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Effectiveness of corticosteroids to treat severe COVID-19: A systematic review and meta-analysis of prospective studies

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ABSTRACT

Objectives: To assess the effects of corticosteroid therapy for patients with severe coronavirus disease 2019 (COVID-19).

Methods: We comprehensively searched articles published in the Cochrane Library, PubMed, Embase, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wanfang, and VIP databases from January 1, 2019, to March 20, 2021.

Results: A total of 6771 patients from eight prospective studies were included in our meta-analysis. The results showed that corticosteroid therapy was associated with lower mortality in severe COVID-19 (OR = 0.70, 95% CI = 0.54–0.92, $P = 0.009$; $I^2 = 54.5\%$). Since the proportion of the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial included in the meta-analysis was as high as 71.88%, we removed it and recalculated the pooled OR. The results of the remaining seven studies still suggested such a survival benefit (OR = 0.65, 95% CI = 0.44–0.96, $P = 0.030$; $I^2 = 59.8\%$). Furthermore, subgroup analysis suggested that the pooled OR of three studies using corticosteroids in the early stages of treatment was much lower (OR = 0.37, 95% CI = 0.25–0.57, $P < 0.001$; $I^2 = 47.8\%$). However, after excluding the RECOVERY trial, the pooled OR of the remaining four studies with unspecific administration timing of corticosteroid therapy no longer supported this result (OR = 0.90, 95% CI = 0.69–1.17, $P = 0.415$; $I^2 = 0.0\%$).

Conclusions: In this meta-analysis, evidence based on seven randomized controlled trials and one prospective cohort study indicates that corticosteroid therapy was associated with a reduction in the mortality of severe COVID-19, especially when administered at an earlier time.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first discovered in Wuhan, China, in December 2019. As of April 15, 2021, there have been 137,866,311 confirmed cases, including 2,965,707 deaths globally.[1] Faced with such a highly infectious respiratory disease, because of the lack of specialized treatment for COVID-19, research on anti-COVID-19 drugs has become an urgent task.

“Cytokine storm” is considered to participate in the development of viral pneumonia, leading to the application of immunosuppressants represented by corticosteroids in the clinical practice of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome

(MERS),[2,3] and COVID-19. In July 2020, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) collaborative group involving 176 hospitals announced that low-dose dexamethasone (6 mg/d for up to 10 days) can help save the lives of severely ill patients, especially those receiving mechanical ventilation.[4] Since then, many randomized controlled trials (RCTs) evaluating the efficacy and safety of corticosteroid therapy have ended recruitment and released the results in advance. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group performed a prospective meta-analysis, including seven RCTs, with a final follow-up to July 7, 2020.[5] However, the debate about the role of corticosteroid therapy in COVID-19 patients was still ongoing in the six months that followed. In particular, the administration timing of severe and critical patients receiving

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; SARS, Severe Acute Respiratory Syndrome; RCTs, Randomized Controlled Trials; REACT, Rapid Evidence Appraisal for COVID-19 Therapies; NOS, Newcastle-Ottawa Scale; OR, Odds Ratio; CI, Confidence Intervals; RECOVERY, Randomized Evaluation of COVID-19 Therapy; CBM, China Biology Medicine; CNKI, China National Knowledge Infrastructure.

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corticosteroid therapy is also a key issue that urgently needs to be resolved. Recently, the results of several prospective studies have been released, some of which assess the effects of corticosteroids in the early stages of treatment. Therefore, an updated systematic review and meta-analysis are needed to evaluate the efficacy and safety of different administration timings of corticosteroid therapy in severe and critical COVID-19 patients.

2. Methods

2.1. Search strategies

Two experienced researchers (Han Li and Bingdi Yan) independently searched the Cochrane Library, PubMed, Embase, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wanfang, and VIP databases by combining the following keywords: (“COVID-19” or “SARS-CoV-2” or “novel coronavirus” or “2019-nCoV”) and (“adrenal cortex hormones” or “betamethasone valerate” or “budesonide” or “corticosteroid” or “cortisone” or “dexamethasone” or “glucocorticoids” or “hydrocortisone” or “methylprednisolone” or “prednisone”) to identify eligible articles published in either the Chinese or English language between January 1, 2019 and March 20, 2021. A detailed search strategy is shown in the [supplementary material](#). The third researcher (Rong Gao) resolved the disagreements.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) participants were adults with severe and critical COVID-19; (2) RCTs and cohort studies; (3) the intervention included any kind of corticosteroid; and (4) outcome indicators included mortality and adverse reactions. Exclusion criteria were as follows: (1) conference abstracts, letters and commentaries; (2) retrospective studies; (3) studies for which we could not retrieve the essential data; and (4) different studies recruited the same patients.

2.2. Data extraction

Two independent researchers (Han Li and Bingdi Yan) extracted data from the included articles in a standardized data collection form, and a third researcher (Jin Ren) validated the data extraction. Extracted data included (1) basic information: first author, region of study, publication date (online), study period and the type of study design; (2) participants: gender distribution, age distribution, and total number of COVID-19 patients; (3) corticosteroid therapy: administration timing, type, dosage and treatment course; and (4) outcomes: mortality and adverse reactions.

2.3. Quality assessment

Two researchers (Han Li and Bingdi Yan) assessed the risk of bias in RCTs using the Cochrane Collaboration risk-of-bias tool and used the Newcastle-Ottawa scale (NOS) to evaluate the quality of cohort studies.

2.4. Statistical analysis

Meta-analyses were performed using Stata (version 14.0; StataCorp). We examined the heterogeneity across studies using the I^2 test and χ^2 test. A random-effects model was used to calculate odds ratios (ORs) and 95% CIs when either $I^2 > 50\%$ or $P < 0.10$ defined significant heterogeneity. Publication bias was assessed by funnel plots.

3. Results

3.1. Search results

We yielded 7786 records from the selected databases, of which 2444 records were duplicates. A total of 5227 records were excluded after reading the title and abstract. The full texts of the remaining 115 articles

were retrieved for a detailed evaluation. Finally, we identified eight articles for our meta-analysis. [4,6–12] The selection flow chart is shown in [Fig. 1](#). The [supplementary material](#) summarizes the risk of bias of the included studies.

3.2. Study characteristics

The meta-analysis included 6771 COVID-19 patients from eight studies, of which 2715 patients received corticosteroids and 4056 patients received standard or usual care without corticosteroids. Of the included studies, one was a cohort study, and seven were RCTs. In addition, corticosteroids were used in the early stages of treatment in three studies and were not specified in the other four studies. The details of each included article are presented in [Table 1](#).

3.3. Outcomes

The eight included studies all reported data on mortality. Among the 2715 patients receiving corticosteroids, 646 died (23.8%). Among the 4056 patients in the control group, 1231 died (30.4%). The pooled OR showed that mortality was lower in patients who received corticosteroids (OR = 0.70, 95% CI = 0.54–0.92, $P = 0.009$; $I^2 = 54.5\%$; [Fig. 2](#)). There was no publication bias on mortality ([Fig. 3](#)). The pooled result was highly dependent on the RECOVERY trial, the proportion of which was as high as 71.88%. However, even if the RECOVERY trial was excluded, the pooled OR of the remaining seven studies still suggested such a survival benefit (OR = 0.65, 95% CI = 0.44–0.96, $P = 0.030$; $I^2 = 59.8\%$; [Fig. 4](#)).

We performed subgroup analysis and found that the pooled OR of three studies using corticosteroids in the early stages of treatment was much lower (OR = 0.37, 95% CI = 0.25–0.57, $P < 0.001$; $I^2 = 47.8\%$; [Fig. 2](#)). The pooled OR of the other five studies with unspecific administration timing of corticosteroid therapy showed a survival benefit (OR = 0.80, 95% CI = 0.71–0.91, $P < 0.001$; $I^2 = 0.0\%$; [Fig. 2](#)). However, after excluding the RECOVERY trial, the pooled OR of the remaining four studies no longer supported this result (OR = 0.90, 95% CI = 0.69–1.17, $P = 0.415$; $I^2 = 0.0\%$; [Fig. 4](#)).

In order to bring more guidance for physicians, we further performed subgroup analysis with different corticosteroids. The pooled OR showed that mortality was lower in patients who received dexamethasone (OR = 0.78, 95% CI = 0.69–0.89, $P < 0.001$; $I^2 = 0.0\%$; [Fig. 5](#)), while neither methylprednisolone (OR = 0.54, 95% CI = 0.15–1.96, $P = 0.349$; $I^2 = 76.9\%$; [Fig. 5](#)) nor hydrocortisone (OR = 0.71, 95% CI = 0.45–1.12, $P = 0.138$; $I^2 = 43.9\%$; [Fig. 5](#)) showed such a survival benefit.

Three studies reported data on bacterial infection. As shown in [Fig. 6](#), there was no relationship between corticosteroid therapy and bacterial infection (OR = 1.29, 95% CI = 0.96–1.73, $P = 0.091$; $I^2 = 36.3\%$; [Fig. 6](#)).

4. Discussion

On January 30, 2020, World Health Organization (WHO) declared the ongoing pandemic of COVID-19 a public health emergency of international concern. Infection by SARS-CoV-2 has irreversibly changed the life of the majority of people and prompted researchers to find efficacious treatments and adequate preventive strategies.

The high mortality of COVID-19 is not only because of uncontrolled viral replication but is also due to the respiratory failure caused by the accompanying “cytokine storm”, which is an excessive immune response from the host to prevent pathogen invasion. The severe “cytokine storm” leads to lung injury, vascular inflammation, disseminated intravascular coagulation, shock, and multiple organ failure. Clinically, corticosteroids are used for the symptomatic treatment of severe pneumonia and to prevent the “cytokine storm” in COVID-19. However, there has been much controversy about whether COVID-19 patients should be treated with corticosteroids. A number of systematic reviews have evaluated the

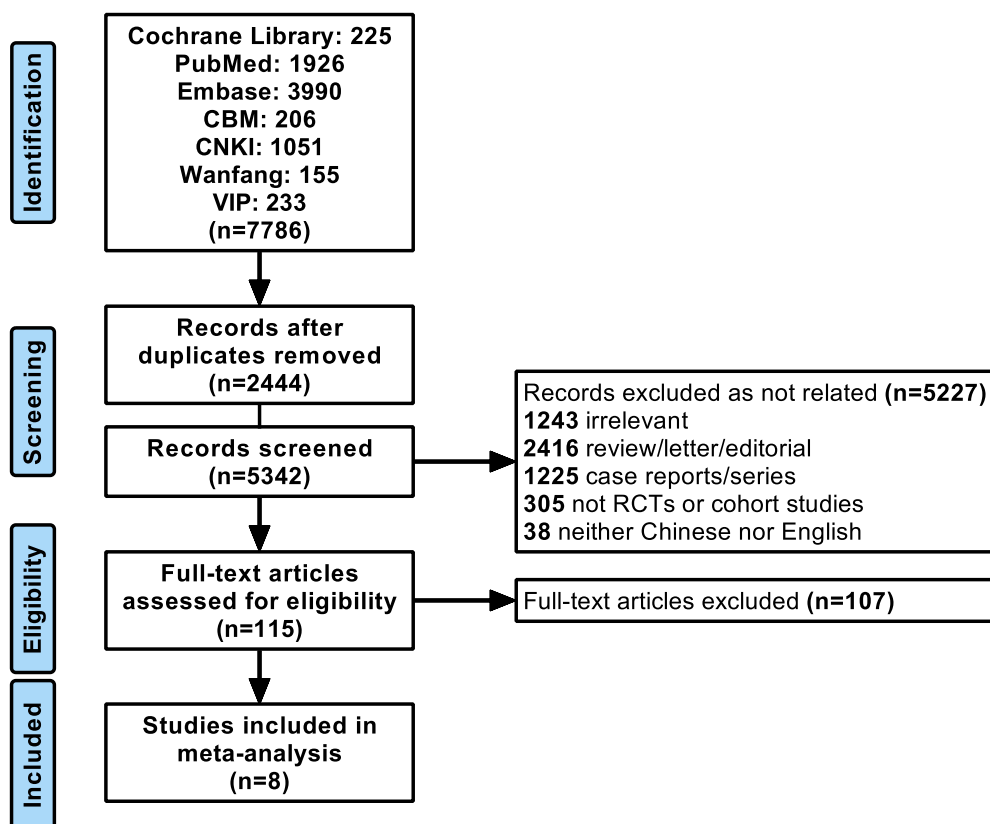


Fig. 1. Flow chart of the literature search and selection of studies.

efficacy of corticosteroids to treat COVID-19 with inconsistent results. Some meta-analyses, including retrospective case-control and cohort studies, concluded that corticosteroid use might not be effective in decreasing mortality.[13–15] However, considering the survivor bias, residual confounding and treatment selection bias of these retrospective observational studies, the conclusions were not credible.

In contrast, in a prospective meta-analysis of clinical trials of critical COVID-19 patients from the REACT Working group, administration of corticosteroids was associated with lower 28-day all-cause mortality.[16] After this finding, WHO recommended corticosteroids for patients with severe or critical COVID-19.[17] However, no specific recommendations are given for the type of corticosteroid, timing of initiation, optimum dose, or duration of treatment. In a recent meta-analysis of 7 RCTs and 6250 severe COVID-19 patients, pooled results suggested that a survival benefit was observed for a low dosage of corticosteroids and a treatment duration not shorter than 7 days.[18] However, the pooled results of the above two meta-analyses depended on the RECOVERY trial. In other words, if the trial had been excluded, there would be no such survival benefit according to the remaining trials.

In this meta-analysis, we evaluated the mortality of severe and critical COVID-19 patients treated with corticosteroids. Our analysis demonstrated that corticosteroids reduced mortality in severe and critical COVID-19 patients compared with no corticosteroids. Unlike the previous meta-analysis, such survival benefits were still present even if the RECOVERY trial was excluded. This confirmed that the combined result in our meta-analysis was authoritative and not determined by a particular trial. Moreover, subgroup analysis of different administration timings of corticosteroid therapy was performed. A significant survival benefit was observed if corticosteroid therapy was administered within 48 h of hospitalization or ICU admission (OR = 0.37, 95% CI = 0.25–0.57, $P < 0.001$; $I^2 = 47.8\%$). In contrast, if the RECOVERY trial was excluded, there was no survival benefit of using corticosteroids in the nonearly stages of treatment (OR = 0.90, 95% CI = 0.69–1.17, $P =$

0.415; $I^2 = 0.0\%$). However, because of the limited studies, more evidence is needed to clarify the potential clinical significance. In addition, compared with other corticosteroids, dexamethasone improves the outcome of severe COVID-19 more significantly (OR = 0.78, 95% CI = 0.69–0.89, $P < 0.001$; $I^2 = 0.0\%$). Unfortunately, due to the different dosages and treatments of corticosteroids, the credibility of the result needs to be considered.

As corticosteroids are broad-spectrum immunosuppressants, they can also hinder B cell-mediated antibody production, reduce the protective function of T cells, and prevent macrophage-mediated clearance of apoptotic cells. This effect can result in an increased risk of secondary infections. One previous meta-analysis indicated that more frequently broad spectrum antibiotics were used in the corticosteroid group.[19] But there is no evidence that the risk of secondary infections is higher in COVID-19 patients assigned to corticosteroids in our analysis and the previous meta-analysis.[16,18] Moreover, as a result of the short time scale since the outbreak of SARS-CoV-2, long-term adverse reactions to corticosteroid therapy are difficult to assess. However, a previous meta-analysis showed that SARS patients who received long treatment durations and high doses of corticosteroids were more likely to develop osteonecrosis.[20] A previous network meta-analysis of 110 studies suggested that, in addition to corticosteroids, the use of tocilizumab, anakinra, high-dose intravenous immunoglobulin, convalescent plasma, and remdesivir were also associated with improved outcomes of hospitalized COVID-19 patients.[21] However, given the lower price of corticosteroids, it is still the first choice of physicians.

The advantage of this meta-analysis is that it included high-quality prospective studies through a comprehensive search strategy and excluded observational retrospective studies. Moreover, our meta-analysis suggested that an earlier administration timing would provide the greatest benefit to corticosteroid treatment by subgroup analysis. However, there are some limitations in this meta-analysis. First, the presence of confounding factors such as age, gender, comorbid

Table 1
Characteristics of studies included in the meta-analysis

First author	Region	Publication date	Study type	Rang of time	Test group size	Timing of corticosteroids	Dosage and duration of corticosteroids	Control group size	Control intervention	Longest follow-up
Horby P	UK	20/7/17	RCT, multicenter	Mar 19 ~ Jun 8	1603	Not specified	Dexamethasone (6 mg/d for up to 10 days)	3287	Usual care	28 days
Jeronimo CMP	Brazil	20/8/12	RCT, single center	Apr 18 ~ Jun 16	194	Not specified	Methylprednisolone (0.5 mg/kg/d for 5 days)	199	Placebo	28 days
Dequin P	France	20/9/2	RCT, multicenter	Mar 7 ~ Jun 1	76	Within 24 h of the onset of the first severity criterion	Hydrocortisone for 8 or 14 days (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)	73	Standard care	21 days
Angus DC	Australia, Canada, European Union, New Zealand, UK, US	20/9/2	RCT, multicenter	Mar 9 ~ Jun 17	137	Not specified	Hydrocortisone (200 mg/d for 7 days)	101	Usual care	21 days
Tomazini BM	Brazil	20/9/2	RCT, multicenter	Apr 17 ~ Jun 23	151	Not specified	Dexamethasone (20 mg/d for 5 days and then 10 mg/d for 5 days)	148	Standard care	28 days
Edalatifard M	Iran	20/12/24	RCT, multicenter	Apr 14 ~ Apr 29	34	Within 48 h of hospitalization	Methylprednisolone (250 mg/d for 3 days)	28	Standard care	Until hospital discharge or death
Monedero P	Spain	21/1/4	Cohort, multicenter	Mar 12 ~ Jun 29	485	Within 48 h of ICU admission	Methylprednisolone, dexamethasone, or prednisone (for 7 days)	191	Usual care	Until hospital discharge or death
Corral-Gudino L	Spain	21/2/3	Partial RCT, multicenter	Apr ~ Jul	35	Not specified	Methylprednisolone (40 mg twice daily for 3 days, then 20 mg twice daily for 3 days)	29	Standard care	Until composite endpoint happened

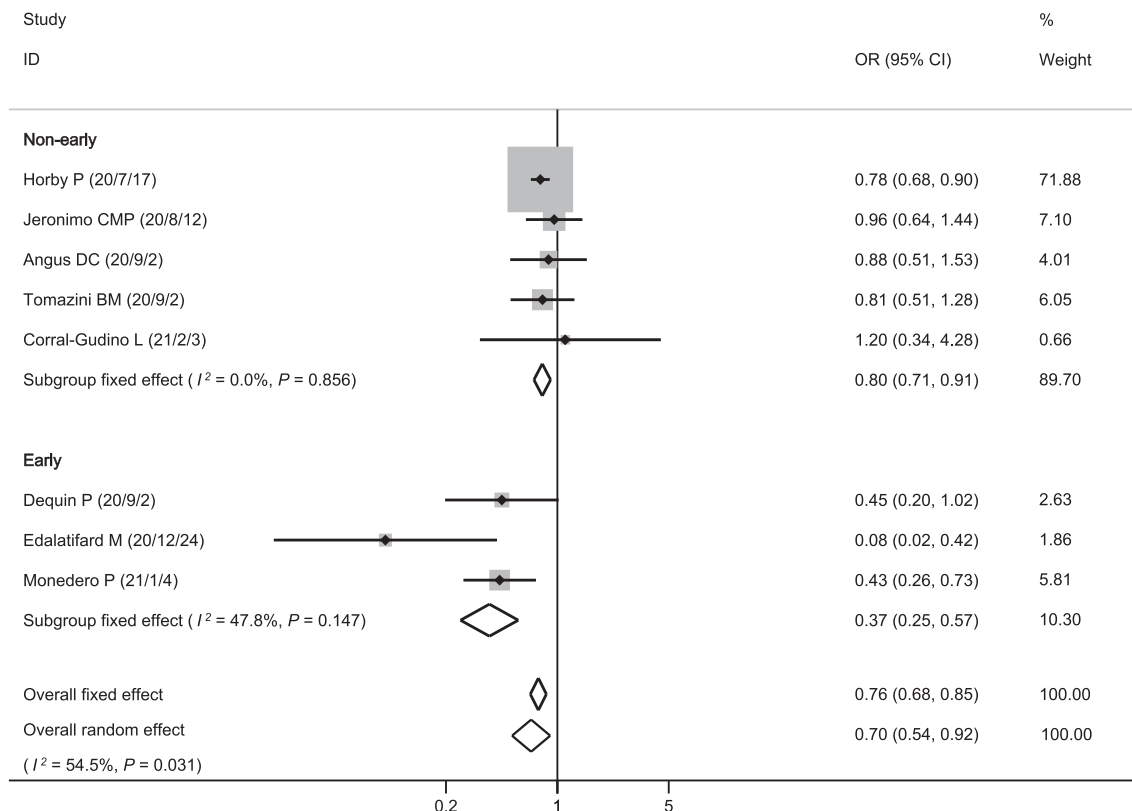


Fig. 2. Effect of corticosteroids on mortality.

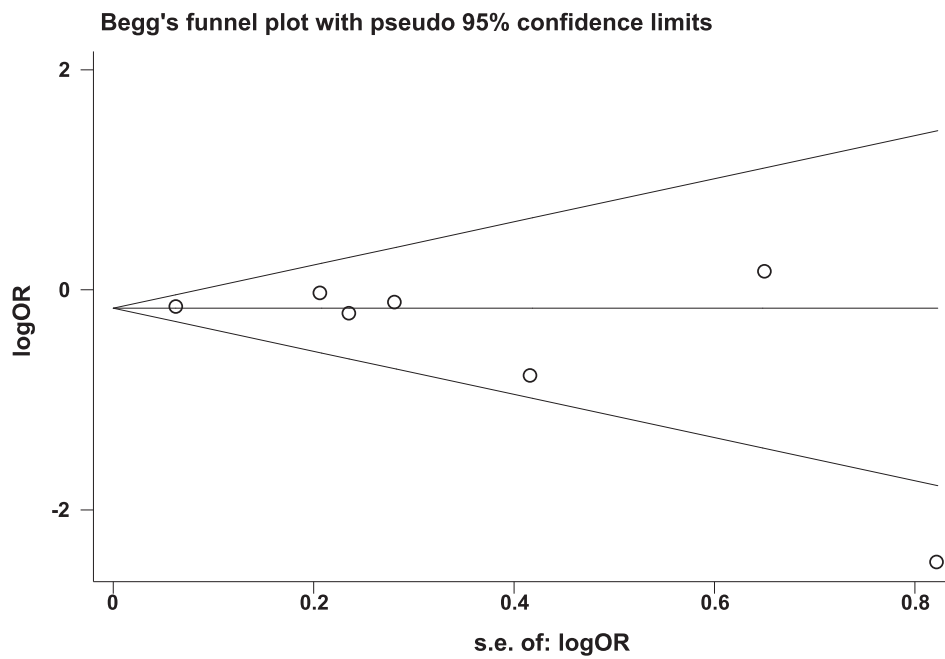


Fig. 3. Funnel plot of mortality.

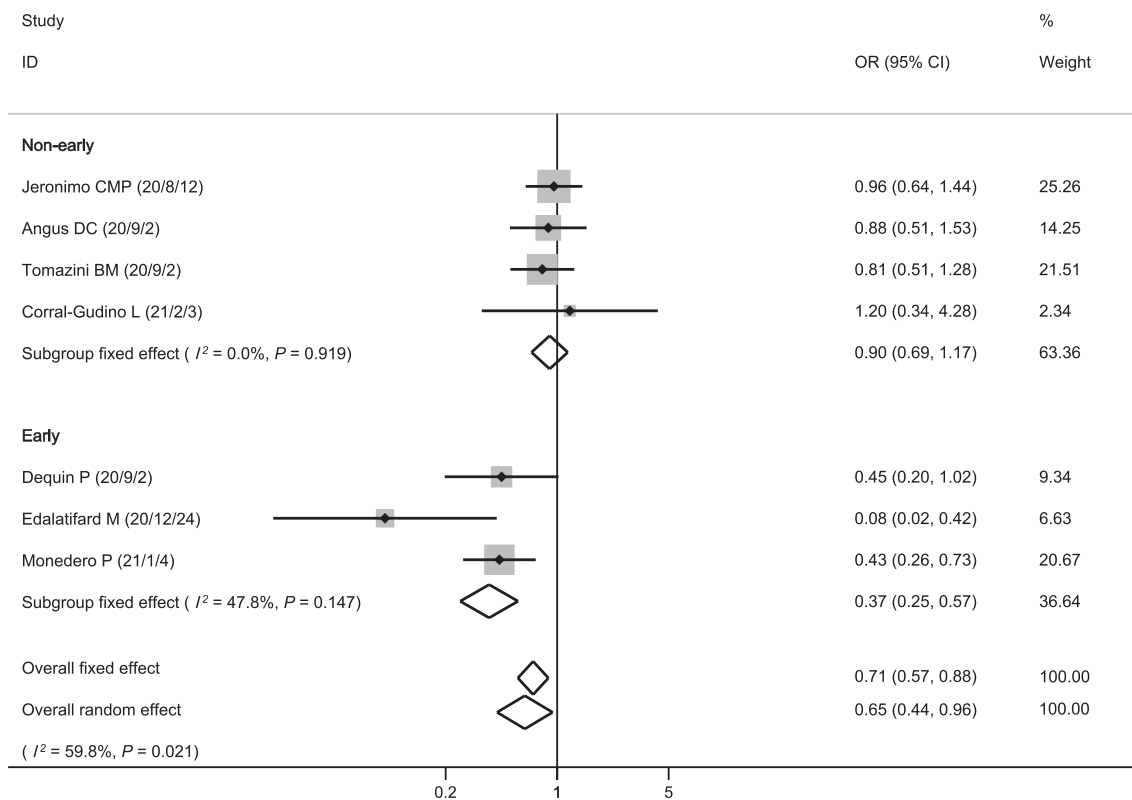


Fig. 4. Effect of corticosteroids on mortality (excluded RECOVERY).

conditions, and other medications which are taken by patients that can affect the relationship between corticosteroid therapy and the mortality of COVID-19 should still be considered. The definition of “severe and critical COVID-19” varies among studies, but the patients received minimally respiratory support at least, including patients receiving invasive or non-invasive mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). Second, the outcome of corticosteroid

therapy may also depend on the corticosteroid type, dosage, treatment duration, and inclusion criteria of participants, but there was no uniform standard in various studies. Considering the limited number of studies, we did not conduct subgroup analyses of the dosages and duration of corticosteroids. Third, among the eight included studies in this meta-analysis, two trials reported mortality at 21 days, and three trials reported mortality at 28 days after randomization which may have an

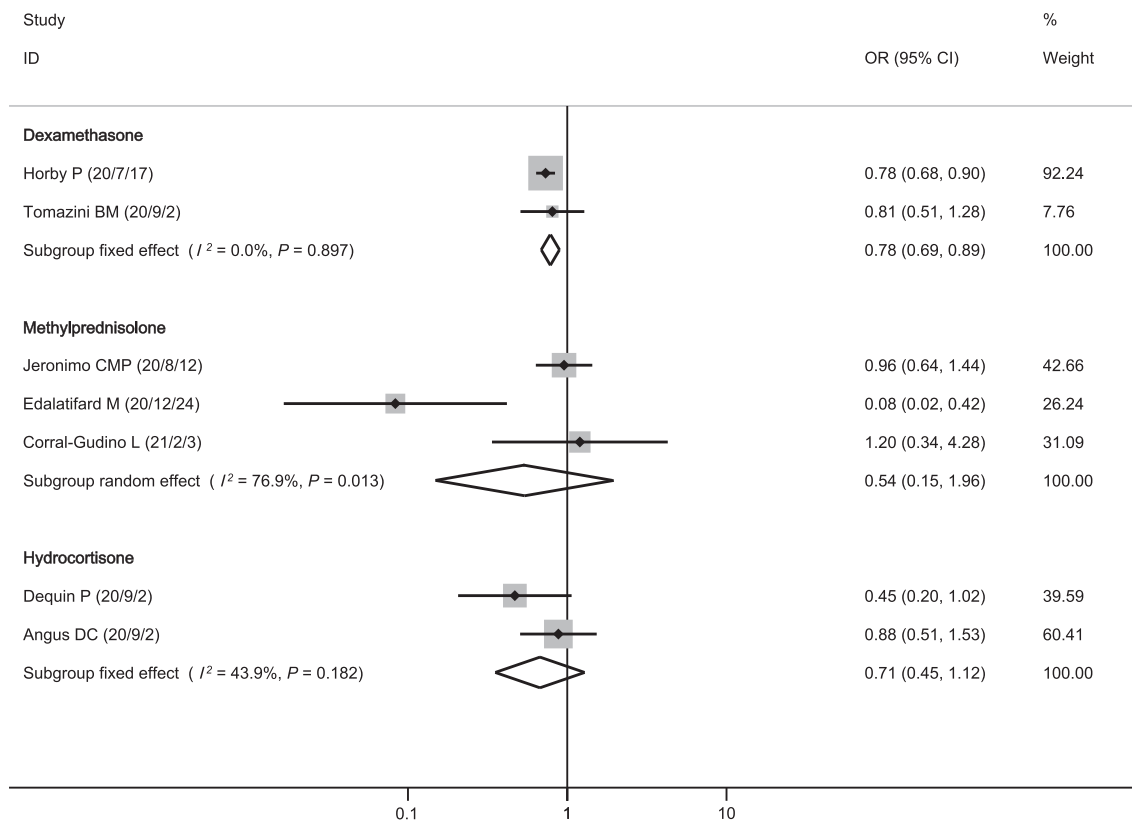


Fig. 5. Effect of different types of corticosteroids on mortality.

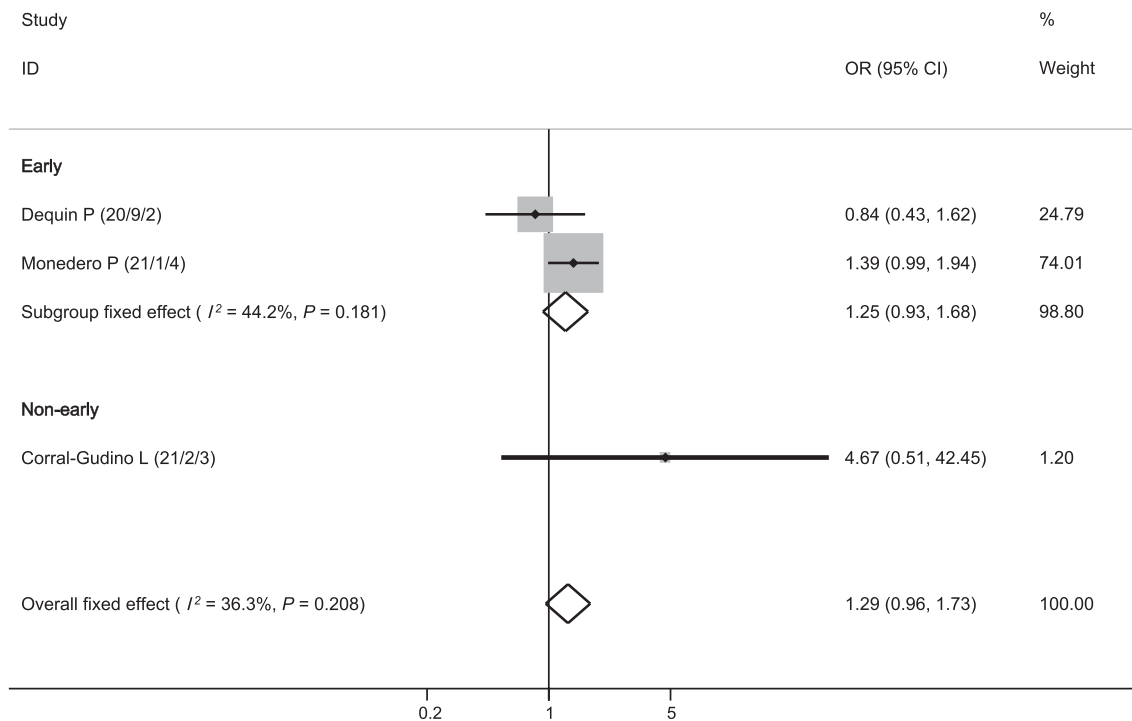


Fig. 6. Effect of corticosteroids on bacterial infection.

impact on the comparison of mortality. Fourth, whether COVID-19 patients received special interventions other than corticosteroids was largely dependent on physicians' decisions, which led to bias.

5. Conclusions

In this meta-analysis of eight prospective studies and 6771 severe and critical COVID-19 patients, pooled results showed that

corticosteroid therapy was associated with lower mortality but not an increase in serious adverse events. Besides, this meta-analysis suggested that an earlier administration timing would provide the greatest benefit to corticosteroid treatment. However, more high-quality RCTs are needed to verify further the authenticity of this conclusion. In addition, the further meta-analysis should be done after adjusted several bias noted in the limitations.

CRedit authorship contribution statement

Han Li: Conceptualization, Methodology, Investigation, Writing – original draft. **Bingdi Yan:** Investigation, Data curation, Writing – review & editing. **Rong Gao:** Investigation, Validation. **Jin Ren:** Investigation, Validation. **Junling Yang:** Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Ethical approval and patient consent are not required since this is an overview based on published studies.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intimp.2021.108121>.

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