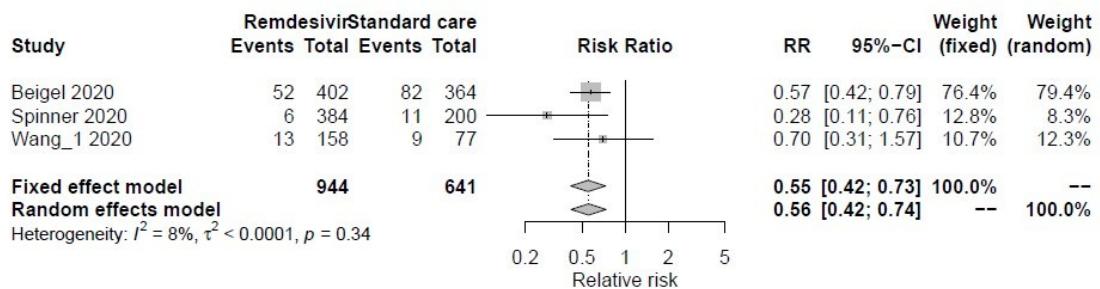
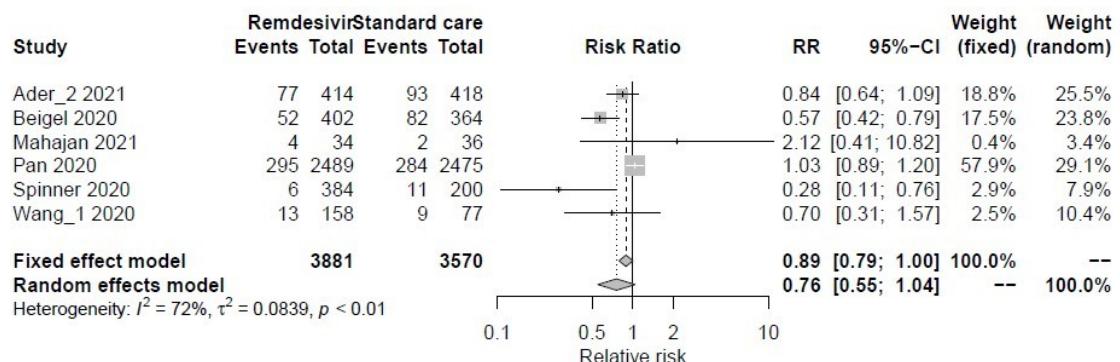
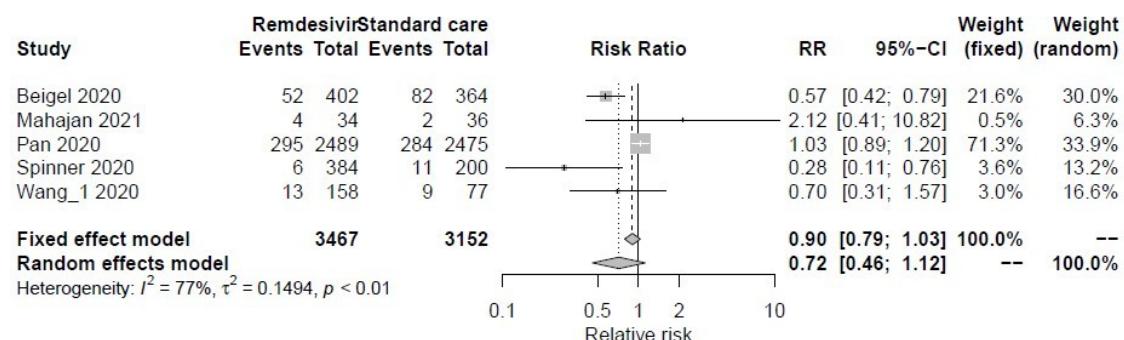


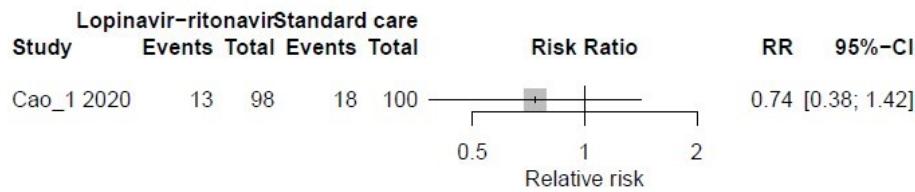
Without preprints



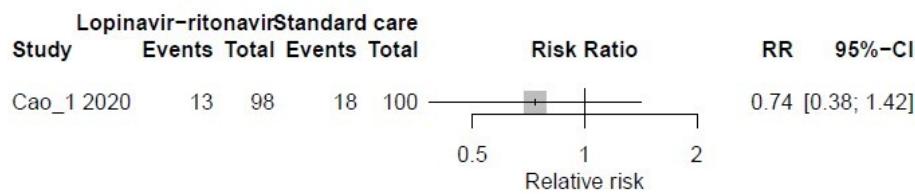
3 months

With preprints*Without preprints***6 months***With preprints**Without preprints*

**Current***With preprints**Without preprints***Lopinavir-ritonavir for mechanical ventilation****1 month***With preprints*

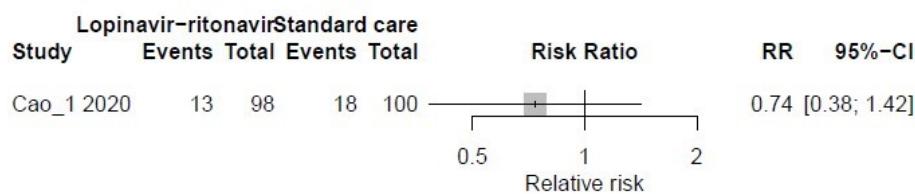


Without preprints

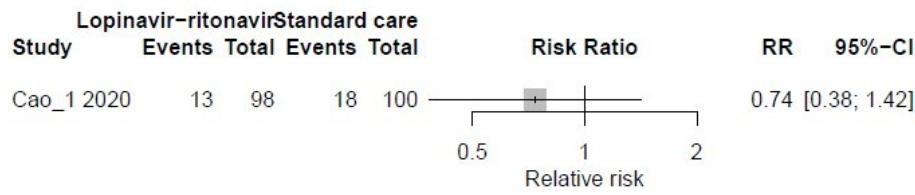


3 months

With preprints

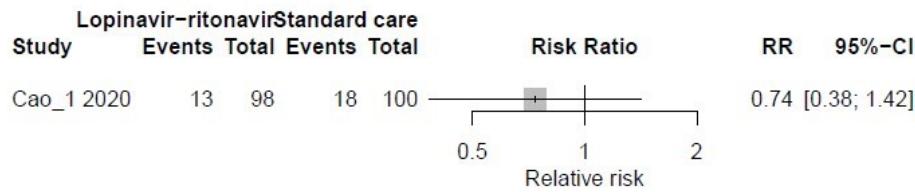


Without preprints

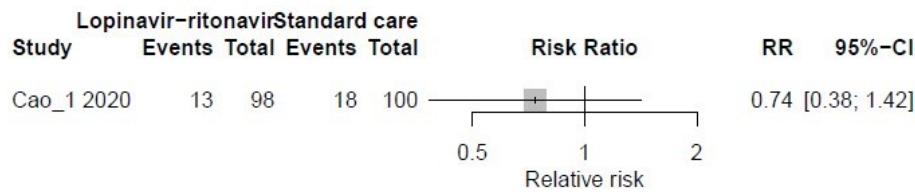


6 months

With preprints

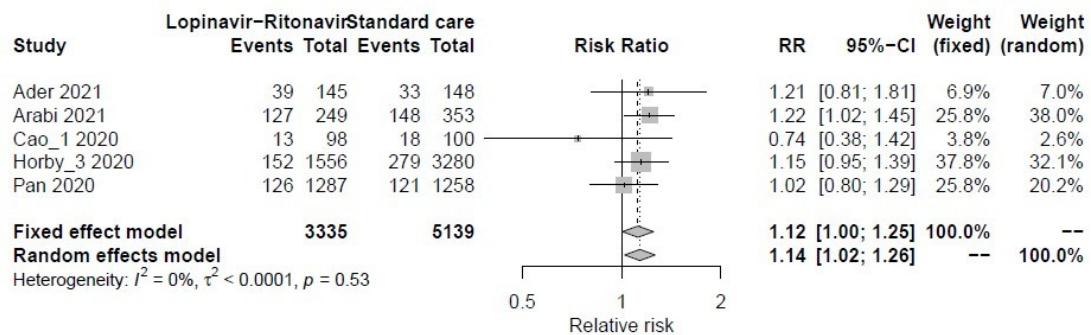


Without preprints

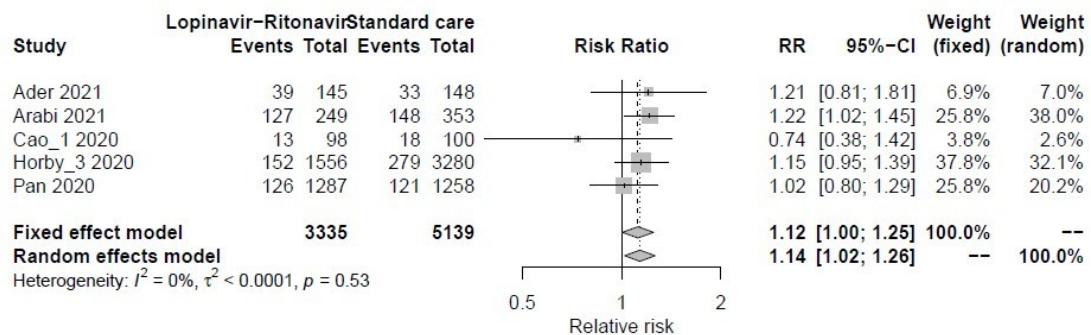


Current

With preprints



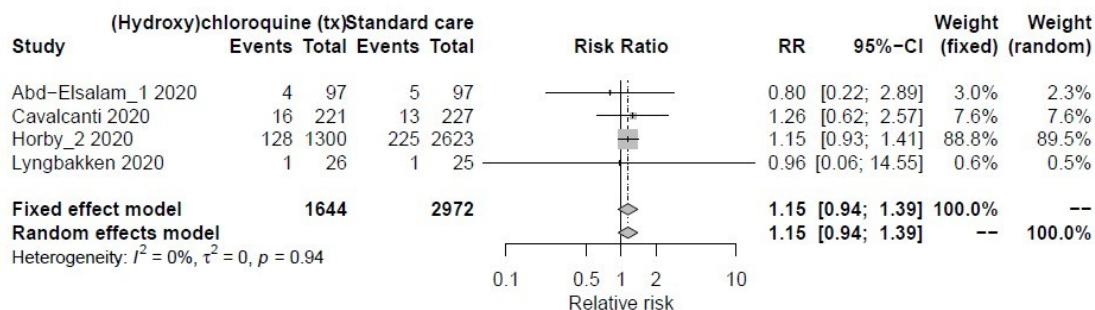
Without preprints



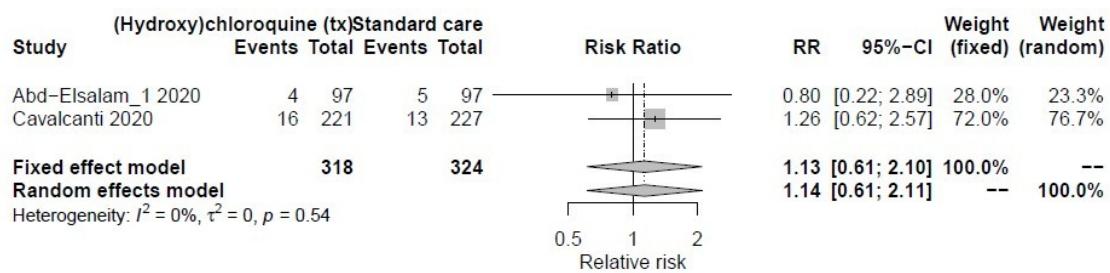
Hydroxy(chloroquine) (treatment) for mechanical ventilation

1 month

With preprints

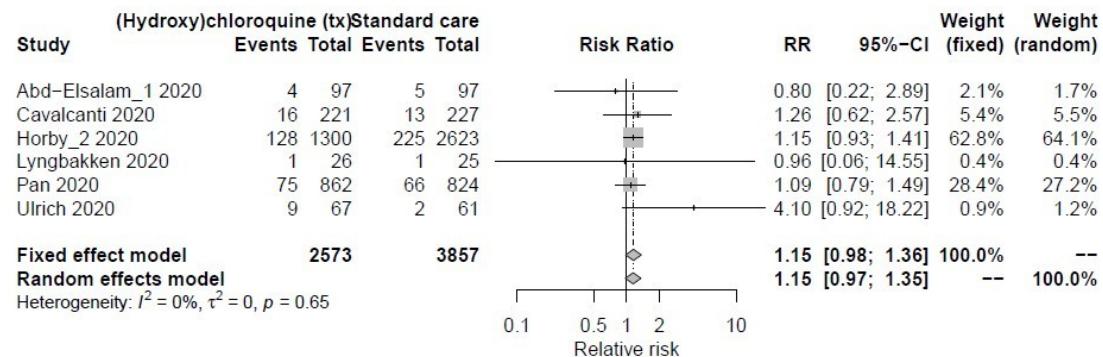


Without preprints

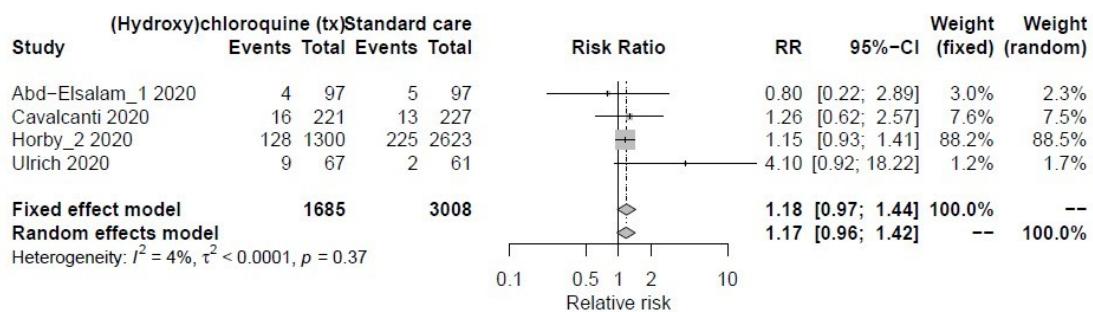


3 months

With preprints

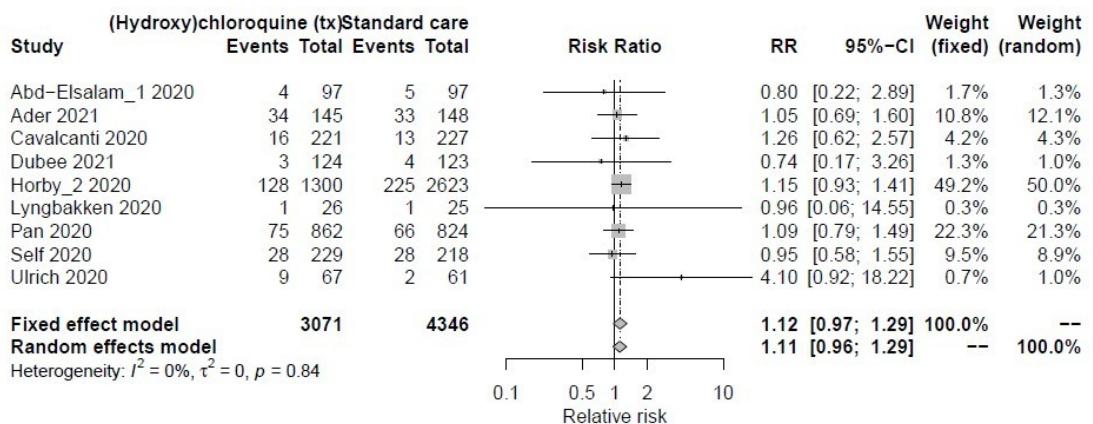


Without preprints

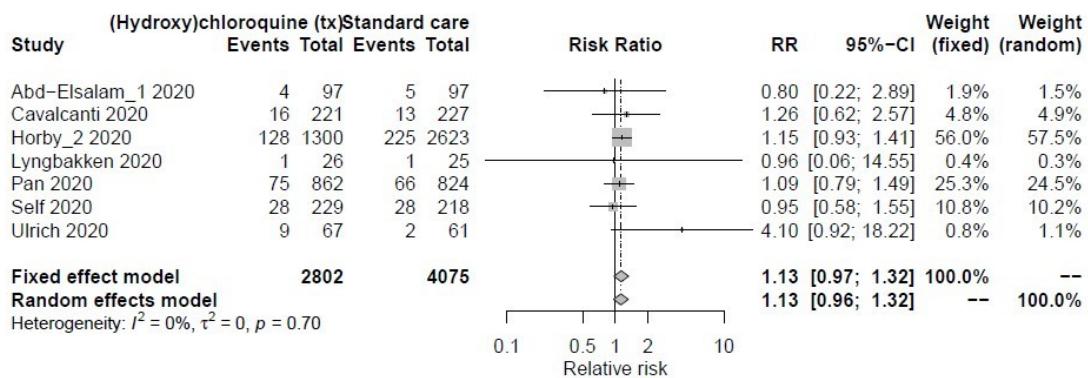


6 months

With preprints

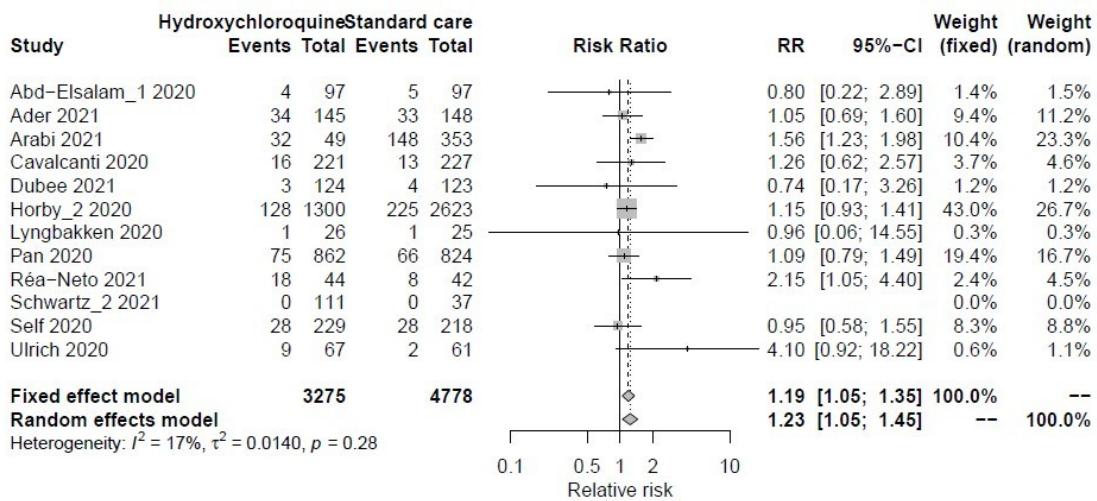


Without preprints

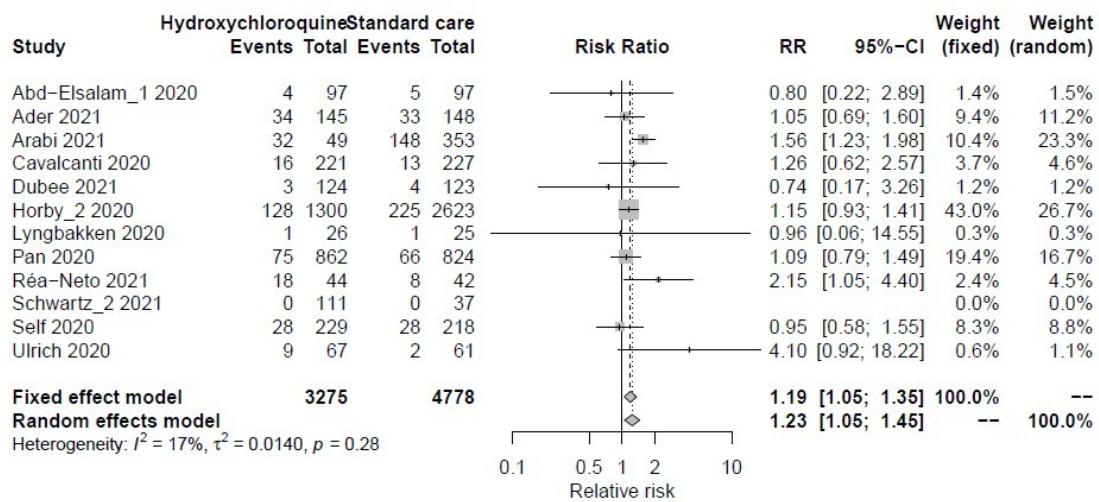


Current

With preprints



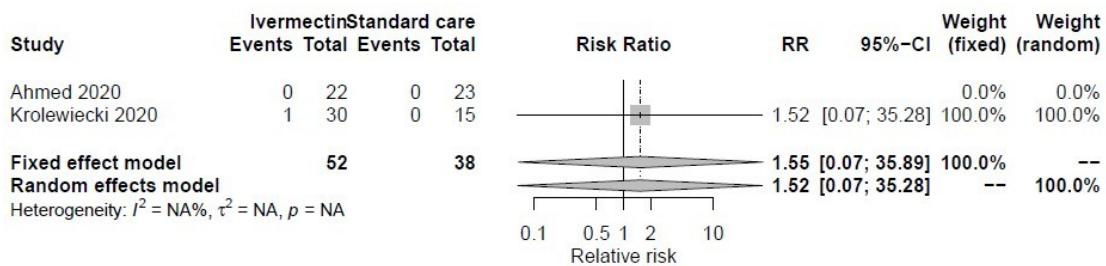
Without preprints



Ivermectin for mechanical ventilation

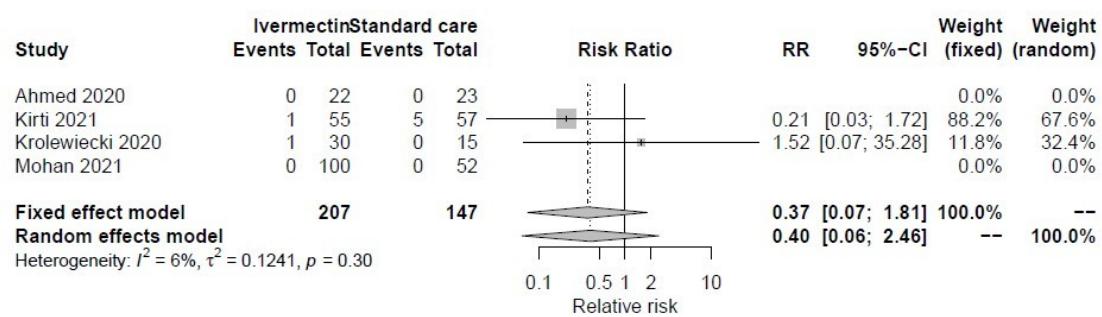
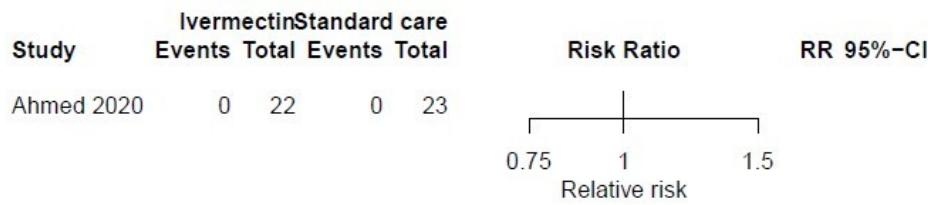
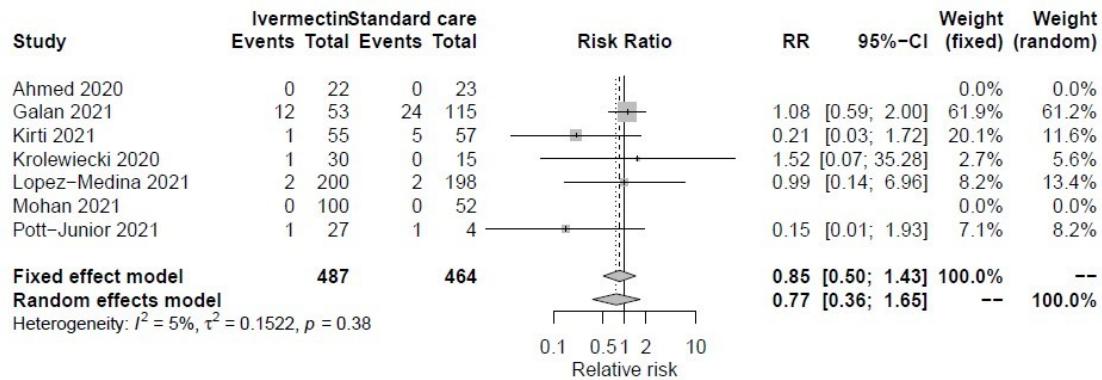
1 month

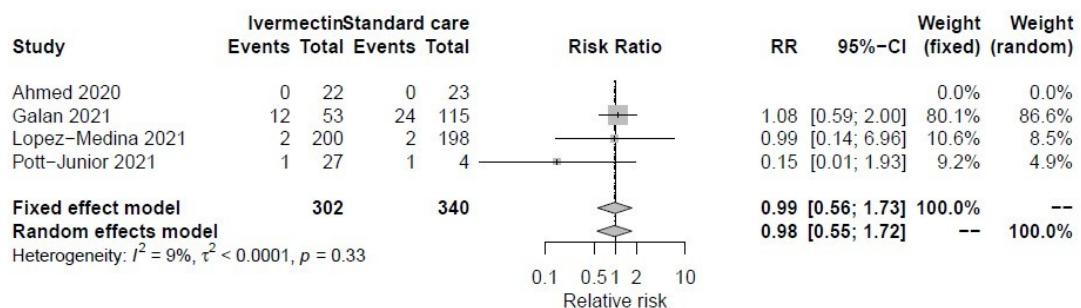
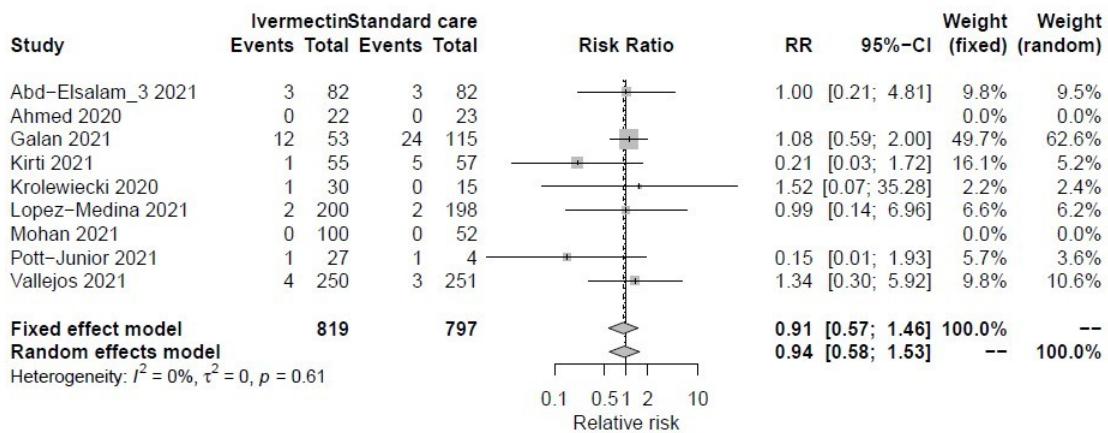
With preprints

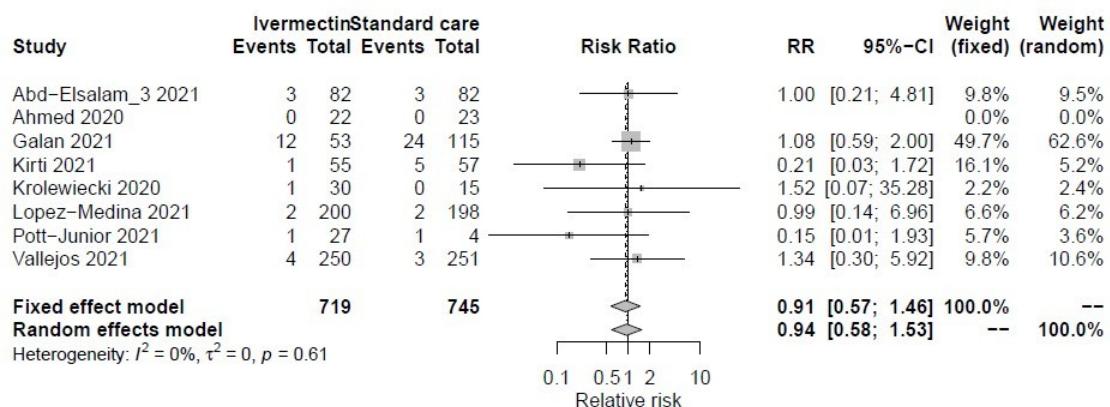


Without preprints



3 months*With preprints**Without pre-prints***6 months***With preprints*

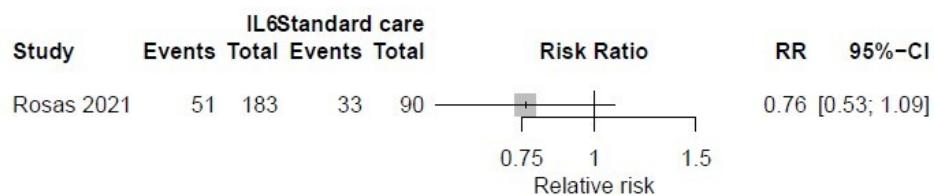
Without preprints**Current***With preprints**Without preprints*



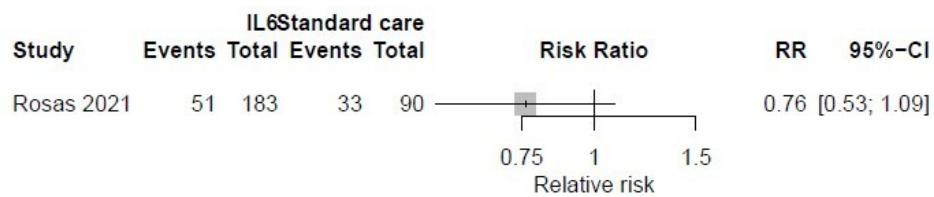
IL-6 receptor blockers for mechanical ventilation

1 month

With preprints

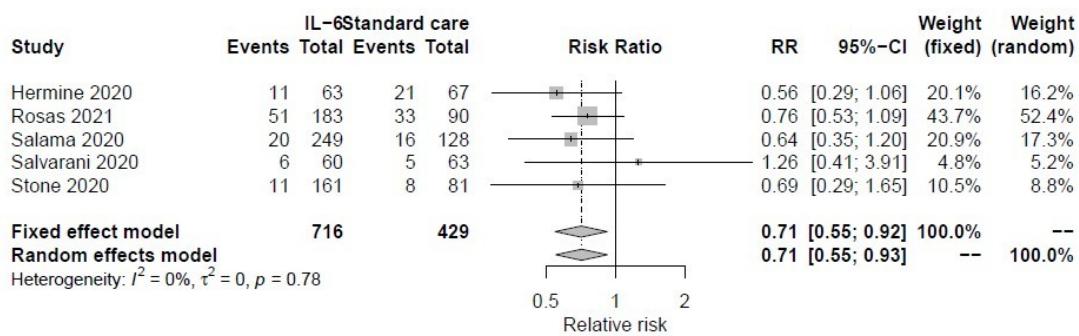


Without preprints

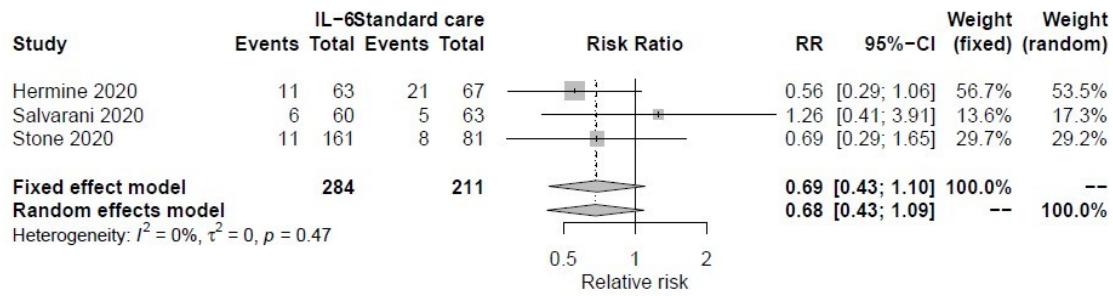


3 months

With preprints

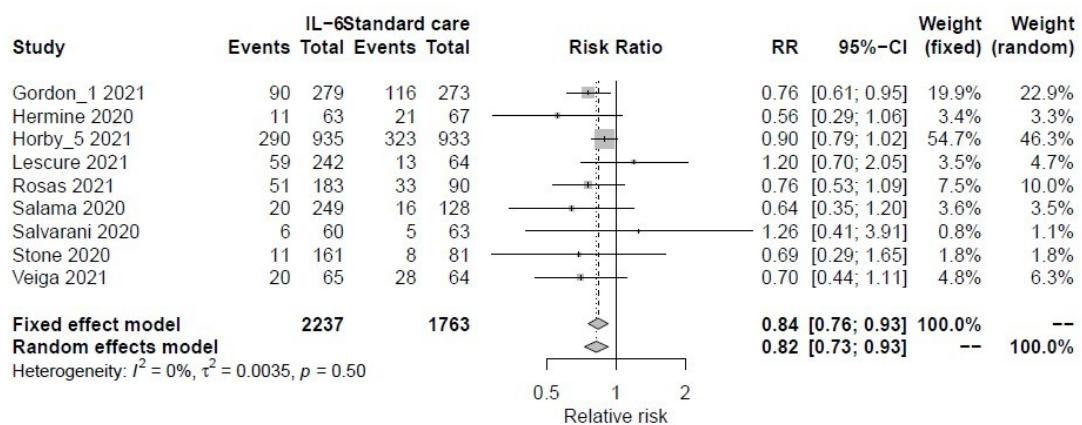


Without preprints

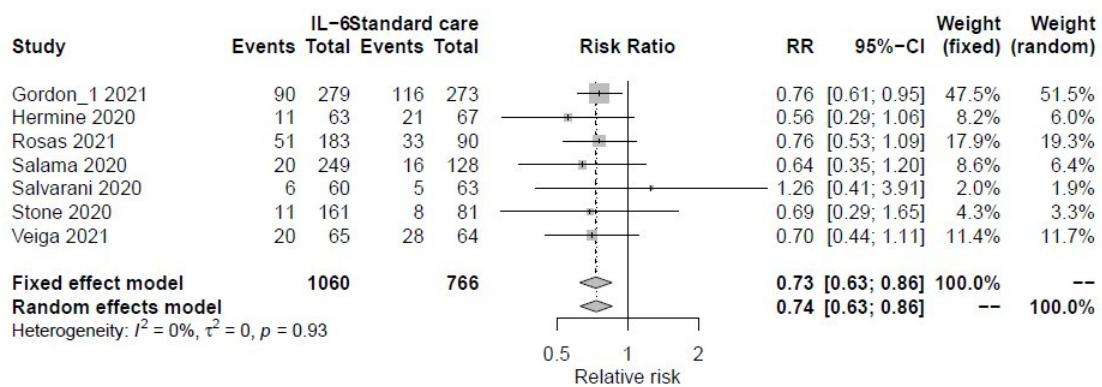


6 months

With preprints

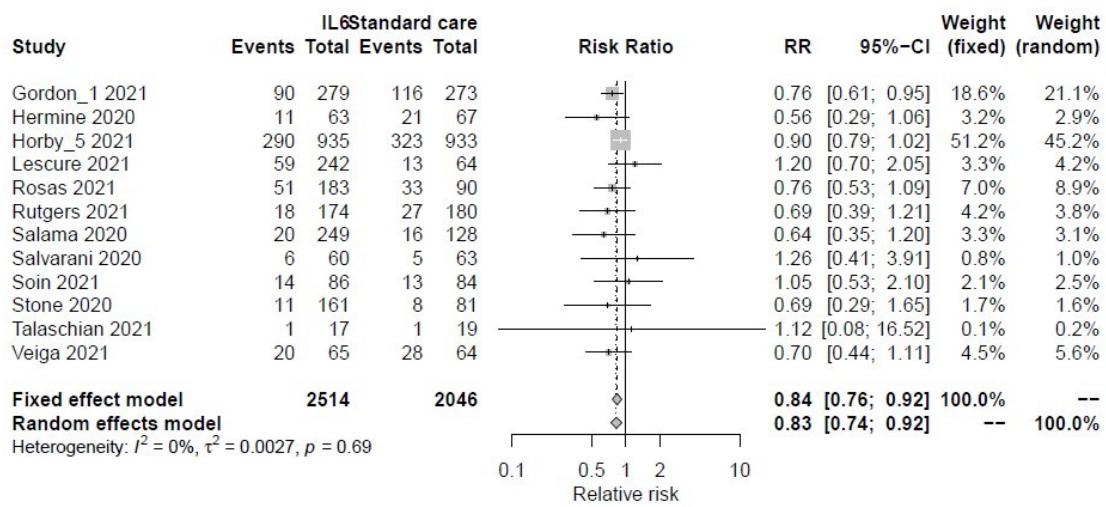


Without preprints

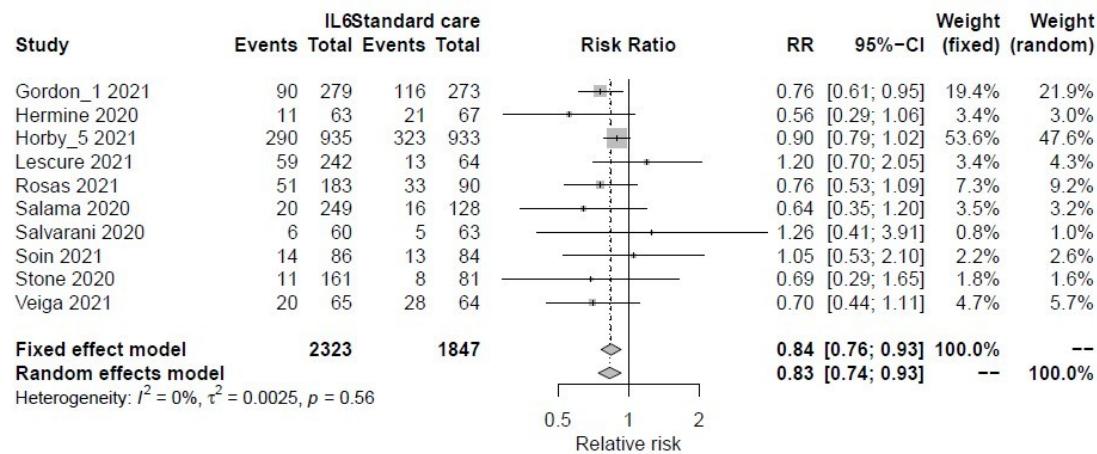


Current

With preprints



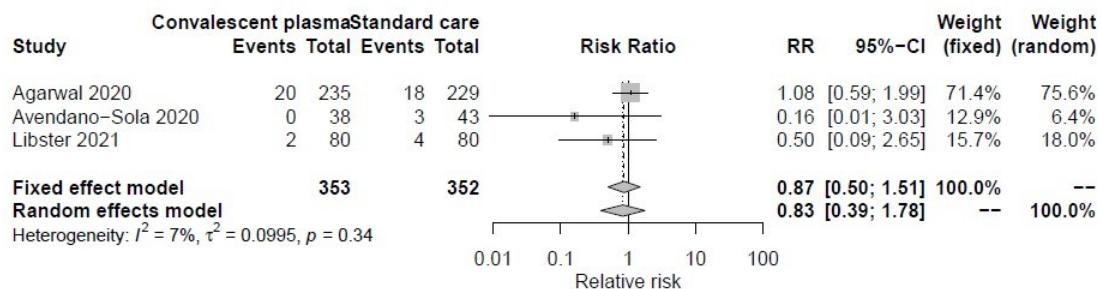
Without preprints



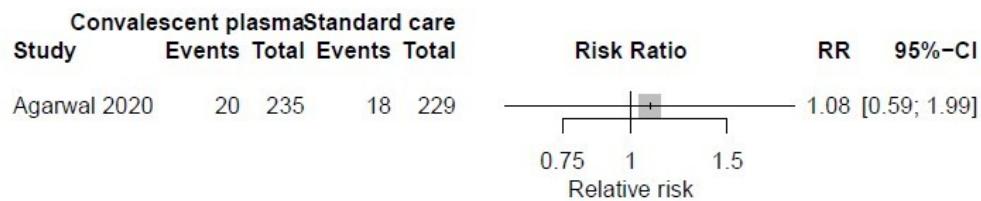
Convalescent plasma for mechanical ventilation

1 month

With preprints

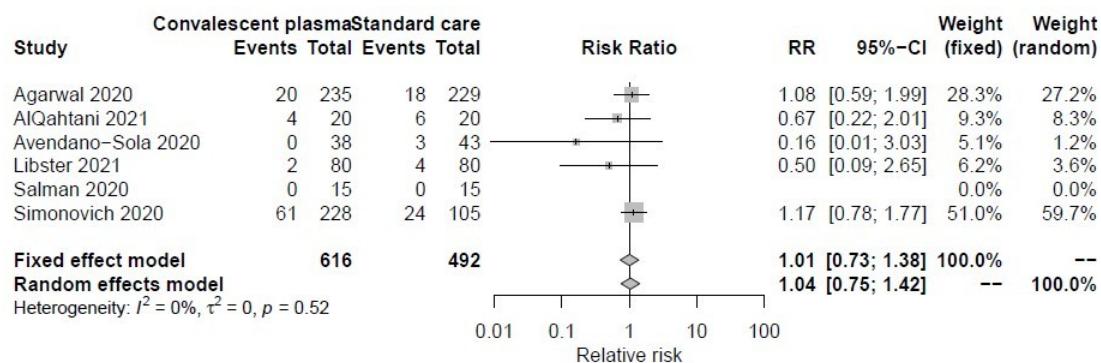


Without preprints

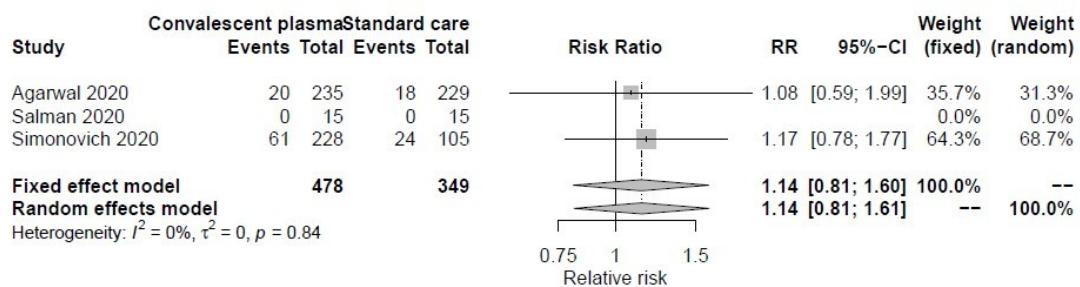
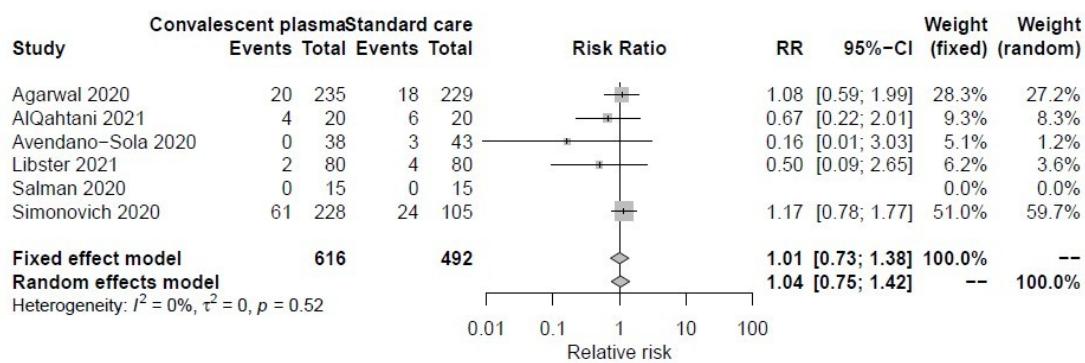
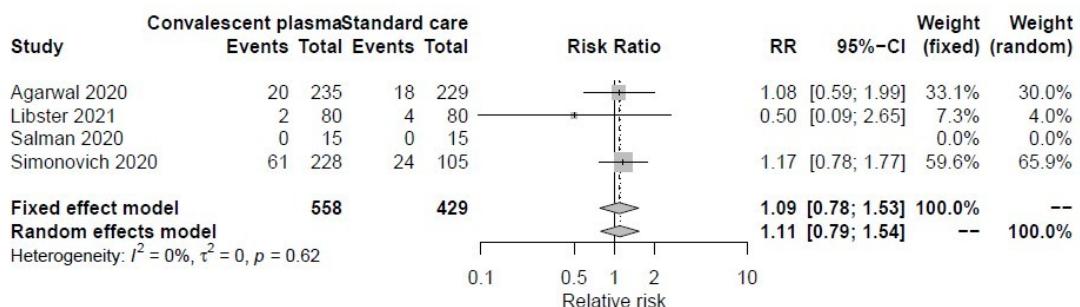


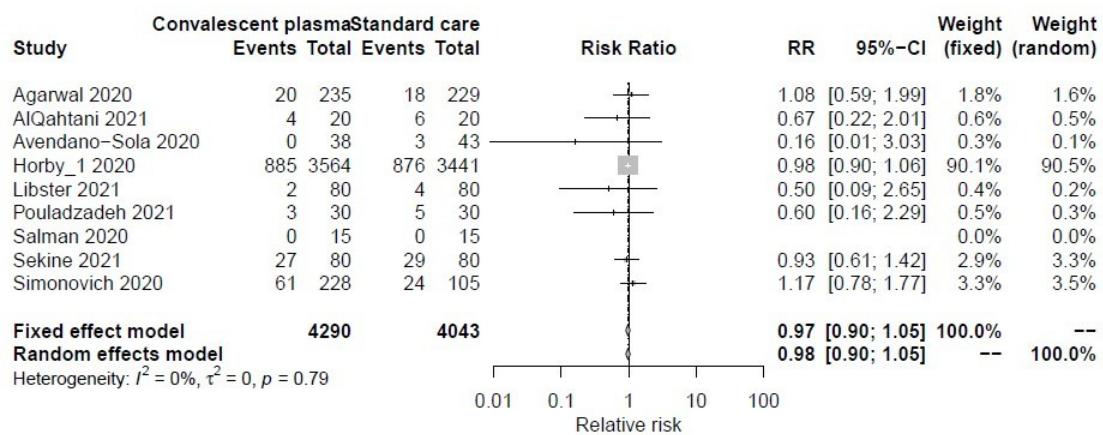
3 months

With preprints



Without preprints

**6 months***With preprints**Without preprints***Current***With preprints*



Without preprints

