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Effect of corticosteroids in patients with COVID-19: a Bayesian network meta-analysis

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ABSTRACT

Objectives: We sought to perform a network meta-analysis to compare the safety and efficacy of the systemic administration of corticosteroids for the treatment of COVID-19.
Methods: A Bayesian network meta-analysis was performed to combine the direct and indirect evidence. The surface under the cumulative ranking curve was obtained to estimate the ranking probability of the treatment agents for each outcome. The efficacy outcome was 28-day all-cause mortality. The safety outcome was serious adverse events.
Results: A total of 16 trials with 2992 patients comparing four treatments (dexamethasone, hydrocortisone, methylprednisolone, and placebo) were identified. Direct analysis showed that corticosteroids were associated with a reduced risk of 28-day mortality compared with usual care (risk ratio [RR] 0.83; 95% confidence interval [CrI] 0.70-0.99). Network analysis showed that the pooled RR was 0.63 (95% CrI 0.39-0.93) for all-cause mortality at 28 days comparing methylprednisolone with usual care or placebo (surface under the cumulative ranking curve: 91%). Our analysis demonstrated that patients who received a low dose of corticosteroids (RR 0.80; 95% CrI 0.70-0.91) and a long course of treatment (RR 0.81; 95% CrI 0.71-0.91) had higher survival rates than patients in the placebo group.
Conclusion: Administration of corticosteroids was associated with a reduced all-cause mortality at 28 days compared with placebo or usual care. Our analysis also confirmed the mortality benefit associated with low-dose and long-term treatment with corticosteroids.

1. Introduction

As of August 5, 2022, nearly 600 million persons have been diagnosed with COVID-19, and more than 6 million individuals have died because of this disease (World Health Organization, 2022). Evidence has shown that a severely dysregulated immune response plays a critical role in patients with COVID-19 (Prete *et al.*, 2020; Vabret *et al.*, 2020).

Corticosteroids are nonspecific immunosuppressants and have been proposed as a potential treatment agent for acute respiratory distress syndrome. Corticosteroid treatment may reduce pulmonary and systemic injury in this group of patients by improving tissue damage caused by excessive generation of inflammatory mediators (Steinberg *et al.*, 2006; Tomashefski, 2000; Villar *et al.*, 2020). However, uncertainty exists as to whether other types of corticosteroids, such as methylprednisolone or hydrocortisone, differ from dexamethasone in efficacy for treating patients with COVID-19 (El Mezzeoui *et al.*, 2021).

A recently published meta-analysis pooled results from randomized controlled trials (RCTs) in patients with COVID-19. This study showed that the use of systemic corticosteroids reduced all-cause mortality at 28 days (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020). These results provide a strong recommendation for corticosteroids in critically ill patients with COVID-19. However, the conclusions were

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based mostly on the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the largest trial included in the analysis, and the only trial that showed a significant association between corticosteroids and mortality (RECOVERY Collaborative Group *et al.*, 2021). Without this largest trial, the result of the study turned out to be insignificant. Therefore, there is still an urgent need to evaluate the effectiveness of corticosteroids in this group of patients. Ongoing questions mainly related to the type of corticosteroids, optimal dosage, and duration (Confalonieri *et al.*, 2021; Du Plessis *et al.*, 2021; Zhang *et al.*, 2021).

Hence, we conducted a network meta-analysis of RCTs to investigate the efficacy and safety of three different types of corticosteroids (*i.e.,* dexamethasone, hydrocortisone, and methylprednisolone), as well as different doses of corticosteroids (*i.e.,* high and low doses), in patients with COVID-19. This study aimed to provide robust evidence for the clinical application of these corticosteroids.

2. Materials and methods

2.1. Protocol and guidance

This study was registered in the international prospective register of systematic reviews database (CRD42022325173) and the Open Science Framework platform (https://osf.io/7s8md). The methods and reporting of the systematic review with network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension Statement for Network Meta-analyses (Hutton *et al.*, 2015).

2.2. Search strategy and data sources

We searched the Ovid MEDLINE, Ovid Embase, https://www.clinicaltrials.gov/, and Cochrane Central Register of Controlled Trials from inception to August 10, 2021. There were no language restrictions for the search. The search was updated on July 15, 2022. We also manually searched the reference lists of the included articles and previously published systematic reviews on this topic to identify any additional eligible studies. The search strategy was designed and performed by an experienced researcher (Supplemental Table 1).

2.3. Selection criteria

The eligibility of studies was determined based on the participants, interventions, comparators, outcomes, and study design criteria, as follows: (i) population: patients with COVID-19; (ii) intervention: any type of corticosteroid agent including dexamethasone, hydrocortisone, and methylprednisolone; a predefined cut-off was used to determine whether the study used low or high doses of corticosteroids, that is 15 mg/d dexamethasone, 400 mg/d hydrocortisone, and 1 mg/kg/d methylprednisolone (Annane *et al.*, 2017); (iii) comparison: placebo, usual care, or a different type of corticosteroid; (iv) outcome: efficacy outcome was all-cause mortality at 28 days (if mortality at this time point was not reported, we assessed the time point nearest 28 days), and the safety outcome was serious adverse events (opportunistic infections, muscle weakness, gastrointestinal bleeding, and hyperglycemia); and (v) study design: RCTs.

In addition, we excluded studies with observational design, nonrandomized trials, single-arm trials, and trials that compared corticosteroids with other active substances.

2.4. Selection process

Based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension Statement for Network Meta-analyses guidelines, we excluded duplicate publications, and then, we screened the titles and abstracts to assess eligibility. Then, we excluded studies based on the participants, interventions, comparators, outcomes, and study design criteria after screening the full texts of the articles.

Two authors reviewed the publications and completed this process together. Disagreements were resolved by consulting an independent author.

2.5. Data extraction

Data related to the following categories were extracted onto a standardized form: (i) study characteristics: primary author, geographical location, publication year, and the number of centers in each study; (ii) treatment characteristics: type, dosage, duration of treatment, and administration of corticosteroids; and (iii) patient characteristics: age and sex. We classified the included trials according to dosage and duration of therapy, and the cut-offs we used were based on the previous studies in the same field (Chaudhuri *et al.*, 2021; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020).

Two authors independently extracted data and completed this process. Disagreements were resolved by consulting an independent author.

2.6. Quality of evidence and assessment of risk of bias

The Cochrane Collaboration Risk of Bias tool was used to evaluate the risk of bias for all RCTs across seven domains: random sequence generation; incomplete outcome data, blinding of study participants, allocation concealment, selective reporting, blinding of outcome assessment, and other potential bias (Higgins *et al.*, 2011). Each domain was assessed as having either a low, unclear, or high risk of bias. We contacted the original study investigators for more information if necessary.

The Grading of Recommendations Assessment, Development, and Evaluation framework was used to assess the quality of evidence for each outcome estimate to rank the evidence quality (Guyatt *et al.*, 2011). Our confidence assessment addressed publication bias, indirectness, limitations in design, inconsistency, and imprecision.

2.7. Statistical analysis

To incorporate direct and indirect comparisons, we performed Bayesian network meta-analyses with a consistency model in the R environment. The comparative safety and efficacy of any two treatment regimens were modeled for each treatment agent relative to the reference treatment agent. We conducted random effects and fixed effects models to pool the network results and selected the preferred model by comparing the deviance information criteria (McGavock *et al.*, 2020; Spiegelhalter *et al.*, 2002). The models were based on 30,000 iterations after a burn-in of 10,000 iterations. The risk ratio (RR) and the corresponding 95% credible interval (CrI) were obtained from the 97.5th and 2.5th percentiles of the posterior distribution. We also reported the RR and relevant 95% confidence interval (CI) from direct comparisons. The surface under the cumulative ranking curve (SUCRA) was obtained to estimate the ranking probability of the treatment agents for each outcome (Salanti *et al.*, 2011). The SUCRA values range from 0-100% and summarize treatment rankings. A larger area under the curve means a higher ranking of therapy effectiveness. The heterogeneity of treatment effects among the included studies was examined using the I^2 statistic. An I^2 value of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. We also performed sensitivity analysis by excluding trials that were assessed as having a high risk of bias.

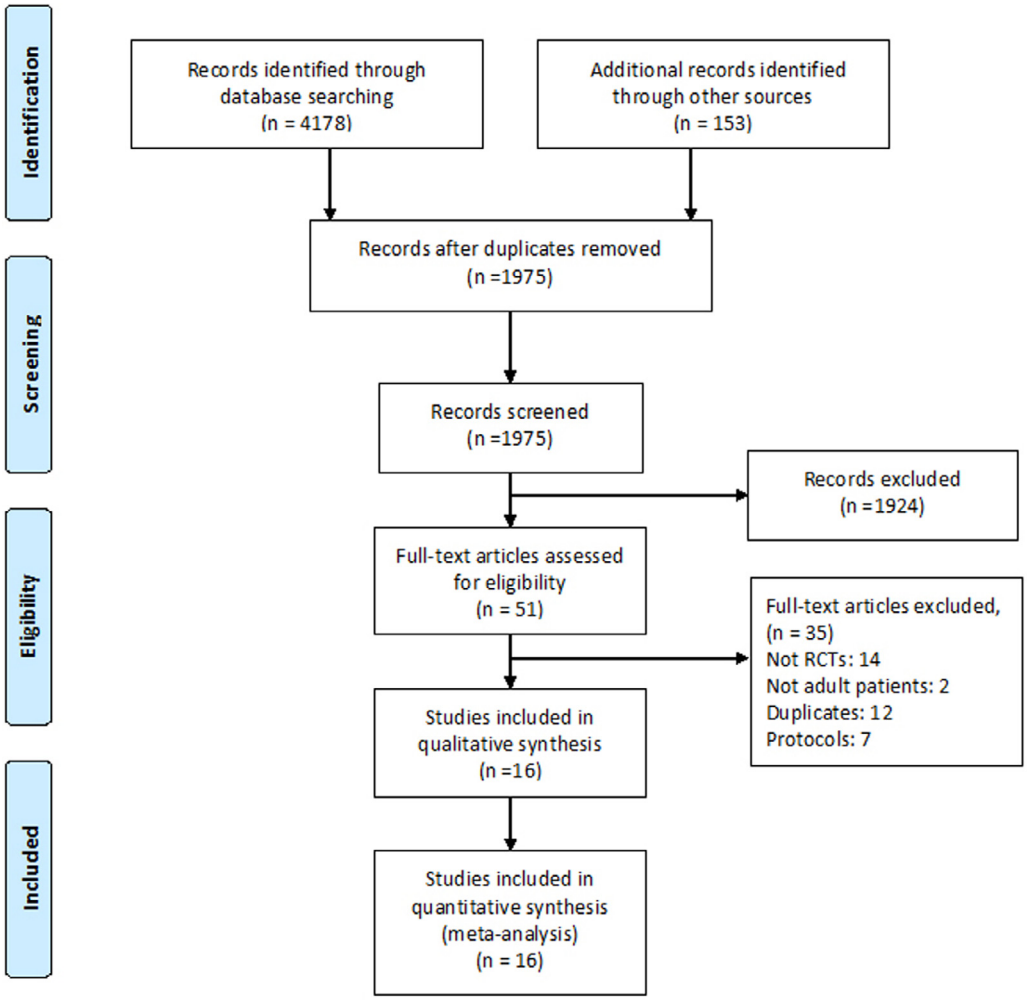


Figure 1. Summary of study selection process.
RCT: randomized clinical trial.

All analyses were performed in R software (release version 4.0.3, gemtc package) and RevMan (5.4.0; The Cochrane Collaboration). A two-sided *P*-value of <0.05 was considered to indicate statistical significance.

3. Results

3.1. Eligible studies and study characteristics

Our search generated 4178 publications. Finally, 16 trials were deemed eligible and included in the network meta-analysis (Angus *et al.*, 2020; Corral-Gudino *et al.*, 2021; Dastenae *et al.*, 2022; Dequin *et al.*, 2020; Edalatifard *et al.*, 2020; Jamaati *et al.*, 2021; Jeronimo *et al.*, 2021; Munch *et al.*, 2021; Ranjbar *et al.*, 2021; RECOVERY Collaborative Group *et al.*, 2021; Salvarani *et al.*, 2022; Soliman *et al.*, 2022; Tang *et al.*, 2021; Tomazini *et al.*, 2020; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020). The publication screening process and a list of excluded studies with reasons for exclusion are summarized in Figure 1.

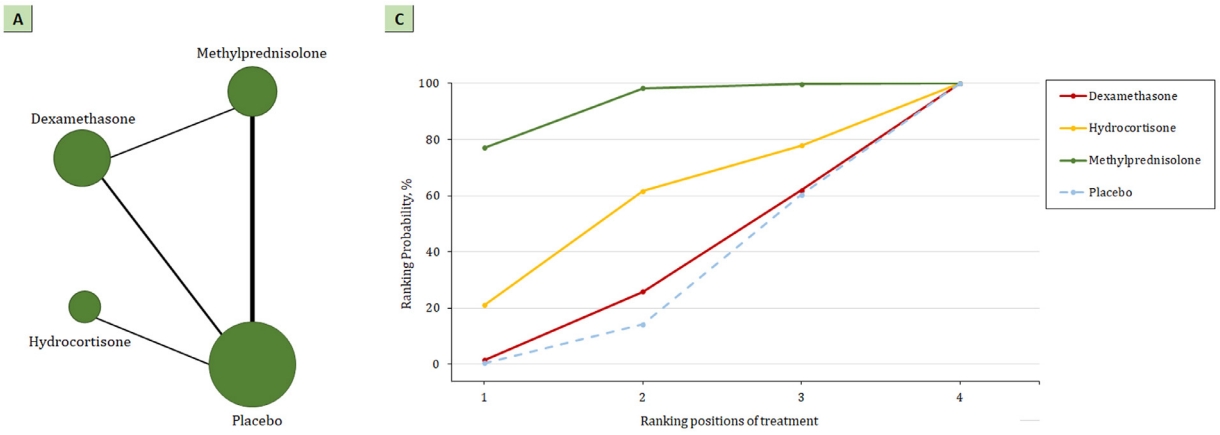
Table 1 summarizes the characteristics of each trial. We included seven RCTs from a previously published meta-analysis addressing the topic. The updated search generated nine additional RCTs. Finally, a total of 16 RCTs met the eligibility criteria and were included in the present analysis, which involved a total of 2992 patients. There was one study each conducted in the United Kingdom, Denmark, Italy, Egypt, and France. Two studies were conducted in Brazil, two were conducted in China, four were conducted in Iran, and two were conducted in Spain. One trial was conducted in multiple countries. Population sizes ranged from 19 to 1007 patients, and the mean age was 62 years. In most included studies, the majority of patients were male. A total of four trials compared dexamethasone with placebo or usual care, three trials compared hydrocortisone with control, six trials compared methylprednisolone with placebo or usual care, and three trials compared dexamethasone with methylprednisolone. Eight RCTs provided usual care to their control group, whereas five trials administered a placebo.

Of these studies, eight studies were rated as having an overall "low risk of bias" (Angus *et al.*, 2020; Dequin *et al.*, 2020; Jeronimo *et al.*, 2021; Munch *et al.*, 2021; Ranjbar *et al.*, 2021; RECOVERY Collaborative Group *et al.*, 2021; Salvarani *et al.*, 2022; Tomazini *et al.*, 2020). The remaining studies were assessed as having an overall "high risk of bias" (Corral-Gudino *et al.*, 2021; Dastenae *et al.*, 2022; Edalatifard *et al.*, 2020; Jamaati *et al.*, 2021; Soliman *et al.*, 2022; Tang *et al.*, 2021; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020). The high risk of bias was mainly due to the lack of blinding of outcome assessment. The risk of bias is shown in Figure S1 and Figure S2 in the Supporting Information.

Table 1
Characteristics of studies included in the systematic review and meta-analysis.

Study	Registration	No. of patients	Country	Mean age (% male)[a]	Intervention	Dosage and administration	Dose classification	Control	Mortality outcomes
DEXA-COVID 19 (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020)[c]	NCT04325061	19	Spain	62 (57.1)	Dexamethasone	20 mg/d for 5 days and then 10 mg/d for 5 days	High	Usual care	28-day
CoDEX (Tomazini et al., 2020)	NCT04327401	299	Brazil	62.7 (65.6)	Dexamethasone	20 mg/d for 5 days and then 10 mg/d for 5 days	High	Usual care	28-day
RECOVERY (RECOVERY Collaborative Group et al., 2021)	NCT04381936	1007	UK	65.8 (64)	Dexamethasone	6 mg/d for up to 10 days	Low	Usual care	28-day
Jamaati (2021) (Jamaati *et al.*, 2021)	IRCT20151227025726N17	50	Iran	62 (72)	Dexamethasone	20 mg/d for 5 days and then 10 mg/d for 5 days	High	Usual care	28-day
CAPE COVID (Dequin *et al.*, 2020)	NCT02517489	149	France	66.3 (68.5)	Hydrocortisone	200 mg/d for 4 d or 7 d, then 100 mg/d for 2 days or 4 days and 50 mg/d for 2 days or 3 days	Low	Placebo	21-day
COVID STEROID (Munch *et al.*, 2021)[c]	NCT04348305	29	Denmark	Not applicable	Hydrocortisone	200 mg/d for 7 days	Low	Placebo	28-day
REMAP-CAP (Angus *et al.*, 2020)	NCT02735707	197	Multiple countries [b]	59.9 (71.3)	Hydrocortisone	50 mg every 6 h for 7 days	Low	Usual care	28-day
Steroids-SARI (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020)[c]	NCT04244591	47	China	62 (78)	Methylprednisolone	40 mg twice daily for 5 days	High	Usual care	30-day
Ranjbar (2021) (Ranjbar *et al.*, 2021)	IRCT20200204046369N1	86	Iran	61.3 (52.4)	Methylprednisolone	2 mg/kg per day for 10 days	High	Dexamethasone (6 mg per day for 10 days); Low	28-day
Jeronimo (2021) (Jeronimo *et al.*, 2021)	NCT04343729	393	Brazil	57 (64.3)	Methylprednisolone	0.5 mg/kg twice daily for 5 days	Low	Placebo	28-day
Tang (2021) (Tang *et al.*, 2021)	NCT04273321	86	China	55 (46.5)	Methylprednisolone	1 mg/kg per day for 7 days	Low	Placebo	In-hospital
GLUCOCOVID (Corral-Gudino *et al.*, 2021)	2020-001934-37	64	Spain	66 (55)	Methylprednisolone	40 mg twice daily for 3 days, followed by 20 mg twice daily for another 3 days	High	Usual care	28-day
Edalatifard 2020 (Edalatifard *et al.*, 2020)	IRCT20200404046947N1	62	Iran	61.7 (53.6)	Methylprednisolone	250 mg per day for 3 days	High	Usual care	In-hospital
Salvarani (2022) (Salvarani *et al.*, 2022)	NCT04673162	301	Italy	64.0 (70.7)	Methylprednisolone	1 g per day for 3 days	High	Placebo	28-day
Soliman (2022) (Soliman *et al.*, 2022)	NCT04909918	60	Egypt	58.1 (46.7)	Methylprednisolone	1 mg/kg/ per day for 7 days	Low	Dexamethasone (8 mg per day for 7 days); Low	7-day
Dastenae 2022 (Dastenae *et al.*, 2022)	IRCT20210223050466N1	143	Iran	64.5 (58.6)	Methylprednisolone	60 mg/ per day for 7 days	Low	Dexamethasone (8 mg per day for 10 days); Low	28-day

[a] This data was extracted from control group.
[b] Australia, Canada, European Union, New Zealand, UK, US.
[c] Age was presented in median.



B

Treatment	Risk Ratio (95 %CrI)
Dexamethasone vs. Placebo	0.97 [0.64, 1.55]
Hydrocortisone vs. Placebo	0.84 [0.45, 1.69]
Methylprednisolone vs. Placebo	0.63 [0.39, 0.93]
Hydrocortisone vs. Dexamethasone	0.86 [0.40, 1.93]
Methylprednisolone vs. Dexamethasone	0.65 [0.36, 1.00]
Methylprednisolone vs. Hydrocortisone	0.76 [0.31, 1.54]

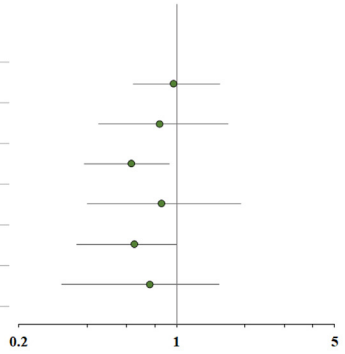


Figure 2. (a) Network plot of all-cause mortality. The width of the lines is proportional to the number of studies comparing every pair of treatments, and the size of each circle is proportional to the number of participants. (b) SUCRA-based ranking probabilities graph of each medication. The SUCRA values for each treatment were as follows: 92% for methylprednisolone; 53% for hydrocortisone; 30% for dexamethasone. (c) The forest plot shows the risk ratio and CrI.
CrI, credible interval; SUCRA, surface under the cumulative ranking curve.

3.2. 28-day all-cause mortality

The network plot for head-to-head comparisons between the different management strategies for 28-day all-cause mortality is presented in Figure 2a. There were 410 deaths among 1457 patients randomized to receive corticosteroids, and 566 deaths among 1498 patients randomized to receive placebo or standard care. This corresponds to an absolute mortality risk of 28% for corticosteroids compared with an absolute risk of 38% for placebo or standard care. According to the direct analysis, corticosteroids showed better efficacy in reducing all-cause mortality than placebo or standard care (RR 0.83; 95% CI 0.70-0.99; Figure A3). Network analysis (Figure 2b; Table A2) showed that the pooled RR was 0.63 (95% CrI 0.39-0.93) for all-cause mortality at 28 days comparing methylprednisolone with usual care or placebo (nine trials, 613 participants). The analysis also demonstrated that methylprednisolone showed better efficacy in reducing 28-day mortality than dexamethasone (RR 0.65; 95% CrI 0.36-1.00; RR 0.53; 95% CI 0.33-0.84; Figure A4). However, the summary RR did not indicate statistically significant differences between dexamethasone and usual care or placebo (seven trials, 647 participants; RR 0.97; 95% CrI 0.64-1.55) or between hydrocortisone and usual care or placebo (three trials, 197 participants; RR 0.84; 95% CrI 0.45-1.69) for patients with COVID-19.

For the outcome of mortality, methylprednisolone had the highest probability of being the best management strategy in patients with COVID-19, with a SUCRA value of 0.92; this result was statistically significant. The second-best strategy for mortality was hydrocortisone (SUCRA 0.53). The least beneficial intervention was dexamethasone (SUCRA 0.30). SUCRA values for mortality are shown in Figure 2c. SUCRA values in the sensitivity analysis remained consistent after excluding specified studies (Supplementary Table 3).

3.3. Serious adverse events

The network plot for head-to-head comparisons between the different management strategies for serious adverse events is presented in Figure 3a. The associations between corticosteroids vs placebo or standard care and serious adverse events are presented in Figure 3b and Figure A5. A total of 10 trials, including 1216 participants reported serious adverse events. Among them, 109 events occurred among 626 patients randomized to the treatment group, and 102 events occurred among 590 patients randomized to placebo or standard care (17% *vs* 17%). The serious events reported by each trial are summarized in Table 2. The summary RR did not show statistically significant differences in any of the comparisons.

SUCRA values for serious adverse events are shown in Figure 3c. For prespecified safety outcomes, SUCRA values ranked dexamethasone (RR 0.47; 95% CrI 0.08-2.63; SUCRA 0.84) as the most beneficial intervention for the prevention of serious adverse events. Methylprednisolone (RR 1.14; 95% CrI 0.35-3.97; SUCRA 0.37) and hydrocortisone (RR 1.28; 95% CrI 0.30-10.95; SUCRA 0.32) were ranked as the second and third most beneficial interventions for this outcome.

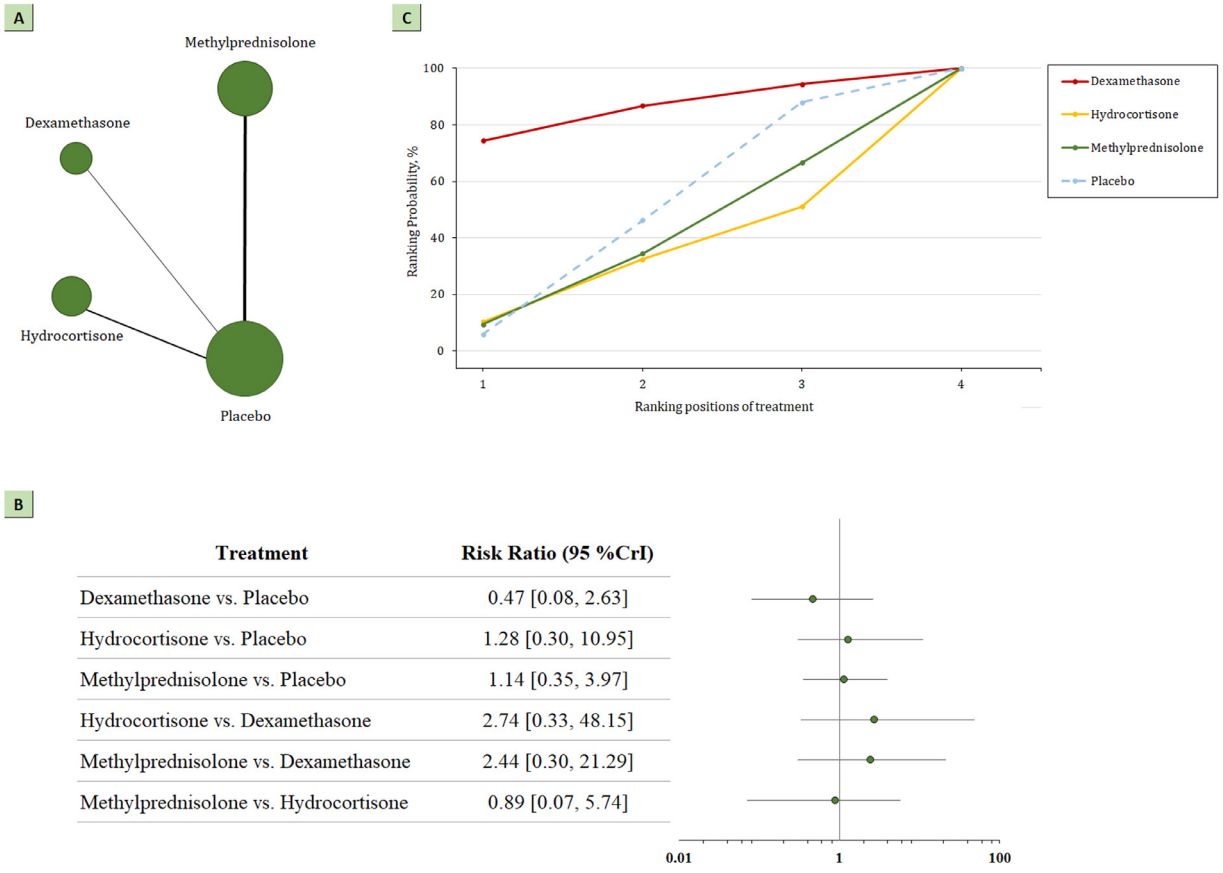


Figure 3. (a) Network plot of serious adverse events. The width of the lines is proportional to the number of studies comparing every pair of treatments, and the size of each circle is proportional to the number of participants. (b) SUCRA-based ranking probabilities graph of each medication. The SUCRA values for each treatment were as follows: 86% for dexamethasone; 35% for methylprednisolone; 30% for hydrocortisone. (c) The forest plot shows the risk ratio and CrI.
CrI, credible interval; SUCRA, surface under the cumulative ranking curve.

Table 2
Serious adverse events in intervention group.

Trial	Intervention	Dose classification	Treatment-related adverse events
DEXA-COVID 19 (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020)	Dexamethasone	High	Secondary pneumonia, sepsis, pulmonary embolism
CoDEX (Tomazini *et al.*, 2020)	Dexamethasone	High	Acute myocardial infarction, deep vein thrombosis, gastrointestinal perforation, unspecified hyperglycemia, and pneumothorax
RECOVERY (RECOVERY Collaborative Group *et al.*, 2021)	Dexamethasone	Low	NA
Jamaati (2021) (Jamaati *et al.*, 2021)	Dexamethasone	High	NA
CAPE COVID (Dequin *et al.*, 2020)	Hydrocortisone	Low	Cerebral vasculitis, pulmonary embolism
COVID STEROID (Munch *et al.*, 2021)	Hydrocortisone	Low	Septic shock, invasive fungal infection, clinically important gastrointestinal bleeding, or anaphylactic reaction
REMAP-CAP (Angus *et al.*, 2020)	Hydrocortisone	Low	Severe neuromyopathy, fungemia
Steroids-SARI (WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.*, 2020)	Methylprednisolone	High	Secondary bacterial infections, barotrauma, severe hyperglycemia, gastrointestinal bleeding requiring transfusion, acquired weakness
Ranjbar (2021) (Ranjbar *et al.*, 2021)	Methylprednisolone	High	NA
Jeronimo (2021) (Jeronimo *et al.*, 2021)	Methylprednisolone	Low	NA
Tang (2021) (Tang *et al.*, 2021)	Methylprednisolone	Low	Hyperglycemia, secondary pneumonia
GLUCOCOVID 2020 (Corral-Gudino *et al.*, 2021)	Methylprednisolone	High	Hyperglycemia, nosocomial infection
Edalatifard 2020 (Edalatifard *et al.*, 2020)	Methylprednisolone	High	Infection, edema
Salvarani (2022) (Salvarani *et al.*, 2022)	Methylprednisolone	High	Cardiac disorders, gastrointestinal disorders, infections and infestations, respiratory, thoracic and mediastinal disorders, surgical and medical procedures, vascular disorders
Soliman (2022) (Soliman *et al.*, 2022)	Methylprednisolone	Low	NA
Dastenae 2022 (Dastenae *et al.*, 2022)	Methylprednisolone	Low	NA

NA: not applicable.

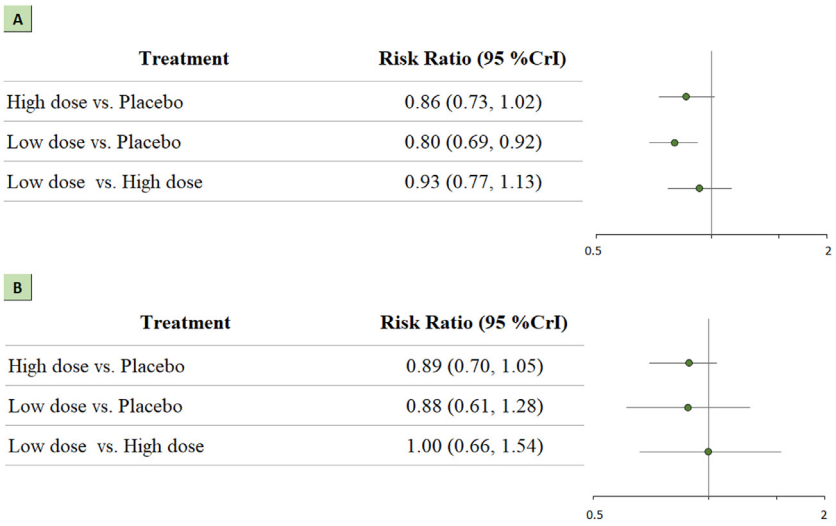


Figure 4. Network analysis for high-dose vs low-dose of corticosteroids. (a) The forest plot for all-cause mortality. (b) The forest plot for serious adverse events. CrI: credible interval.

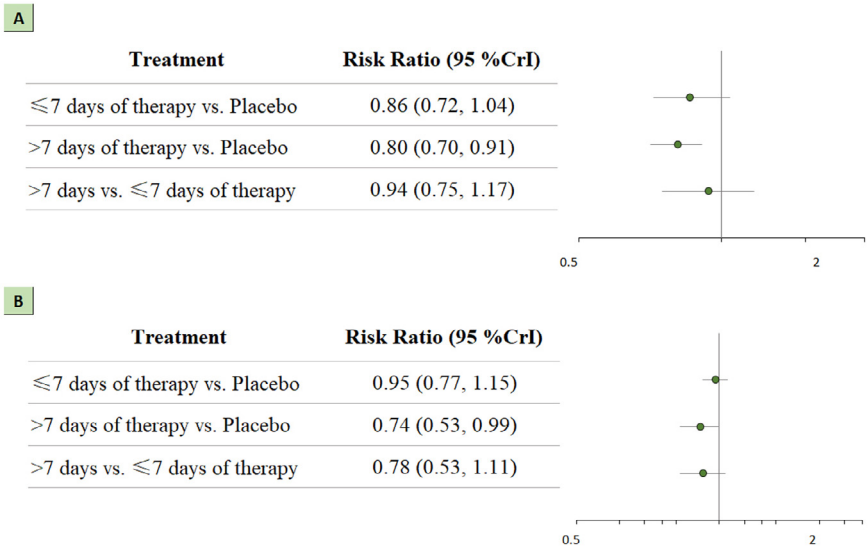


Figure 5. Network analysis for long course treatment (>7 days) vs short course treatment (≤7 days). (a) The forest plot for all-cause mortality. (b) The forest plot for serious adverse events. CrI: credible interval.

3.4. Dosage and duration of therapy

A total of 1862 patients were administered low-dose treatment, and 807 patients were administered high-dose treatment. Patients who received a low dose of corticosteroids had higher rates of survival than those who received a placebo (RR 0.80; 95% CrI 0.70-0.92). However, we did not observe the same favorable effect of a high dose of corticosteroids with respect to 28-day mortality (RR 0.87; 95% CrI 0.73-1.02). The summary RR did not show significant differences regarding serious adverse events. These results are shown in Figure 4a and 4b.

A total of 1145 patients were administered a short course of treatment (≤7 days), and 1524 patients were administered a long course of treatment (>7 days). Patients in the long course of treatment group had higher rates of survival than those in the placebo group (RR 0.80; 95% CrI 0.70-0.91). This treatment regimen also showed a significant association with serious adverse events (RR 0.74; 95% CrI 0.53-0.99). These results are presented in Figure 5a and 5b.

4. Discussion

In this Bayesian network meta-analysis of 16 randomized clinical trials with 2992 patients with COVID-19, we aimed to explore the optimal treatment agent for this group of patients. Compared with usual care or placebo, administration of methylprednisolone was associated with a lower 28-day all-cause mortality. The quality of evidence for these findings was rated as “moderate” due to inconsistency. In addition, our findings suggested that patients might benefit more from low-dose corticosteroids and a long course of treatment.

4.1. Comparison with other studies

Previous direct meta-analyses also explored the association between the administration of corticosteroids and all-cause mortality at 28 days in patients with COVID-19. In 2020, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *et al.* (2020) concluded that the use of systemic corticosteroids

was associated with lower 28-day mortality (odds ratio [OR] 0.66; 95% CI 0.53-0.82). They conducted a subgroup analysis for different drugs and found that only dexamethasone was associated with decreased all-cause mortality (OR 0.64; 95% CI 0.50-0.82). In 2021, Chaudhuri *et al.* (2021) included 18 RCTs with 2826 patients with COVID-19 or non-COVID-19 acute respiratory distress syndrome (ARDS). They came to a similar conclusion that patients with ARDS, either derived from COVID-19 or not, could benefit from the use of corticosteroids because the drug probably reduces mortality (RR 0.82; 95% CI 0.72-0.95). However, only patients with non-COVID-19-related ARDS showed significant results (RR 0.71; 95% CI 0.54-0.92). Moreover, this study included patients with both COVID-19-related and non-COVID-19-related ARDS, leading to potential clinical heterogeneity. Similar conclusions were drawn by Li *et al.* (2021) in their study. They included both RCTs and observational studies, thereby extending the sample size on the one hand but also downgrading the quality of evidence due to selection bias.

Most of the previous studies were designed as direct meta-analyses, which provided only partial information in this case and therefore did not optimally inform decision making on the comparative effectiveness of different treatment agents. The present study used network analysis, which can help evaluate the comparative effectiveness of various treatment regimens. This method is useful for improving the precision of the outcome estimate and allows the estimation of the comparative effectiveness of different types of corticosteroids.

4.2. Study implications

Although the guidelines of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine recommend applying corticosteroids in patients with moderate to severe ARDS within 14 days after disease onset, the evidence of the administration of corticosteroids in patients with COVID-19 is heavily complex and paradoxical (Annane *et al.*, 2017). The RECOVERY trial provided evidence in favor of systemic corticosteroid use, where there was a significantly lower risk of mortality with the administration of dexamethasone than usual care (RR 0.83; 95% CI 0.75-0.93) in critically ill patients with COVID-19 (RECOVERY Collaborative Group *et al.*, 2021). Nevertheless, it remains unclear which types, doses, and courses of corticosteroid treatment are more effective. In this study, we assessed the differences between high doses and low doses of corticosteroids in terms of all-cause mortality and serious adverse events (Annane *et al.*, 2017), and the pooled results indicated that low doses of corticosteroids were beneficial for 28-day mortality. In addition, the RECOVERY trial confirmed the mortality benefit associated with low-dose dexamethasone treatment (6 mg per day orally or intravenously for up to 10 days). To obtain a robust conclusion, more RCTs should be included.

The timing of glucocorticoid treatment is another issue that should be considered. For example, Tsai *et al.* (2020) conducted a multicenter, retrospective cohort study to assess the effectiveness of corticosteroids in patients presenting with influenza-associated ARDS in Taiwan. This study included 241 patients overall and found that patients who received corticosteroids early had a significantly higher in-hospital mortality rate than those who did not (43.5% *vs* 19.2%; $P < 0.001$). The study also revealed that early corticosteroid treatment was an independent factor associated with an increased overall rate of in-hospital mortality (adjusted OR 5.02; 95% CI 2.39-10.54; $P < 0.001$). In addition, according to their findings, earlier treatment was related to a significantly increased OR of subsequent bacteremia (adjusted OR 2.37; 95% CI 1.01-5.56). An ongoing trial (NCT04530409) may provide straight views on early *versus* late administration of corticosteroid treatment on mortality in patients with COVID-19.

4.3. Strength and limitations

Given the limited comparative effectiveness of different types of corticosteroids in patients with COVID-19, a Bayesian network meta-analysis was established. To determine the best approach benefiting the patients most, we used 28-day all-cause mortality to evaluate the efficacy and serious adverse events to evaluate the safety. In addition, our method included explicit eligibility criteria and a comprehensive search strategy. Thus, our analysis is strong and extends and integrates the recent guidelines in a novel way.

Although SUCRA scores and ranking scales provide a convenient approach to compare the effects of different outcomes in network meta-analysis, caution is necessary when interpreting the SUCRA values (Mbuagbaw *et al.*, 2017). The values should not be interpreted in isolation because they do not capture the extent of differences in outcomes among different treatment regimens; the value needs to be interpreted in combination with the certainty of evidence. Furthermore, SUCRA values may differ for one intervention across outcomes. Although an intervention may be ranked higher for its significant effectiveness, it might be ranked down for safety concerns. Therefore, treatment rankings should be interpreted with other outputs from a network analysis that display the magnitude of effect sizes. Clinicians need to consider these factors before interpreting the SUCRA and adapting any intervention in their practice.

The last consideration is the limitations of the study. First, the definitions and reporting of serious adverse events varied across different trials. These serious adverse events mainly focused on secondary infections and sepsis. Second, one trial reported mortality at 30 days after randomization, two trials reported in-hospital mortality in-hospital, and one trial reported mortality at 21 days, potentially leading to inconsistency. Third, the optimal dose of each corticosteroid agent could not be determined due to the limited the number of eligible studies. Therefore, we compared the differences between high-dose treatment and low-dose treatment, and the results showed that a low dose of corticosteroids was more favorable. Regarding the duration of therapy, we did not detect any difference between long-course treatment and short-course treatment because both treatment strategies showed better efficacy than placebo. Further studies should conduct direct comparisons to validate the current findings. Fourth, nearly all the studies reported mortality at 28 days; however, it is also important to report on longer-term mortality. Future research should pay attention to this problem.

5. Conclusion

Among patients with COVID-19, administration of corticosteroids was associated with a reduced 28-day mortality compared with usual care. The analysis suggested a potential superiority of methylprednisolone over dexamethasone. However, the level of evidence regarding this comparison was downgraded due to imprecision and indirectness. Large trials with an adequate number of patients are necessary to validate this finding. Moreover, our analysis confirmed the mortality benefit associated with a low dose and a long course of treatment with corticosteroids.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

Not required.

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Author contributions

XW, LM, and CY designed the meta-analysis; XW and DW searched for relevant studies; JY, QH and CT selected the studies and extracted the relevant information; XW, CT, and LM synthesized the data; and XW wrote the first draft of the paper. All authors revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.10.021.

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