Higher versus lower dose corticosteroids for moderate to severe COVID-19: a systematic review and dose response meta-analysis

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eProtocol

This protocol is registered on Open Science Framework but also presented here for ease of access.

Title: Higher versus lower dose corticosteroids for moderate to severe COVID-19: A systematic review, dose response and network meta-analysis

Introduction:

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection results in a wide range of clinical presentations, including asymptomatic, mild upper respiratory syndromes to acute respiratory distress syndrome (ARDS), as well as extrapulmonary manifestations (1, 2). As of January 6, 2022, there have been more than 300,468,306 million cumulative cases of coronavirus disease 19 (COVID-19) worldwide and 5,488,801 deaths (3). In an attempt to improve outcomes for patients with COVID-19, investigators have, with varying results, repurposed several drugs. There is compelling evidence that corticosteroids, interleukin-6 inhibitors (IL-6), Jak-inhibitors and monoclonal antibodies improve outcomes for patients with COVID-19 (4).

Corticosteroids have become part of standard of care since the publication of the RECOVERY trial, which showed a reduction in mortality in moderate to severe COVID-19 with dexamethasone 6 mg daily for 10 days, due in part to their accessibility and low cost (5). The typical dose prescribed is 6 mg of dexamethasone for 10 days (a cumulative dose of 60 mg). However, increasing evidence suggests that higher dose corticosteroids may be superior to lower doses in preventing mortality (6).

Our objective is to perform a systematic review, dose response and network meta-analysis of the existing COVID-19 trials addressing higher dose versus lower dose corticosteroids for severe COVID-19 infection.

Methods:

We will register a protocol in accordance with the PRIMSA extension statement for network meta-analysis and register a protocol on Open Science Framework.

Eligibility criteria

We will include all randomized controlled trials (RCTs) that randomized adult patients (>=18 years old) with moderate or severe COVID-19 to corticosteroids versus standard care/placebo or to alternative doses of corticosteroids.

Information sources and search strategy:

An experienced research librarian will search MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Med archive, and Web of Science. We also perform a hand-search of MedRxiv.

Data management, selection, and data collection process:

We will upload all citations to COVIDENCE, a citation screening platform and screened independently and in duplicate (7). If a reviewer selected a citation as relevant, it will be advanced on to the next stage. If there are discrepancies in reviewer selections, we will resolve by consensus or adjudication by a third reviewer. Citations chosen in the screening process were screened fully for inclusion or exclusion in the analysis. We will document the reasons for exclusion in the full text screening stage. Data collection will happen in similar fashion, by two extractors using a pilot tested data collection form.

Data items and outcomes:

From each eligible trial, we will collect data on trial characteristics, such as year of publication and country of enrollment, patient characteristics, such as age, sex, and type of supportive care, and our outcomes of interest, which included all-cause mortality (closest to 90 days), requirement of mechanical ventilation, duration of mechanical ventilation, duration of hospitalization, and risk of infections. For dichotomous outcomes, we will collect the number of participants analyzed and number of events in each arm, and for continuous outcomes, we collected the number of participants analyzed, measure of central tendency (mean or median), and measure of variability (e.g., SD, IQR) for each arm.

In addition, we plan to perform sensitivity analyses for 1) duration of corticosteroids 2) patients receiving oxygen only (without mechanical ventilation) and 3) patients receiving mechanical ventilation only.

Risks of bias:

Reviewers, working independently and in duplicate, will assess risk of bias using a revision of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) (8). We will the trials as either at i) low risk of bias, ii) probably low risk of bias) iii) probably high risk of bias or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered

protocol and bias arising from early termination for benefit. We will resolve discrepancies by discussion and, when not possible, with adjudication by a third party.

Statistical methods:

We will summarize the effects of interventions using relative risks (RR) and corresponding 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MD) with 95% CI for continuous outcomes. To facilitate interpretation of results, we will calculate absolute effects using the median risk across the placebo/standard care arms and report risk differences.

We will conduct a network meta-analysis comparing higher and lower doses of corticosteroids with standard care/placebo and dose-response meta-analyses.

For our network meta-analysis, we will classify corticosteroids into higher dose corticosteroids and lower dose corticosteroid nodes based on the cumulative corticosteroid dose administered in the trial (i.e., dexamethasone 6 mg/day for 10 days = 60 mg total dose). Cumulative corticosteroid doses of less than or equal to 60 mg of dexamethasone will be placed in the low dose node and those greater than 60 mg of dexamethasone were placed in the high dose node. We will use the following conversions to convert different corticosteroids into equivalent doses of dexamethasone: 1 mg (dexamethasone) = 26.7 mg (hydrocortisone) = 5.3 mg (methylprednisolone/prednisolone) (9, 10).

For all outcomes in our network meta-analysis, we will conduct a frequentist random-effects network meta-analysis using the *netmeta package in R* and produced network plots using the network map command of Stata version 17.0 (StataCorp, College Station, TX) (11, 12).

For all outcomes for dose response, we will conduct a linear random-effects one-stage dose-response meta-analysis using methods proposed by Greenland and Longnecker and Orsini and colleagues using the *dosresmeta* package in R and the REML heterogeneity estimator (13, 14). For analyses including 5 or more studies, we will test for nonlinearity by using restricted cubic splines with knots at 10%, 50%, and 90% and a Wald-type test. For analyses in which we observe statistically significant nonlinear associations, we will present results from the nonlinear model.

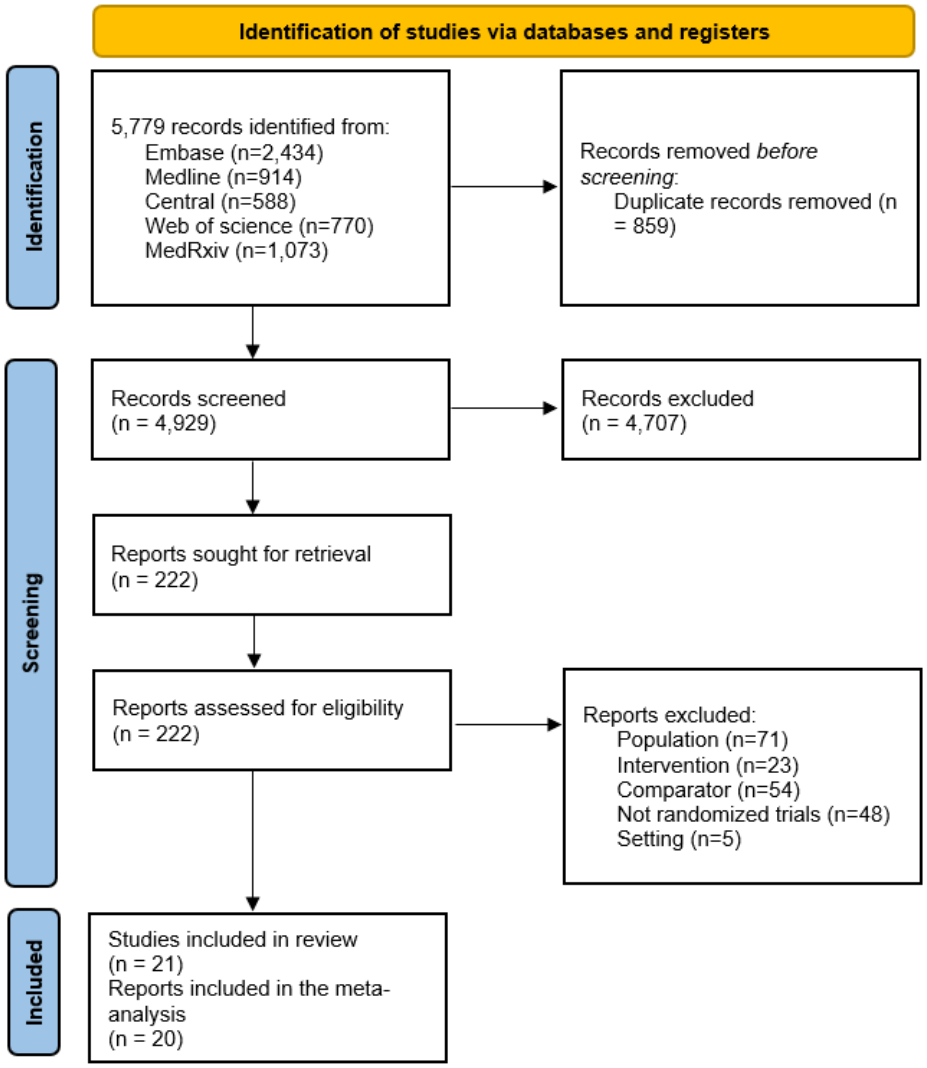
For outcomes with 10 or more studies, we will assess the likelihood of publication bias using both visual inspection of funnel plots and the Egger's test (15).

Certainty of the evidence:

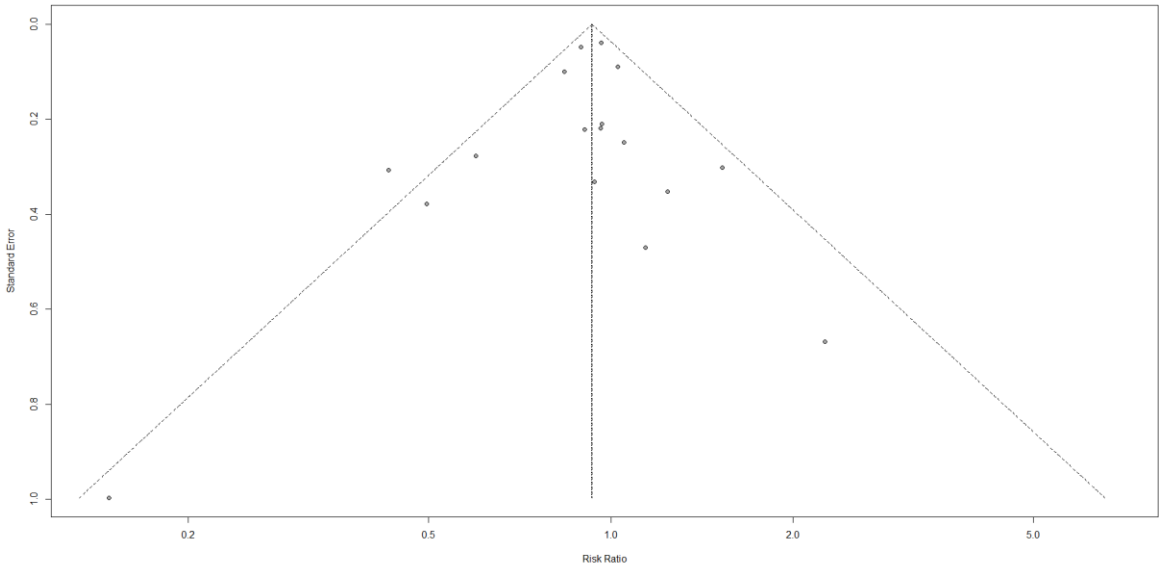
We plan to assess the certainty of the evidence independently and in duplicate using the GRADE approach for network meta-analysis (16).We will rate our dose response meta-analysis in similar fashion. We will rate the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision. We will use a minimally contextualized approach when rating the imprecision (16). Minimally important differences will be sourced from available by consensus by the authors.

We plan to report our results using the simple language guidance for GRADE (17). This involves specifying the certainty of the evidence by specifying the following adjectives: high certainty (drug x reduces mortality), moderate certainty (drug x likely reduces mortality), low certainty (drug x may reduce mortality), and very low certainty (the effect of drug x on mortality is very uncertain). For the principal analysis, we will report the highest certainty evidence in the dose response or the network meta-analysis.

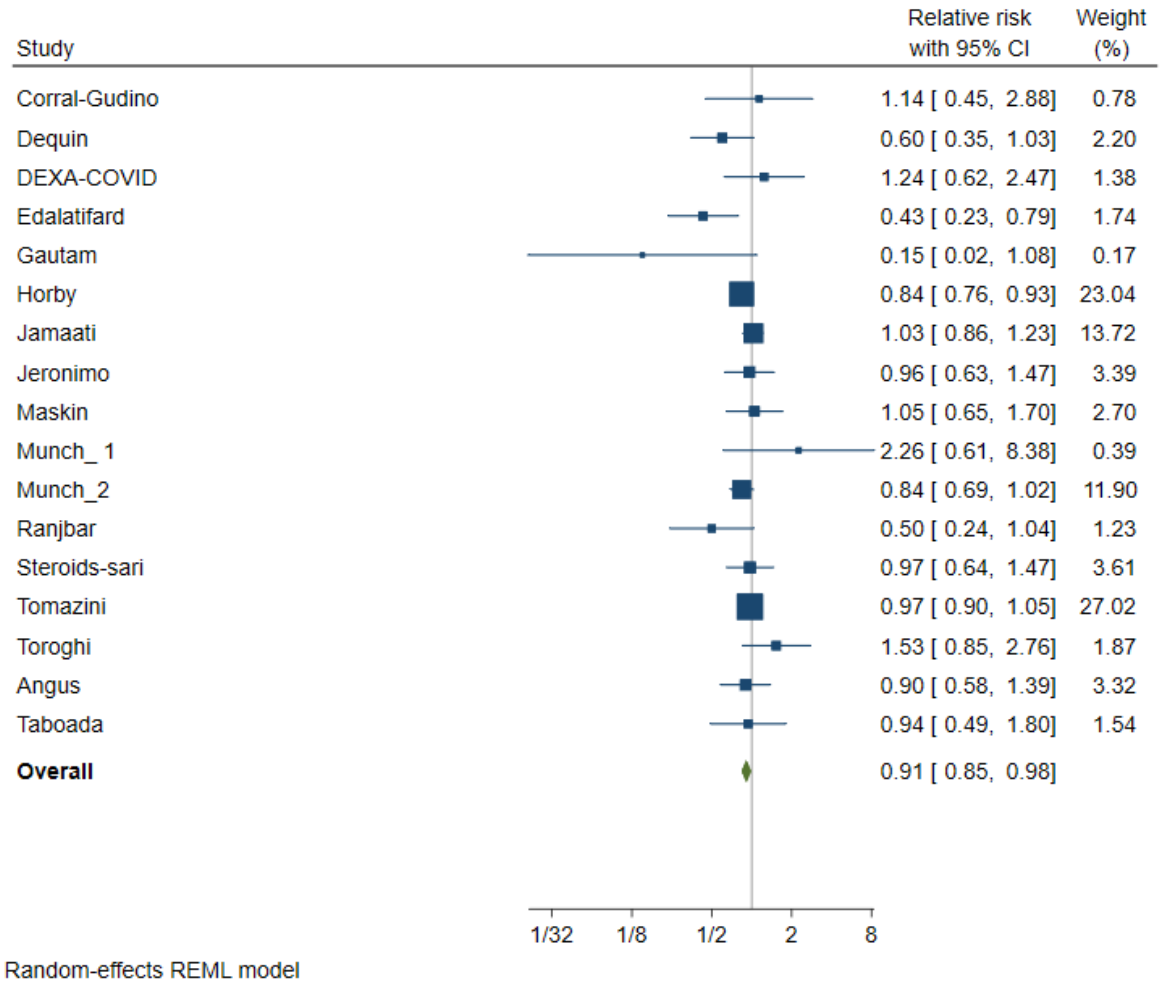
eFigure 1. PRISMA flow diagram



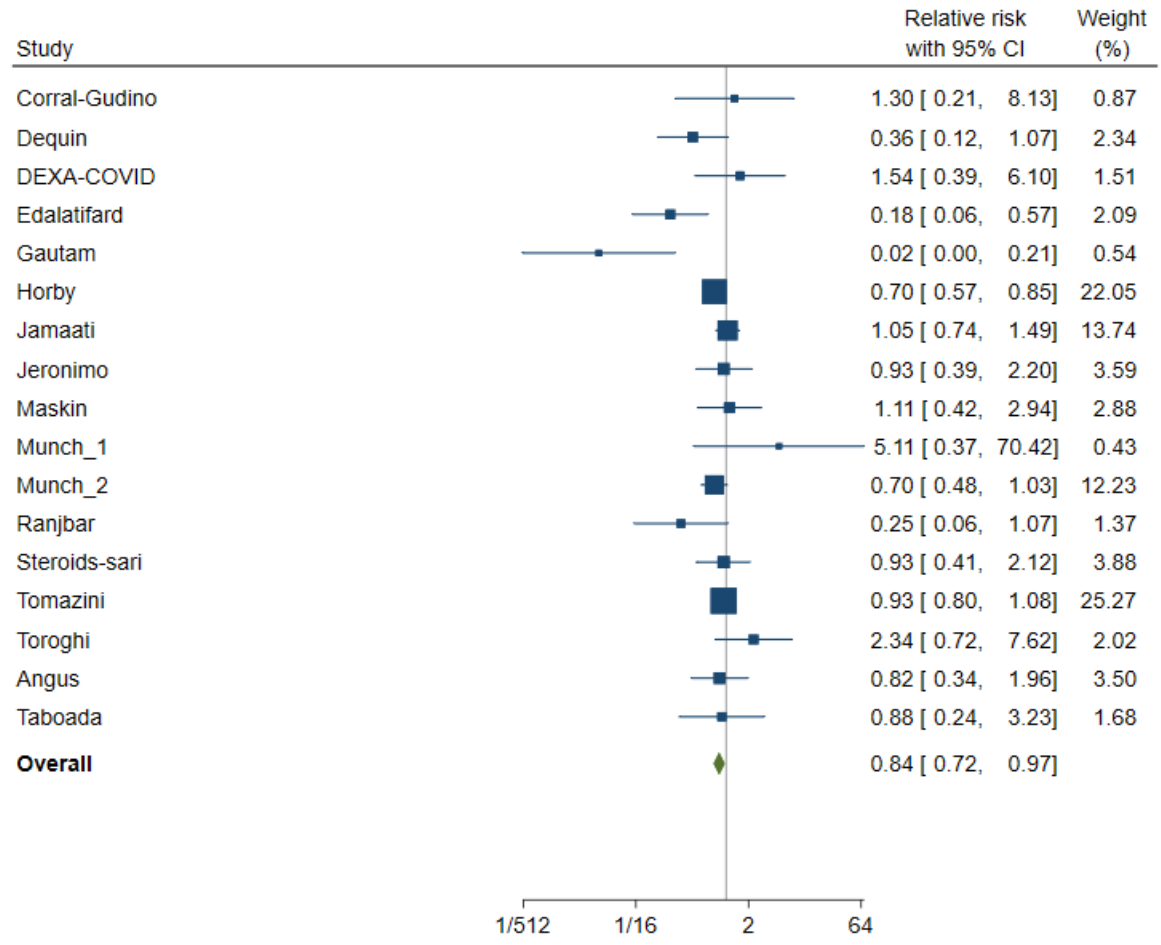
eFigure 2. Funnel plot for mortality (oxygen and mechanical ventilation)



eFigure 3. All-cause mortality forest plot per 6 mg/day for 10 days of dexamethasone equivalents.



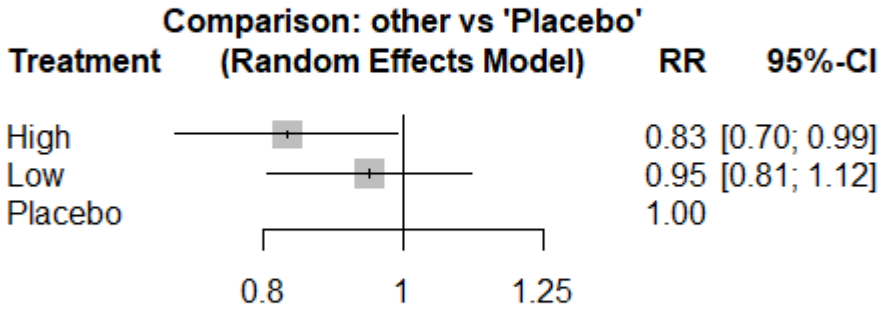
eFigure 4. All-cause mortality forest plot per 12 mg/day for 10 days of dexamethasone equivalents



Random-effects REML model

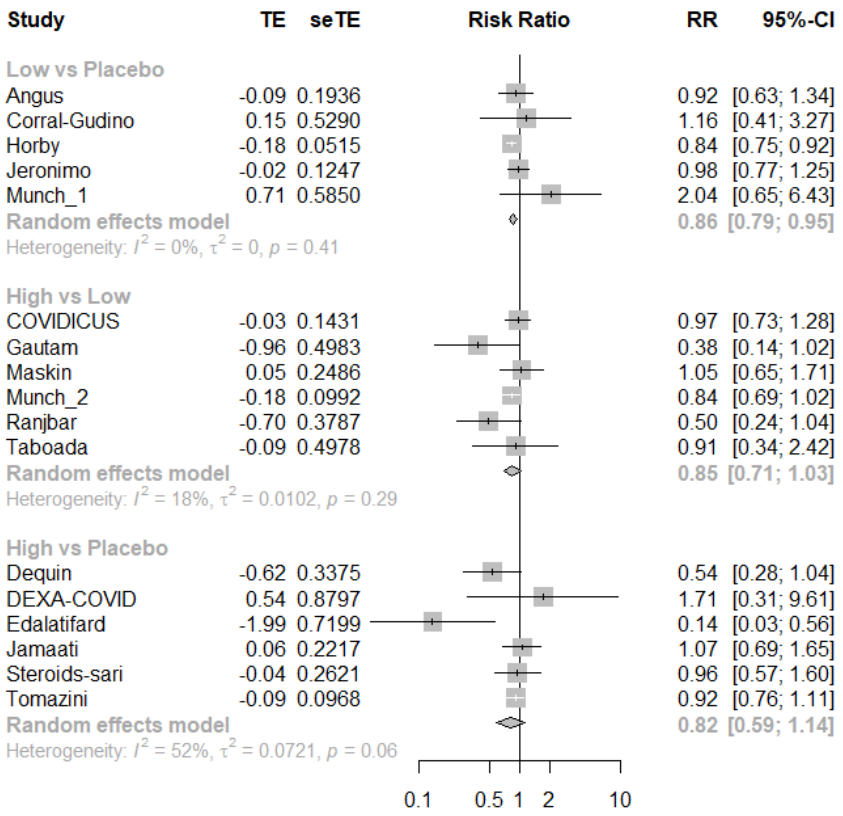
Network meta-analysis

eFigure 5. Mortality forest plot network plot



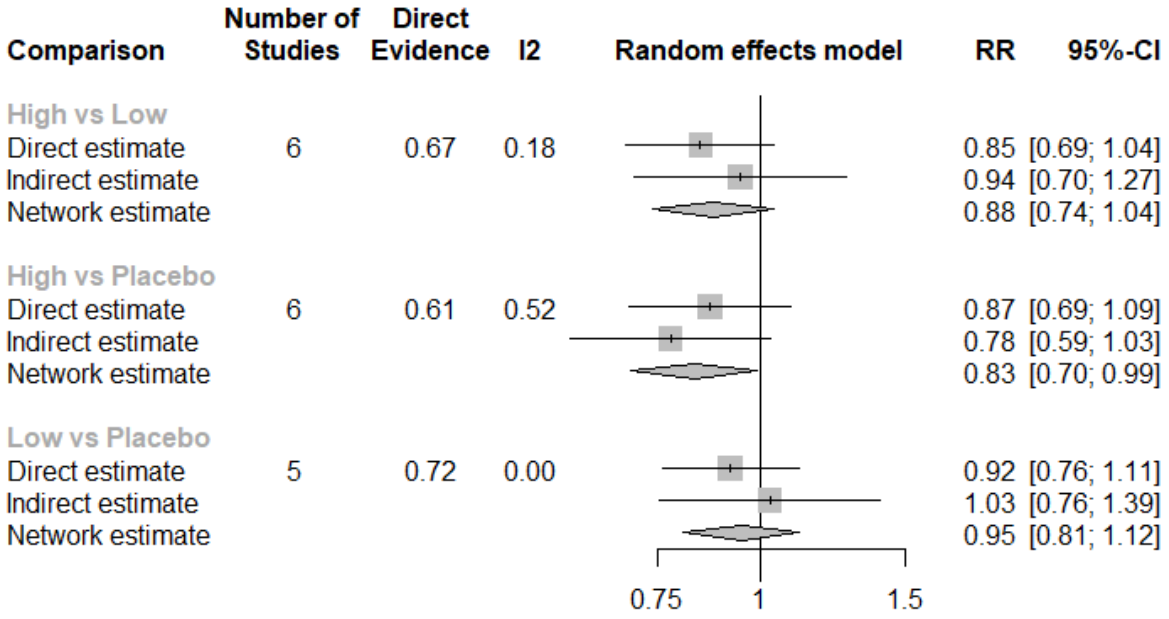
RR=relative risk

eFigure 6. Pairwise analysis



TE = treatment effect
SeTE= standard error of the treatment effect
RR = risk ratio

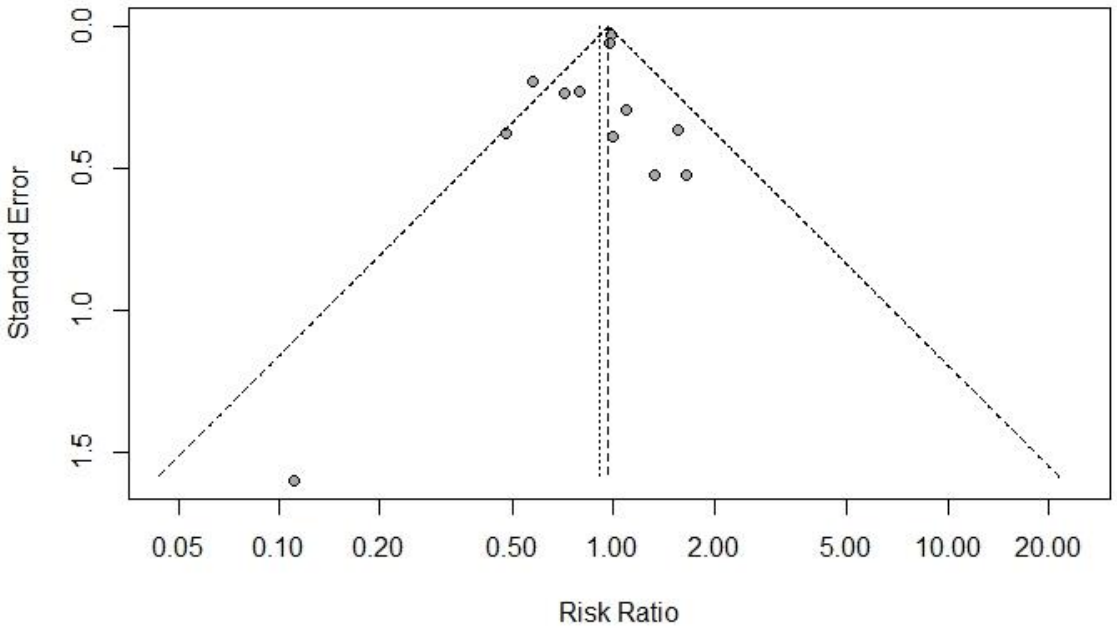
eFigure 7. Node split analysis



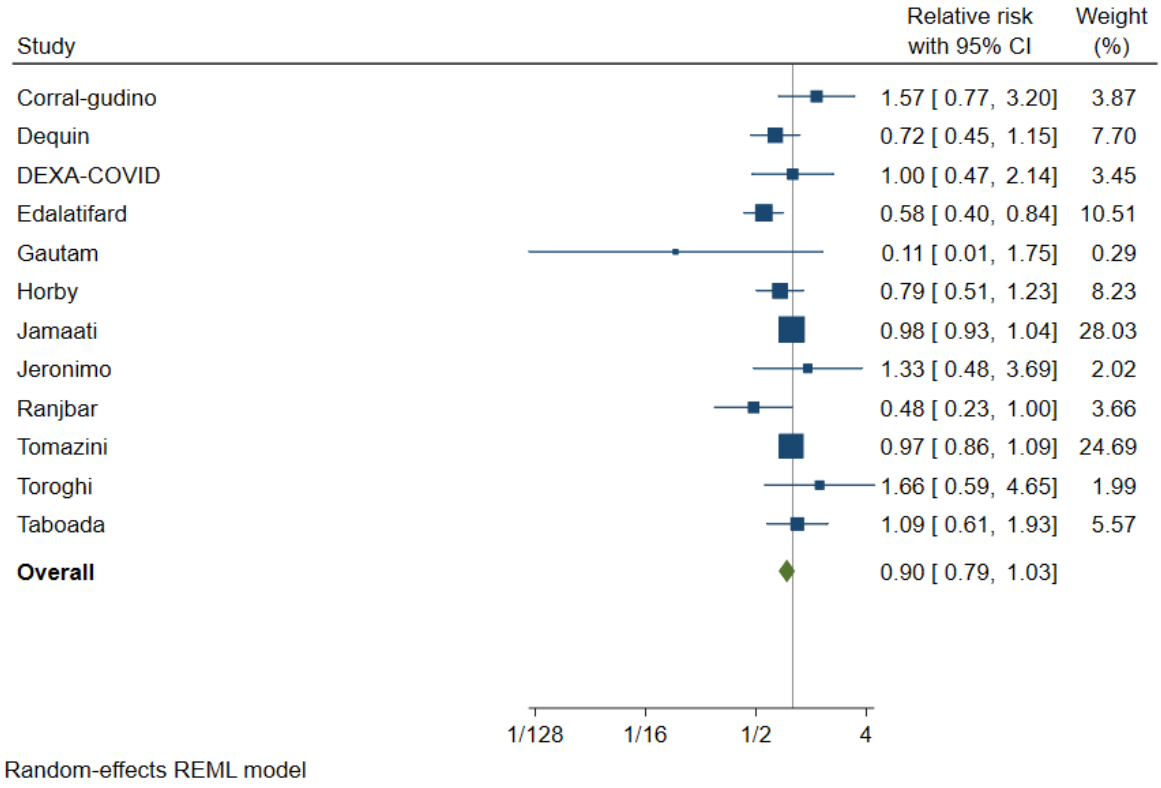
RR= relative risk

95% CI = 95% confidence intervals

eFigure 8.Funnel plot for need for mechanical ventilation

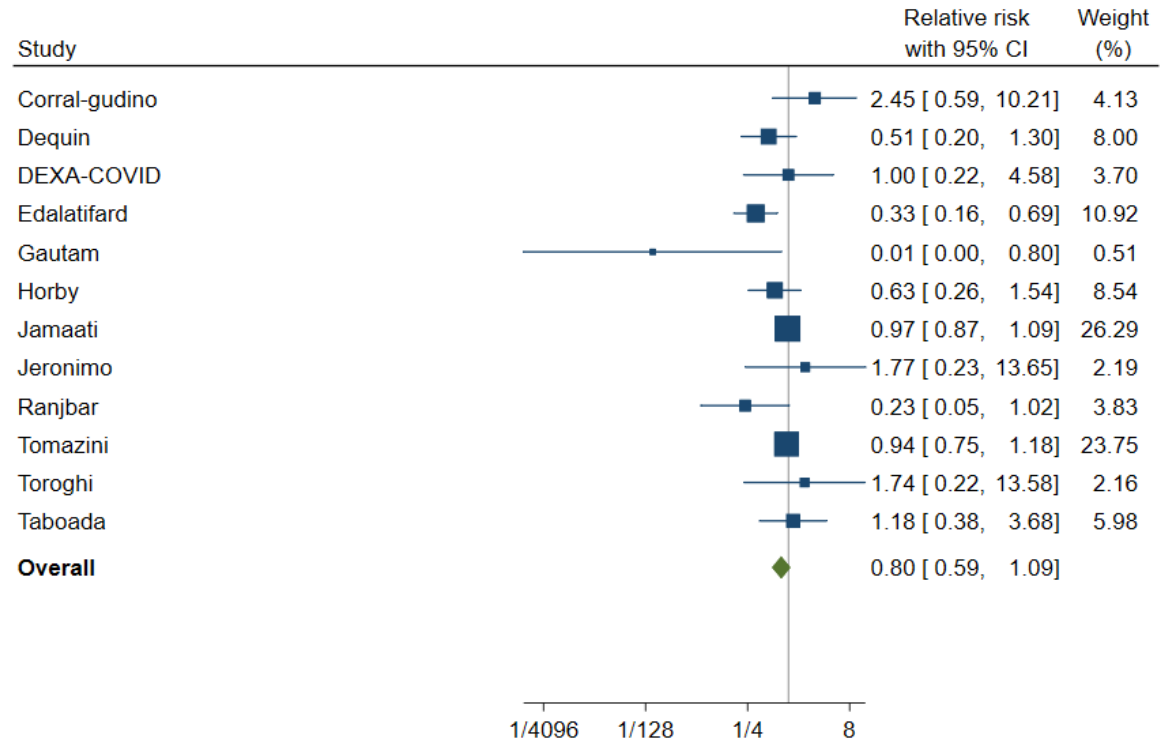


eFigure 9. Need for mechanical ventilation forest plot per 6 mg/day for 10 days of dexamethasone equivalents



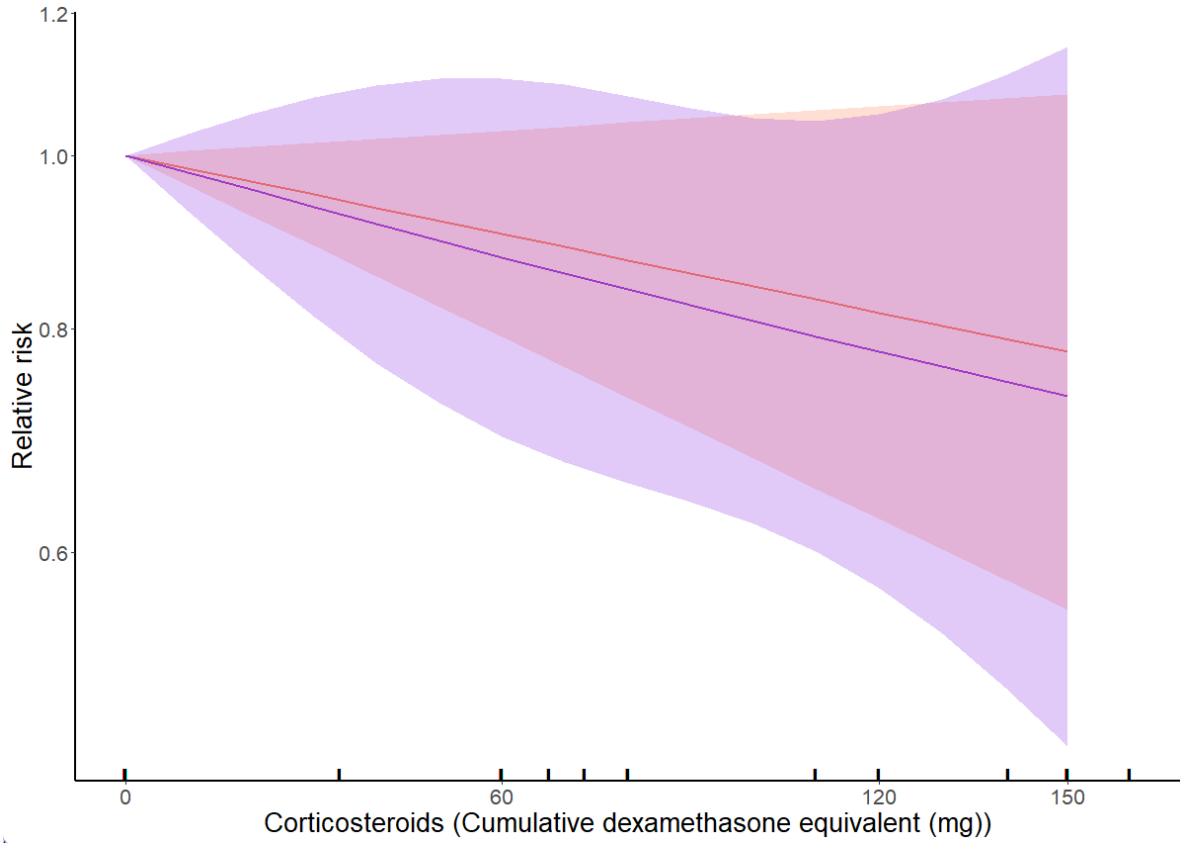
Random-effects REML model

eFigure 10. Need for mechanical ventilation forest plot per 12 mg/day for 10 days of dexamethasone equivalents



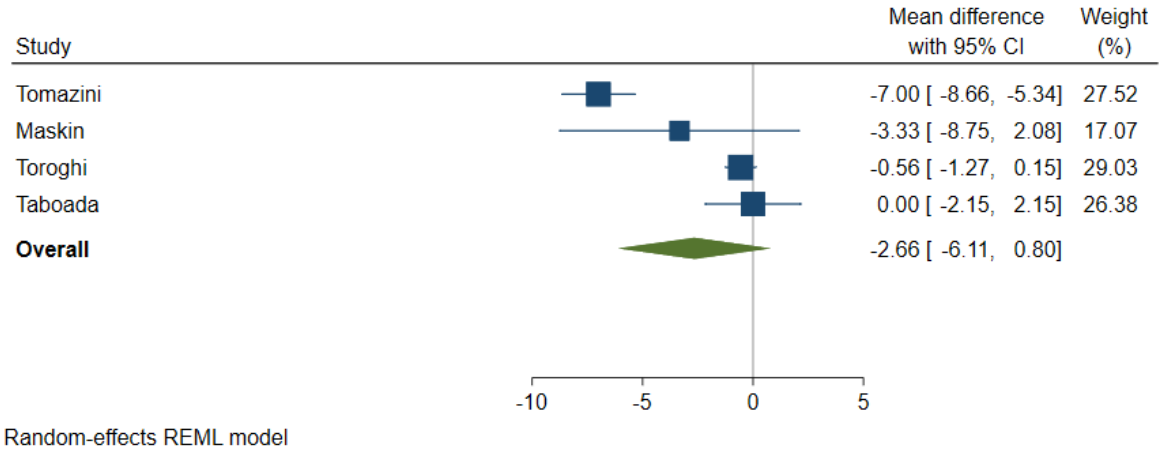
Random-effects REML model

eFigure 11. Need for mechanical ventilation linear/non-linear graph



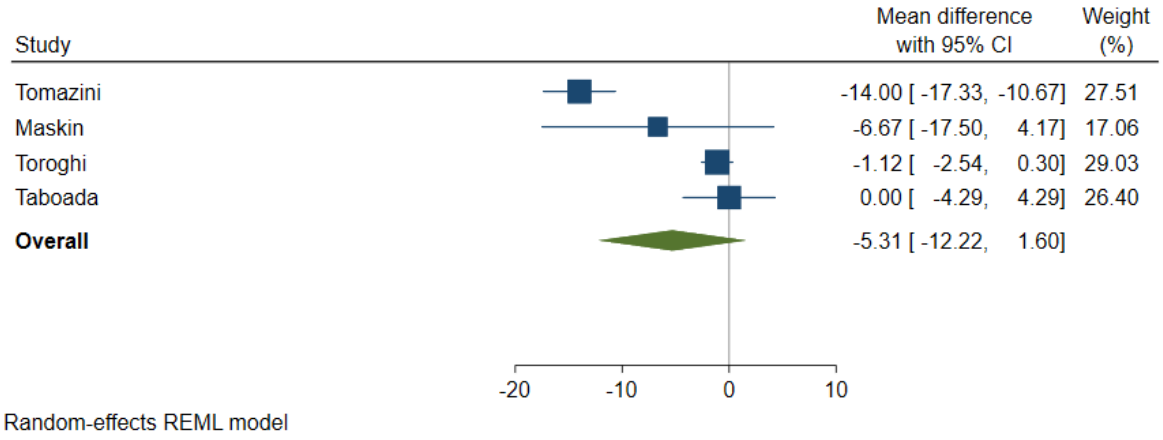
*The yellow line indicates the linear dose response relationship, and the associated yellow ribbons indicate the 95% confidence intervals. The purple line indicates the non-linear dose response relationship, and the purple ribbons indicate the 95% confidence intervals.

eFigure 12. Duration of mechanical ventilation forest plot per 6 mg/day for 10 days of dexamethasone equivalents

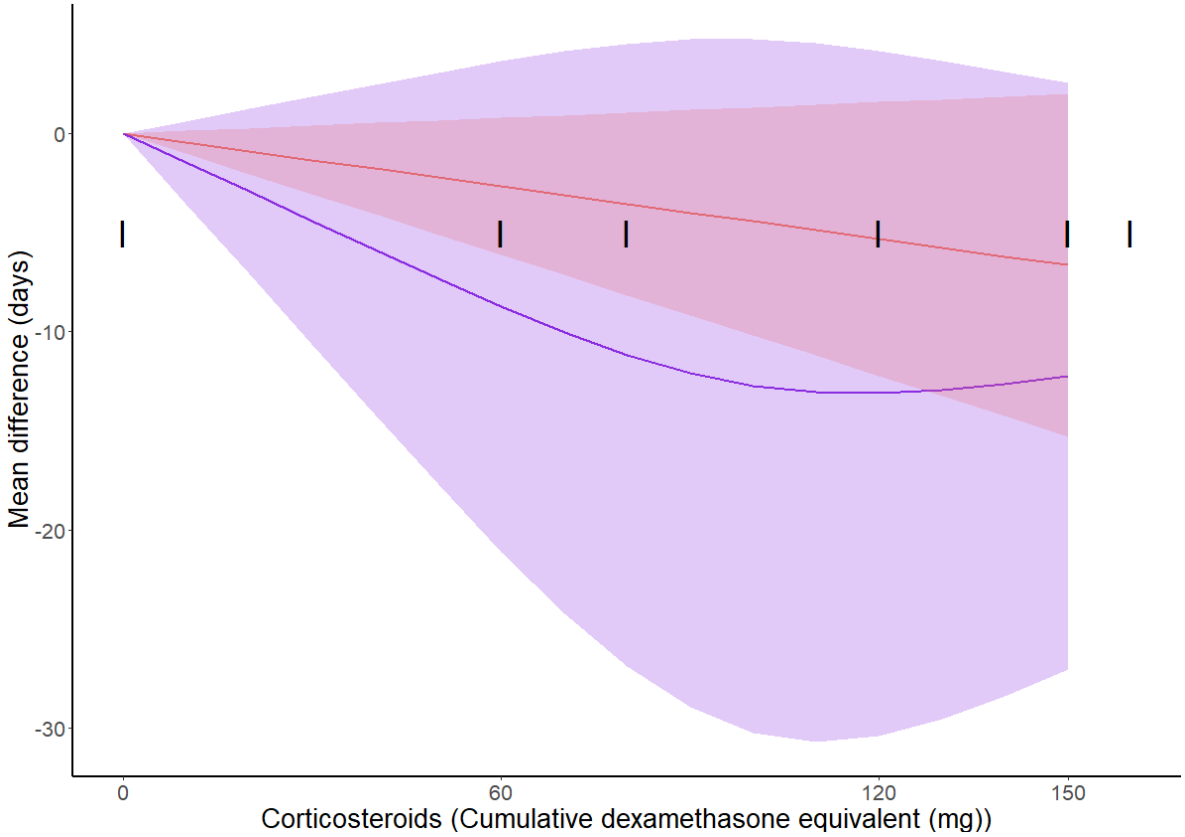


Random-effects REML model

eFigure 13. Duration of mechanical ventilation forest plot per 12 mg/day for 10 days of dexamethasone equivalents

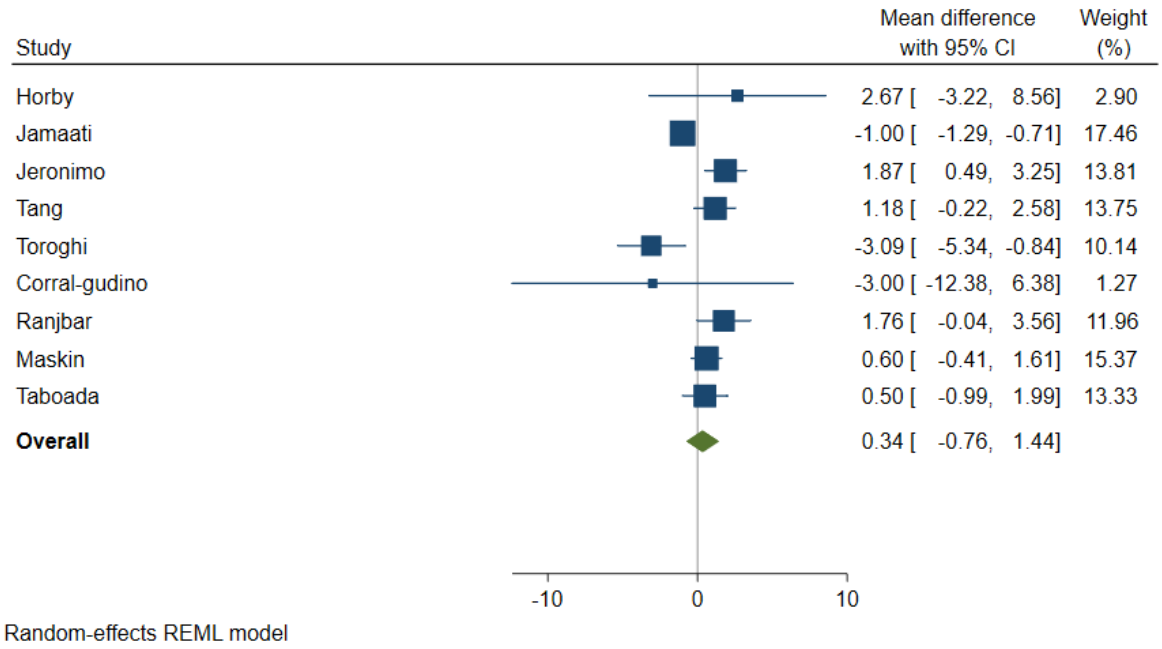


eFigure 14. Duration of mechanical ventilation linear/non-linear graph



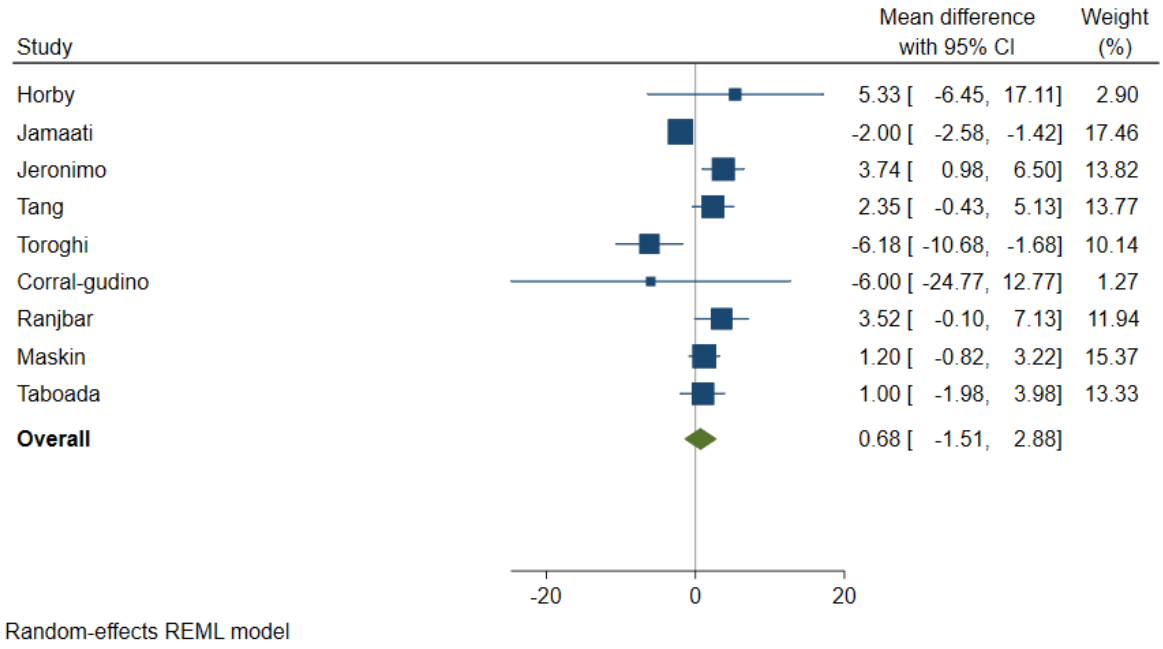
*The yellow line indicates the linear dose response relationship, and the associated yellow ribbons indicate the 95% confidence intervals. The purple line indicates the non-linear dose response relationship, and the purple ribbons indicate the 95% confidence intervals.

eFigure 15. Duration of hospitalization forest plot per 6 mg/day for 10 days of dexamethasone equivalents



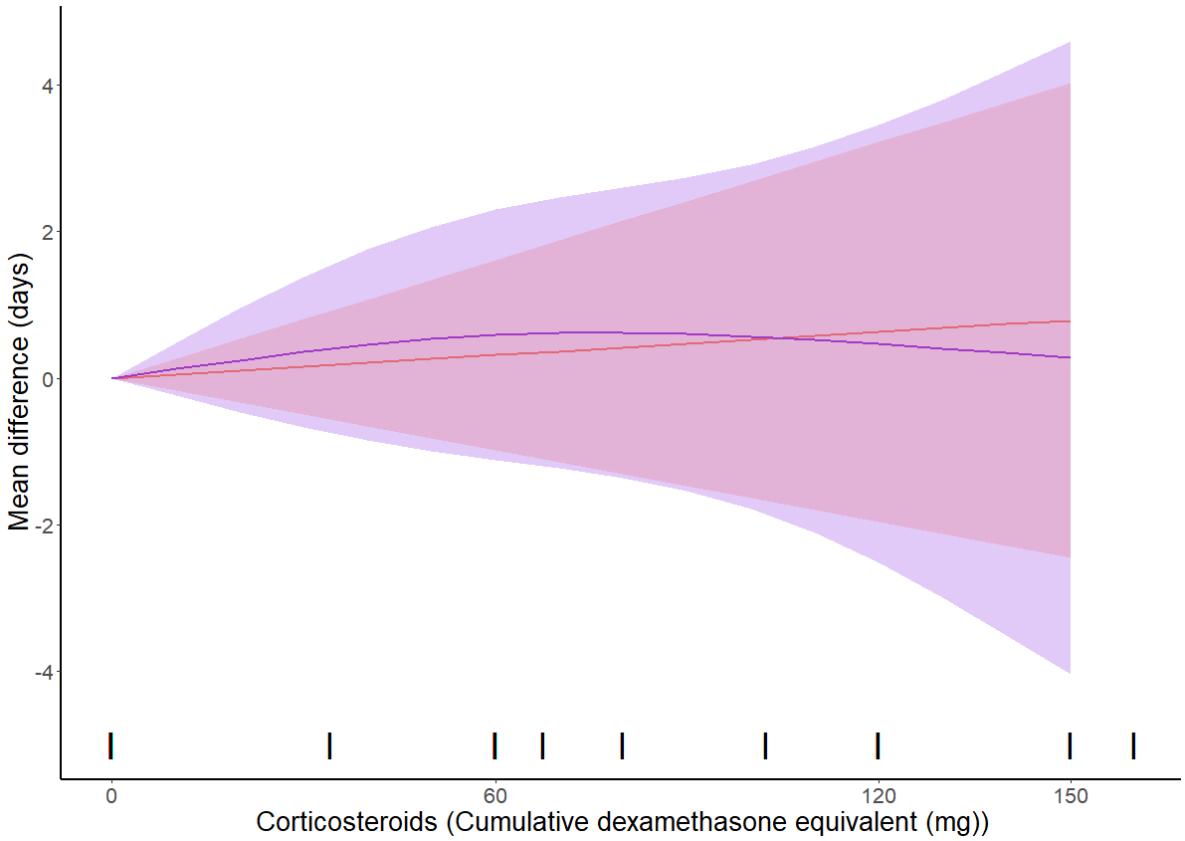
Random-effects REML model

eFigure 16. Duration of hospitalization forest plot per 12 mg/day for 10 days of dexamethasone equivalents



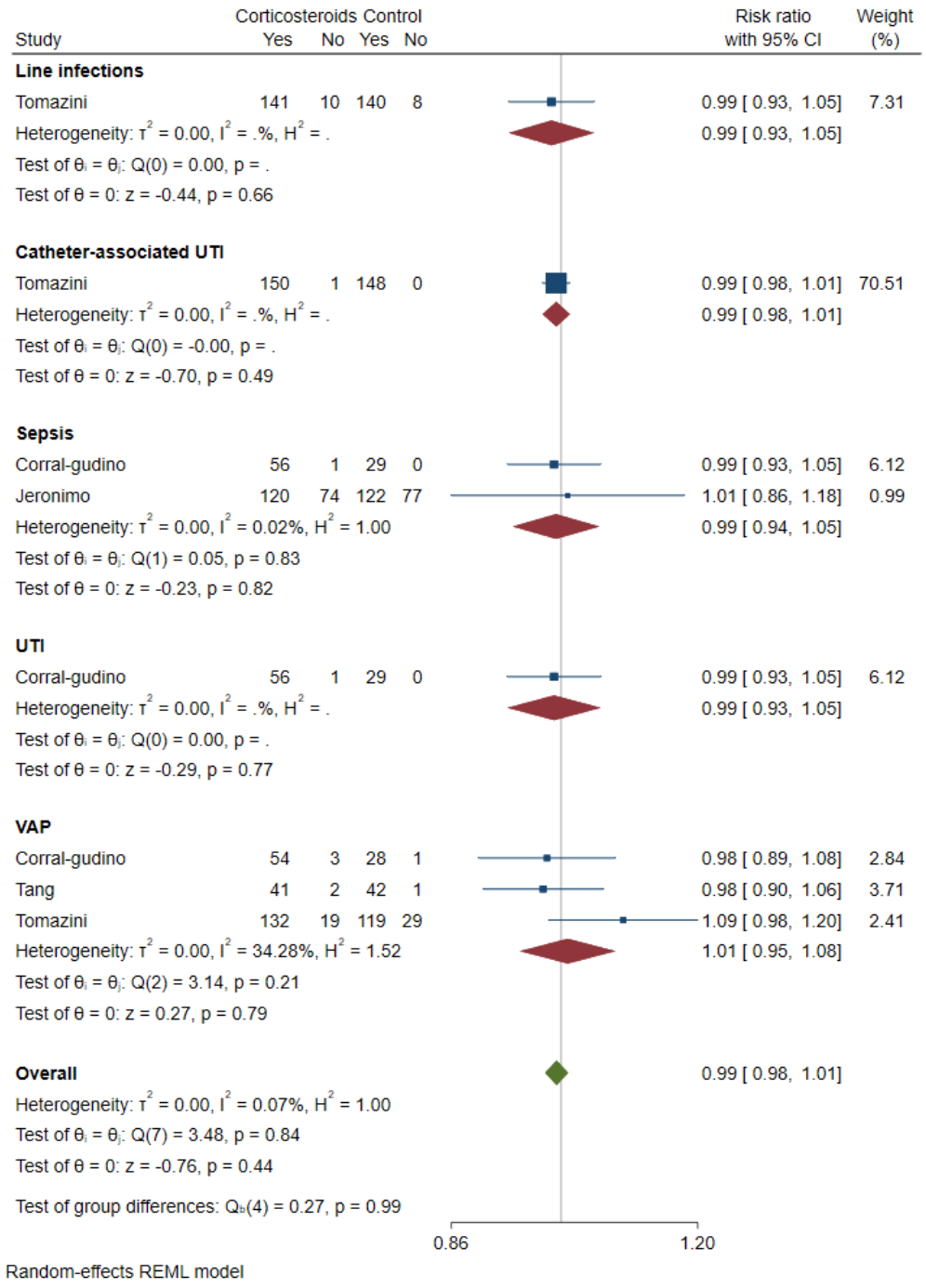
Random-effects REML model

eFigure 17. Duration of hospitalization linear/non-linear graph

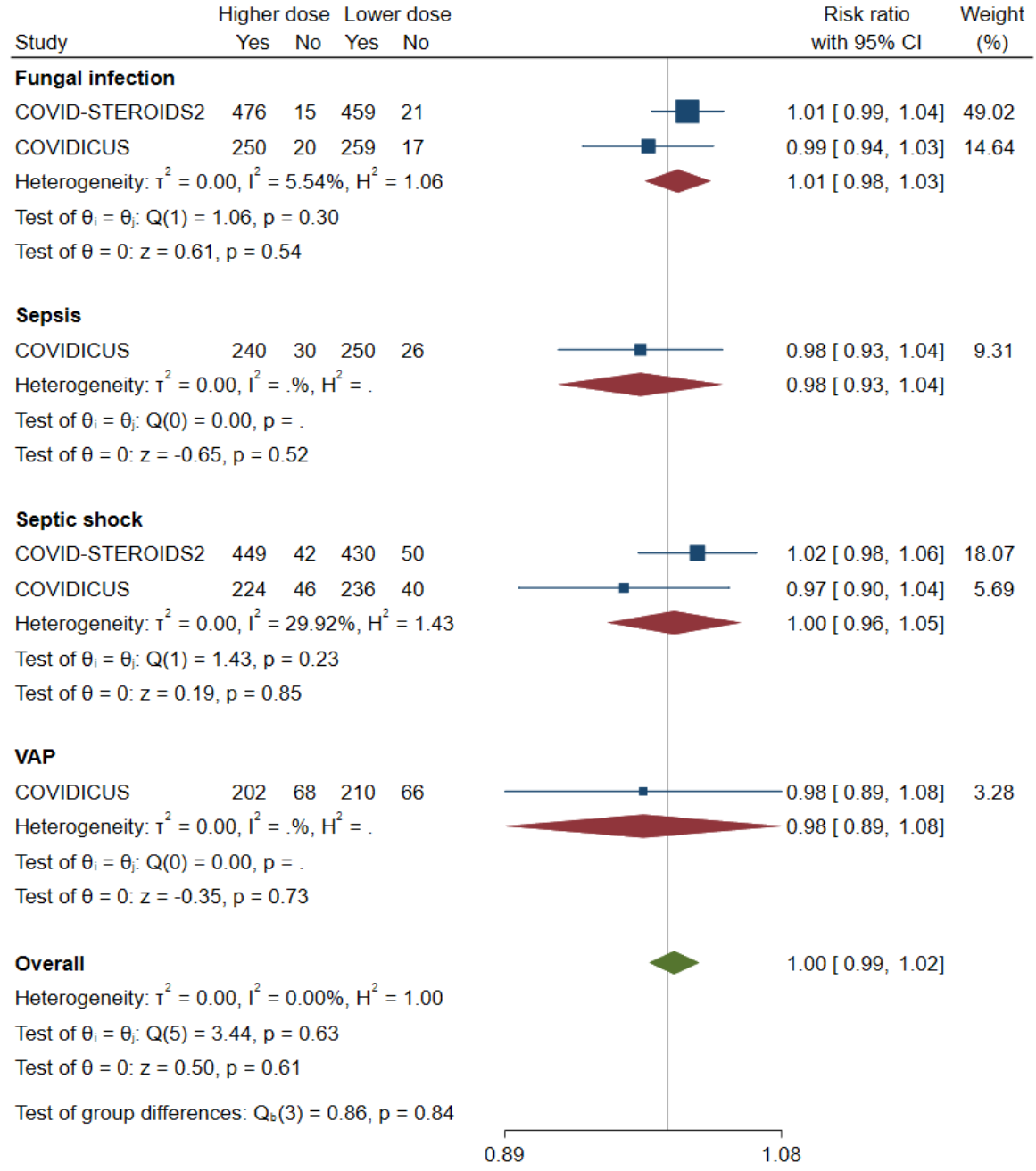


*The yellow line indicates the linear dose response relationship, and the associated yellow ribbons indicate the 95% confidence intervals. The purple line indicates the non-linear dose response relationship, and the purple ribbons indicate the 95% confidence intervals.

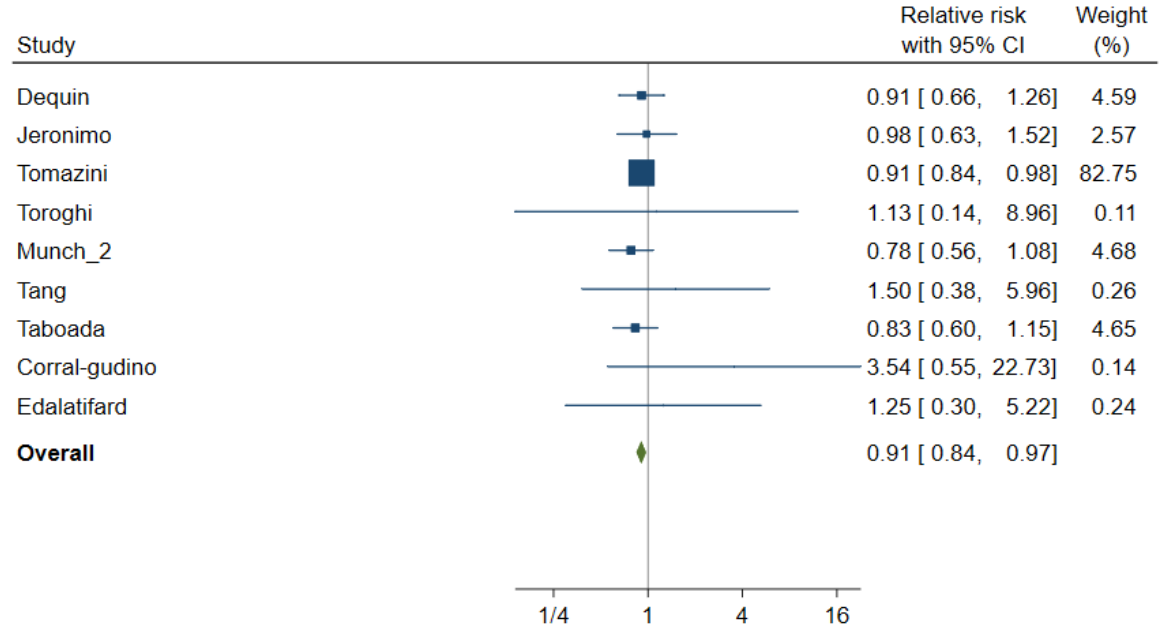
eFigure 18. Infection subtypes for corticosteroids versus control



eFigure 19. Higher versus lower corticosteroid trials and infection subtypes

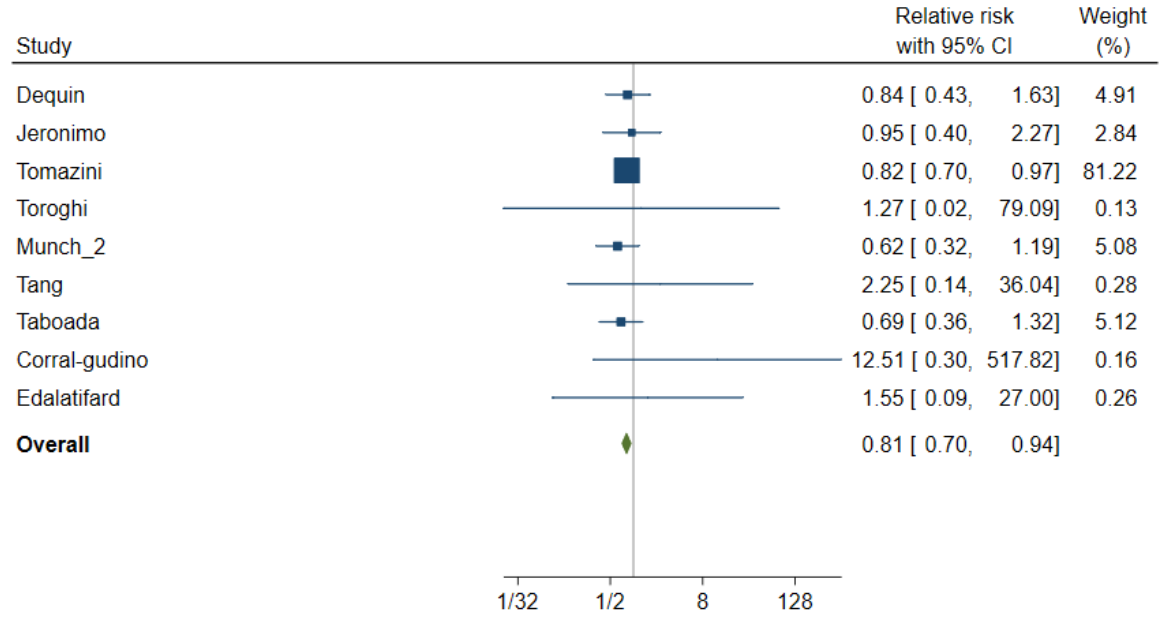


eFigure 20. Infections forest plot per 6 mg/day for 10 days of dexamethasone equivalents



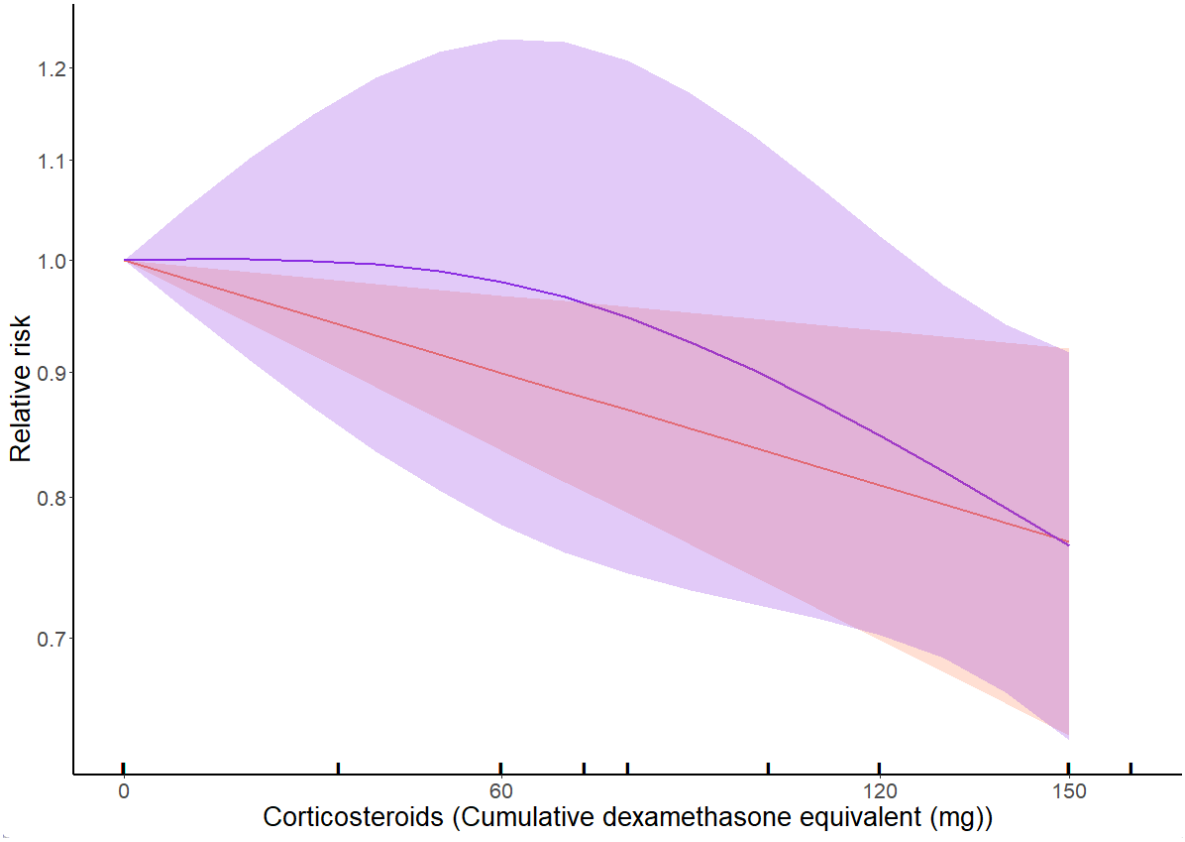
Random-effects REML model

eFigure 21. Infections forest plot per 12 mg/day for 10 days of dexamethasone equivalent



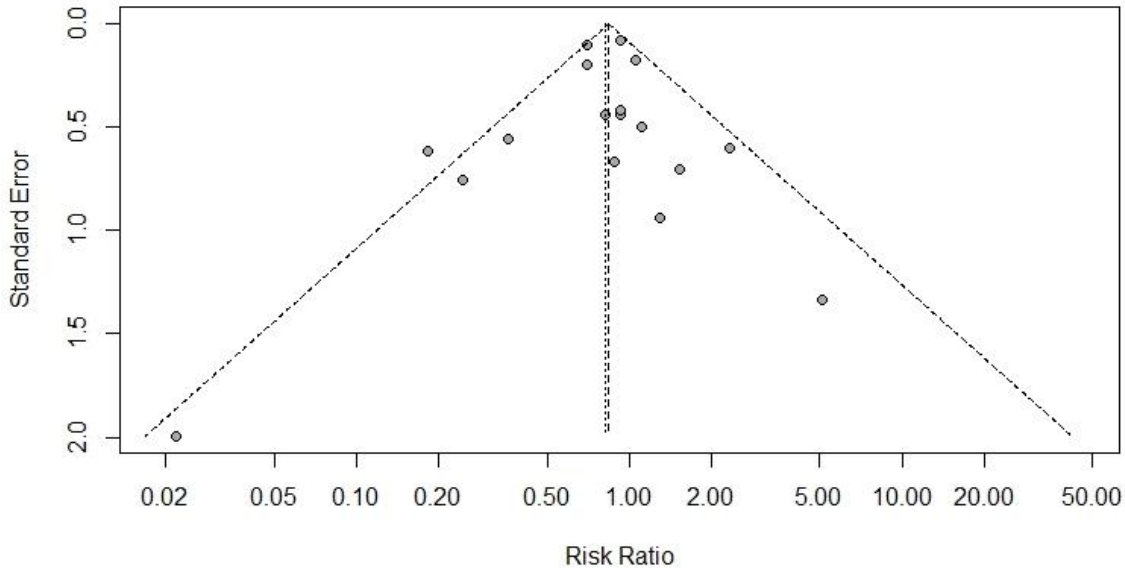
Random-effects REML model

eFigure 22. Infections linear/non-linear graph

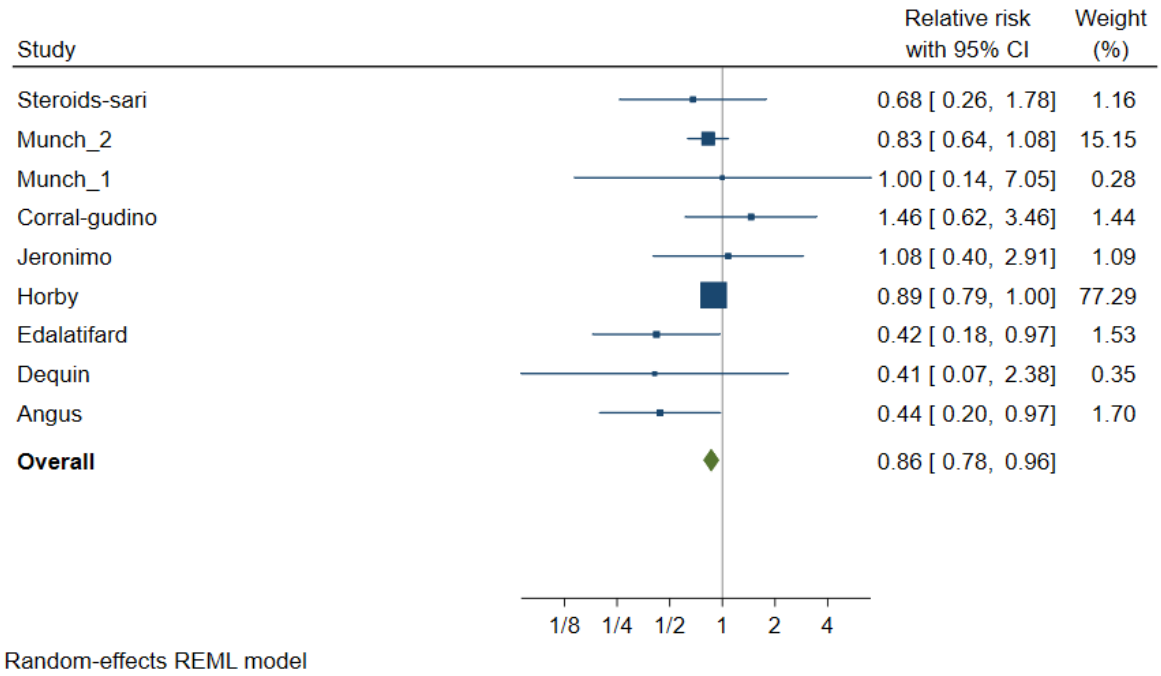


*The yellow line indicates the linear dose response relationship, and the associated yellow ribbons indicate the 95% confidence intervals. The purple line indicates the non-linear dose response relationship, and the purple ribbons indicate the 95% confidence intervals.

eFigure 23. Funnel plot for patients receiving oxygen therapy without mechanical ventilation

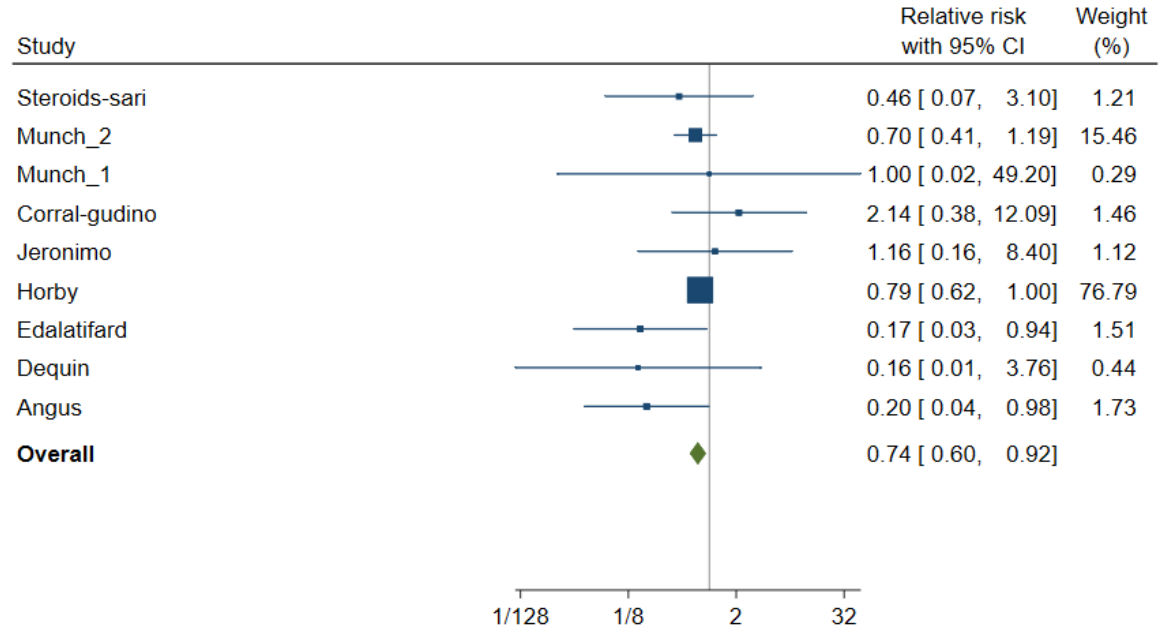


eFigure 24. Forest plot Mortality per 6 mg/day for 10 days - patients only receiving oxygen (excluding mechanical ventilated patients)



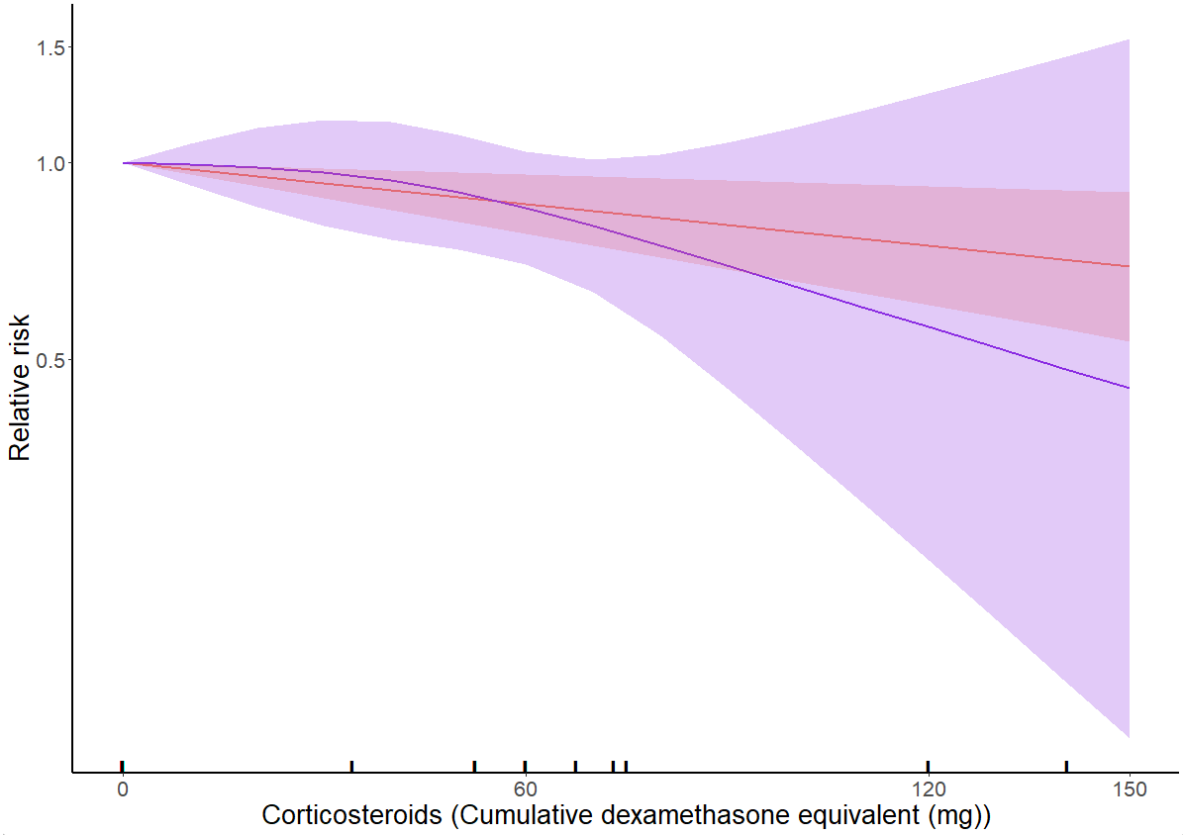
Random-effects REML model

eFigure 25. Forest plot Mortality per 12 mg/day for 10 days - patients only receiving oxygen (excluding mechanical ventilated patients)



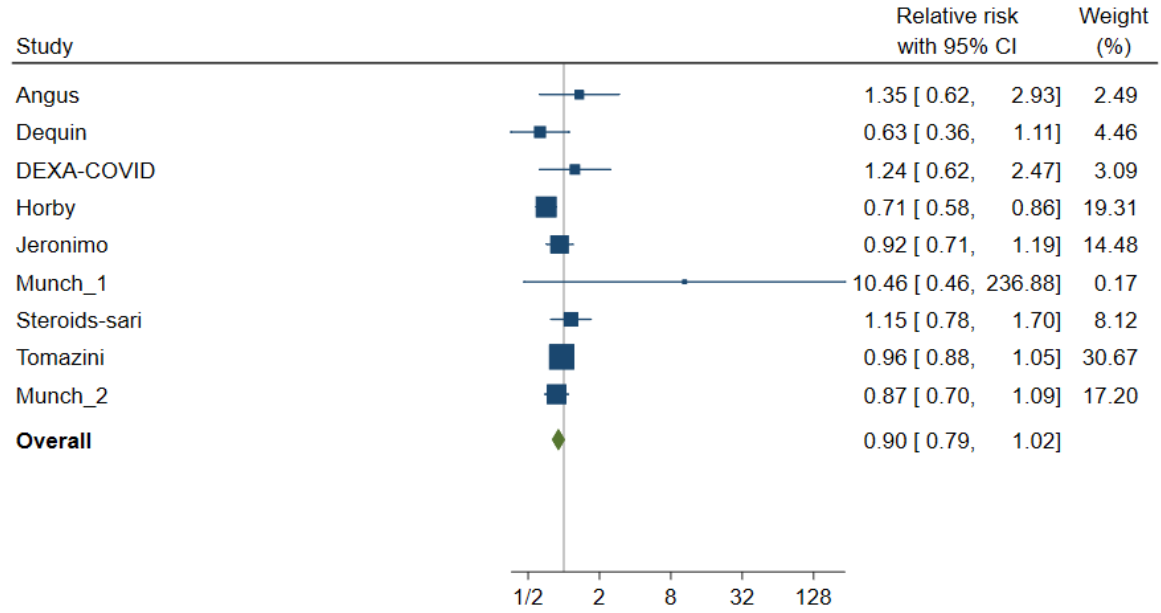
Random-effects REML model

eFigure 26. Linear/non-linear graph mortality - patients only receiving oxygen (excluding mechanical ventilated patients)



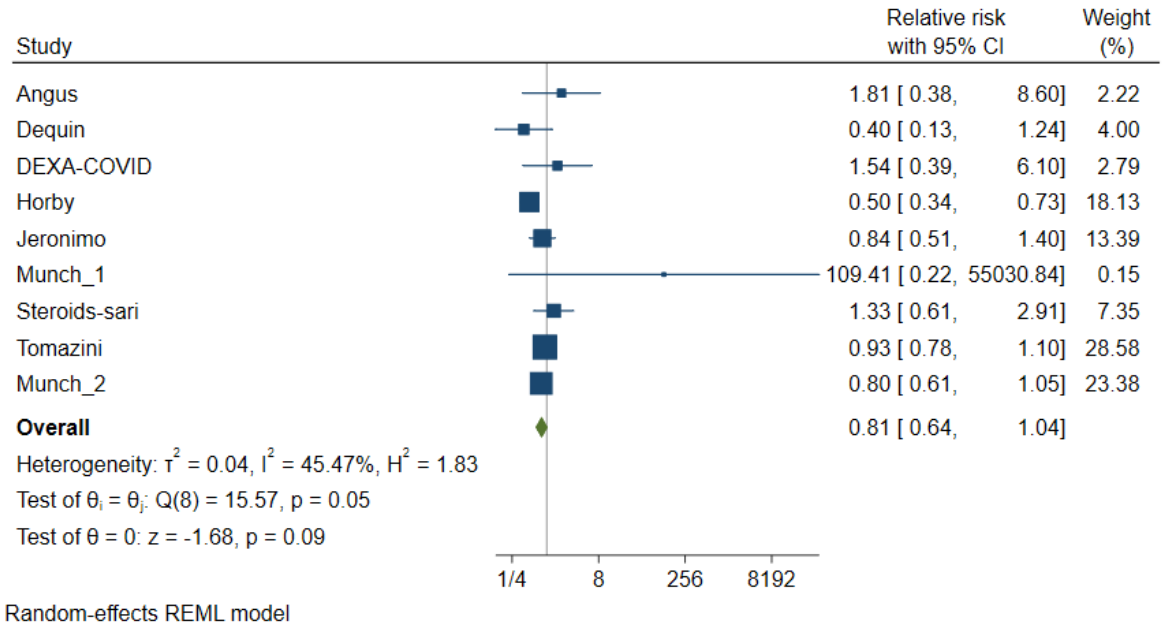
*The yellow line indicates the linear dose response relationship, and the associated yellow ribbons indicate the 95% confidence intervals. The purple line indicates the non-linear dose response relationship, and the purple ribbons indicate the 95% confidence intervals.

eFigure 27. Forest plot Mortality per 6 mg/day for 10 days - patients only receiving invasive mechanical ventilation

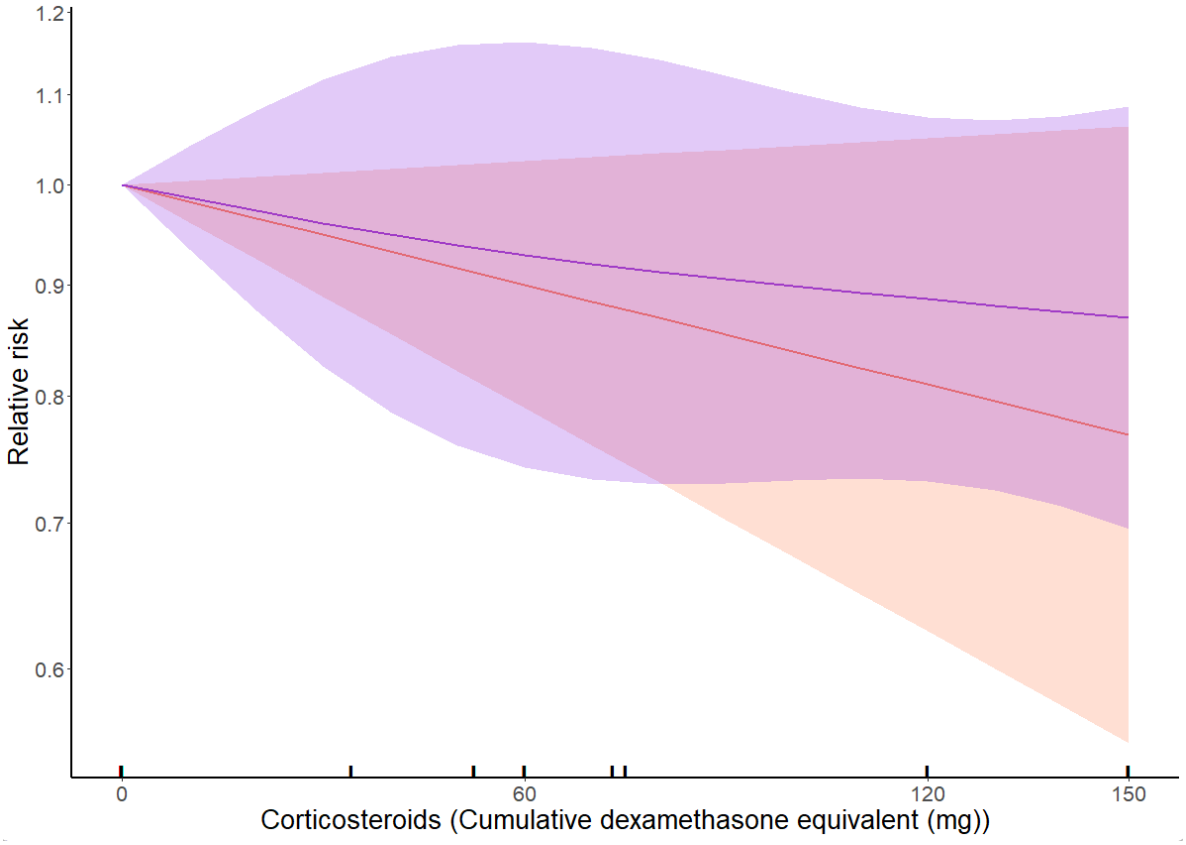


Random-effects REML model

eFigure 28. Forest plot Mortality per 12 mg/day for 10 days - patients only receiving invasive mechanical ventilation



eFigure 29. Linear/non-linear graph mortality - patients only receiving mechanical ventilation*



*The yellow line indicates the linear dose response relationship, and the associated yellow ribbons indicate the 95% confidence intervals. The purple line indicates the non-linear dose response relationship, and the purple ribbons indicate the 95% confidence intervals.

eTable 1. Medline search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to August 1 2022 (Original search January 10 2022)
Search Strategy: ---------- 1 exp Steroids/ (888855) 2 (corticosteroid* or glucocorticoid* or steroid* or dexamethasone or methylpred* or predniso* or hydrocortisone).tw,kf. (503732) 3 exp COVID-19/ (129647) 4 (covid or "covid-19" or covid19 or "cov-2" or cov2 or sarscov2 or "sars-cov-2" or coronavir* or "corona-vir*").tw,kf. (221225) 5 Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or exp Clinical Trial/ (1166819) 6 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or method* or procedure*)).ti,ab,kf. (248752) 7 (((clinical or control*) adj2 trial*) or random*).tw,kf. (1589567) 8 1 or 2 (1170465) 9 3 or 4 (226498) 10 5 or 6 or 7 (2200643) 11 8 and 9 and 10 (914)

eTable 2. Risk of bias instructions

Bias from the randomization process	
Issues to consider: Random sequence generation Allocation concealment	
Definitely low risk of bias	Trials that assign participants to alternative interventions using a randomly generated sequence and maintain allocation concealment. 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. 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. *Note that an explicit description of random sequence generation is not necessary for a rating of low risk of bias.*
Probably low risk of bias	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. *Note that an explicit description of random sequence generation is not necessary for a rating of probably low risk of bias.*
Probably high risk of bias	Trials in which healthcare providers were not blind to the intervention and which provide no information on allocation concealment. 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.

Definitely high risk of bias	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.). 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 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 co interventions for behaviors	
Definitely low risk of bias	Therapy trials in which healthcare providers are blind to the intervention administered and in which there are no significant differences in administered co-interventions. Therapy trials that are described as double or triple blind.
Probably low risk of bias	Therapy trials in which healthcare providers are not blind to the intervention administered and in which there are no important differences in co-interventions across arms. Therapy trials in which healthcare providers are blind to the intervention administered but there are significant differences in administered co-interventions that suggest that blinding may have been compromised. Therapy trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate.
Probably high risk of bias	Therapy trials in which healthcare providers are blind to the intervention administered and in which there are important differences in co-interventions across arms.
Definitely high risk of bias	Therapy trials in which healthcare providers are not blind to the intervention and in which there are important differences in co-interventions across arms.

Bias due to missing data	
Issues to consider: Missing outcome measures Loss to follow-up	
Definitely low risk of bias	Trials in which missing outcome data (including outcome data that has been imputed) < 10%. For in-patient trials, we will assume low risk of bias due to missing data unless otherwise specified.
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 *Note that the judgments may differ across outcomes.*	
Definitely low risk of bias	Trials in which patients are blind to the intervention and in which outcomes are not patient-reported. Trials in which outcomes are measured by a third-party (investigator or clinician) and in which the third-party is blind to the intervention. Trials in which the outcomes are objective. Trials that are described as double or triple blind.

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 *Note that we are only interested in selective reporting for the outcomes for which we are extracting data.* *Note that the judgments may differ across outcomes.*	
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	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. 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).
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 time point at which results are reported is not consistent with the time point 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.

eTable 3. Vaccination status and interventions by study

Author	Trial name	Year	Background therapy	Vaccinated status (%)
Angus	REMAP-CAP	2020	Allowed for concurrent randomization of other active treatments but does not report specific numbers.	0%
Bouadma	COVIDICUS	2022	Standard of care was used equally in boht arms, including antivrals,	
Corral-Gudino	GLUCOCOVID	2020	Standard of care was used equally in both arms, symptomatic treatment with acetaminophen, oxygen therapy, low-molecular weight heparin, and antibiotics for co-infections. Azithromycin, hydroxychloroquine, and lopinavir plus ritonavir were frequently prescribed.	0%
Dequin	CAPECOVID	2020	Standard care was used equally in both arms but does not provide specific details.	0%
DEXA-COVID19	DEXA-COVID 19	2020	Standard care, does not provide details.	0%
Edalatifard	NR	2020	Standard care, does not provide details.	0%

Farahani	NR	2020	Standard care, does not provide details.	0%
Gautam	NR	2021	Standard care, does not provide details.	Not reported, but possible given recruitment times.
Horby	RECOVERY	2020	Standard care, does not provide details.	0%
Jamaati	NR	2021	Patients in both groups received oxygen support (CPAP with pressure of 5–10 cmH2O and FIO2 equal to 60 to achieve SPO2≥90% and the duration was different according to the monitoring of patients' clinical status), fluid support, and lopinavir/ritonavir (200/50 mg, two tablets twice a day).	0%
Jeronimo	Metcovid	2020	No patient received anti–IL-6, anti–IL-1, remdesivir, or convalescent plasma therapy, as none of these interventions were available in the site.	0%
Maskin	NR	2021	Standard care was not regulated by the protocol. Nonetheless, it was suggested to treat the patients according to their institutional protocols or the international guidelines for ARDS, antibiotics, and hemodynamic support for COVID-19 infection	Not reported, but possible some could have been vaccinated given recruitment times.
Munch_1	COVID STEROID	2021	Standard care, does not provide details.	0%

Munch_2	COVID STEROID 2	2021	Standard of care, some patients received remdesivir, convalescent plasma, antibiotics, IL-6 inhibitors, and Janus kinase inhibitors. These were administered in a balanced manner in both arms.	NR, unlikely based on recruitment times.
Ranjbar	NR	2021	Standard care, does not provide details.	0% (stated in paper)
Steroids-Sari	Steroids-SARI	2020	Standard care, does not provide details.	0%
Taboada	HIGHLOWDEXA-COVID	2021	Standard care, does not provide details.	NR (likely some received vaccination given recruitment times)
Tang	NR	2021	Standard care based on Chinese treatment protocol trial 6, includes bed rest, sufficient caloric intake, water balance, oxygen therapy, high flow nasal canula. May include alpha interferon, lopinavir/ritonavir, ribavirin, chloroquine, arbidol, convalescent plasma, blood purification treatment, IL-6 inhibitors, traditional Chinese medications.	0%
Tomazini	CoDEX	2020	Standard care, some patients received hydroxychloroquine, azithromycin, other antibiotics and oseltamivir.	0%

Toroghi	NR	2021	Standard care, some patients received remdesivir, balanced in both groups	0%

eTable 4. Risk of bias assessments on an outcome level

Study	Outcome	Bias arising from the randomization process	Bias due to deviations from the intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results
Angus	Mortality	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Bouadma	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Corral-Gudino	Mortality	Low risk	Probably low risk	Low risk	Low risk	Low risk
Dequin	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Edalatifard	Mortality	Probably high risk	Probably low risk	Probably high risk	Low risk	Low risk
Farahani	Mortality	Probably low risk	Probably low risk	Low risk	Low risk	Probably low risk
Gautam	Mortality	Low risk	Probably low risk	Low risk	Low risk	Low risk
Horby	Mortality	Low risk	Probably low risk	Low risk	Low risk	Low risk
Jamaati	Mortality	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Jeronimo	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Maskin	Mortality	Probably low risk	Probably low risk	Low risk	Low risk	Low risk
Munch_1	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Munch_2	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Ranjbar	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Steroids-sari	Mortality	Probably low risk	Probably low risk	Low risk	Low risk	Low risk
Taboada	Mortality	Low risk	Low risk	Low risk	Low risk	Low risk
Tang	Mortality	Probably low risk	Probably low risk	Low risk	Low risk	Low risk
Tomazini	Mortality	Low risk	Probably low risk	Low risk	Low risk	Low risk
Toroghi	Mortality	Low risk	Probably high risk	Low risk	Low risk	Probably high risk
Villar	Mortality	Low risk	Probably low risk	Low risk	Low risk	Low risk
Angus	Mechanical ventilation	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Corral-Gudino	Mechanical ventilation	Low risk	Probably low risk	Low risk	Low risk	Low risk

Dequin	Mechanical ventilation	Low risk	Low risk	Low risk	Low risk	Low risk
Edalatifard	Mechanical ventilation	Probably high risk	Probably low risk	Probably high risk	Low risk	Low risk
Farahani	Mechanical ventilation	Probably low risk	Probably low risk	Low risk	Low risk	Probably low risk
Gautam	Mechanical ventilation	Low risk	Probably low risk	Low risk	Low risk	Low risk
Horby_1	Mechanical ventilation	Low risk	Probably low risk	Low risk	Low risk	Low risk
Jamaati	Mechanical ventilation	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Jeronimo	Mechanical ventilation	Low risk	Low risk	High risk	Low risk	Low risk
Munch_2	Mechanical ventilation	Low risk	Low risk	Low risk	Low risk	Low risk
Ranjbar	Mechanical ventilation	Low risk	Low risk	Low risk	Low risk	Low risk
Taboada	Mechanical ventilation	Low risk	Low risk	Low risk	Low risk	Low risk
Tang_2	Mechanical ventilation	Probably low risk	Probably low risk	Low risk	Low risk	Probably low risk
Tomazini	Mechanical ventilation	Low risk	Probably low risk	Low risk	Low risk	Low risk
Toroghi	Mechanical ventilation	Low risk	Probably high risk	Low risk	Low risk	Probably high risk
Dequin	Infections	Low risk	Low risk	Low risk	Low risk	Low risk
Jeronimo	Infections	Low risk	Low risk	High risk	Low risk	Low risk
Much_2	Infections	Low risk	Low risk	Low risk	Low risk	Low risk
Taboada	Infections	Low risk	Low risk	Low risk	Low risk	Low risk
Tang	Infections	Probably low risk	Probably low risk	Low risk	Low risk	Low risk
Tomazini	Infections	Low risk	Probably low risk	Low risk	Low risk	Low risk
Toroghi	Infections	Low risk	Probably high risk	Low risk	Low risk	Probably high risk
Toroghi	Infections	Low risk	Probably high risk	Low risk	Low risk	Probably high risk
Maskin	Duration of MV	Probably low risk	Probably low risk	Low risk	Low risk	Probably low risk

Taboada	Duration of MV	Low risk	Low risk	Low risk	Low risk	Low risk
Tomazini	Duration of MV	Low risk	Probably low risk	Low risk	Low risk	Low risk
Toroghi	Duration of MV	Low risk	Probably high risk	Low risk	Low risk	Probably high risk
Angus	Duration of hospitalization	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Corral-Gudino	Duration of hospitalization	Low risk	Probably low risk	Low risk	Low risk	Low risk
Horby	Duration of hospitalization	Low risk	Probably low risk	Low risk	Low risk	Low risk
Jamaati	Duration of hospitalization	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Jeronimo	Duration of hospitalization	Low risk	Low risk	Low risk	Low risk	Probably low risk
Maskin	Duration of hospitalization	Probably low risk	Probably low risk	Low risk	Low risk	Probably low risk
Ranjbar	Duration of hospitalization	Low risk	Low risk	Low risk	Low risk	Low risk
Taboada	Duration of hospitalization	Low risk	Low risk	Low risk	Low risk	Low risk
Tang	Duration of hospitalization	Probably low risk	Probably low risk	Low risk	Low risk	Probably low risk
Toroghi	Duration of hospitalization	Low risk	Probably high risk	Low risk	Low risk	Probably high risk

eTable 5. Gof statistics for all outcomes and subgroups.

Outcome	Linear					Non-linear					
	Deviance	Degrees of freedom	p value	r-squared	Adjusted r-squared	Deviance	Degrees of freedom	p value	R2	Adjusted r-squared	Non-linearity
Mortality	28.03	16	0.031	0.276	0.23	24.96	15	0.05	0.355	0.269	0.21
MV need	18.922	11	0.063	0.1	0.014	18.592	10	0.046	0.122	-0.065	0.86
Infection	1.669	6	0.948	0.829	0.801	1.069	5	0.957	0.891	0.847	0.44
Duration of hospitalization	43.643	7	<0.001	0.361	0.27	34.434	6	<0.001	0.496	0.328	0.64
Duration of mechanical ventilation	51.022	3	<0.001	0.29	0.053	40.706	2	<0.001	0.433	-0.133	0.24
Subgroups											
MV only mortality	15.466	8	0.051	0.277	0.187	13.578	7	0.059	0.365	0.184	0.87
Oxygen only (No IMV)	8.554	8	0.381	0.471	0.405	8.182	7	0.317	0.494	0.35	0.53

eTable 6. Network comparisons mortality

Mortality	***Comparison***	***Network estimate***			***Network estimate***			
MID 1%	***Baseline risk 20%***	***Relative estimate***			***Absolute risk difference per 1000***			
Treatment 1	*Treatment 2*	*Point estimate*	*CI Lower limit*	*CI upper limit*	*Point estimate*	*CI Lower limit*	*CI upper limit*	***Final GRADE rating***
I^2=34.6	*Tau^2=0.13*							
High dose corticosteroids	*Low dose corticosteroids*	*0.88*	*1.0.74*	*1.04*	*-19.92*	*-43.16*	*6.64*	*Low (benefit)*
High dose corticosteroids	*Placebo*	*0.83*	*0.7*	*0.99*	*-34*	*-60*	*-2*	*Moderate (benefit)*
Low dose corticosteroids	*Placebo*	*0.95*	*0.81*	*1.12*	*-10*	*-38*	*24*	*Low (no effect)*

eTable 7. Subgroup analysis based on oxygen status:

We performed subgroup analysis for patients who received only oxygen, excluding mechanical ventilation and also for patients who received only mechanical ventilation. We did not find a statistically significant subgroup (p>0.05).

Subgroup	**RR**	**95% CI**	**I^2**
Oxygen only			
6 mg/day	0.86	0.78 to 0.96	6.50%
12 mg/day	0.74	0.6 to 0.92	6.50%
Only IMV			
6 mg/day	0.89	0.79 to 1.02	48.30%
12 mg/day	0.8	0.68 to 1.04	48.30%

eTable 8. Meta-regression using duration as a moderator

We performed meta-regression with duration of treatment as a moderator. There was no statistically significant effect seen across mortality, mechanical ventilation or infections. There was no variation in the duration of hospitalization or mechanical ventilation.

Outcome	**Coefficient**	**Std. err.**	**z**	**P>z**	**Lower 95% CI**	**Upper 95% CI**
Mortality	1.04	0.0520591	0.77	0.444	-0.0621455	0.1419224
Mechanical ventilation	1.04	0.0605625	0.58	0.559	-0.0833016	0.1540992
Infections	0.98	0.060952	-0.28	0.783	-0.136265	0.1026623