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ORIGINAL RESEARCH

Efficacy and Safety of Corticosteroid Use in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis

Yuqing Cui · Yali Sun · Junyi Sun · Huoyan Liang · Xianfei Ding · Xueyi Sun · Dong Wang · Tongwen Sun

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ABSTRACT

Introduction: We conducted a comprehensive literature review to synthesize evidence for the relationship between corticosteroid use and mortality in patients with COVID-19.

Methods: The PUBMED, EMBASE, and Cochrane Library were searched from inception to March 13, 2021. We searched and analyzed randomized controlled trials (RCTs) and observational studies (OSs) that examined corticosteroid use in patients with COVID-19. The primary outcome was in-hospital mortality, while the secondary outcome was the need for mechanical ventilation (MV) and serious adverse events.

Results: A total of 11 RCTs and 44 OSs involving 7893 and 41,164 patients with COVID-19 were included in the study. Corticosteroid use was associated with lower COVID-19 mortality in RCTs, but was not statistically significant (OR 0.91, 95% CI 0.77–1.07; I^2 = 63.4%). The subgroup analysis of pulse dose corticosteroid showed survival benefit statistically (OR 0.29, 95% CI 0.15–0.56). Moreover, the corticosteroid use may reduce the need for MV (OR 0.67, 95% CI 0.51–0.90; I^2 = 7.5%) with no significant increase in serious adverse reactions (OR 0.84, 95% CI 0.30–2.37; I^2 = 33.3%). In addition, the included OSs showed that the pulse dose (OR 0.66, 95% CI 0.45–0.95; I^2 = 30.8%) might lower the mortality in patients with COVID-19. The pulse dose of methylprednisolone (OR 0.60, 95% CI 0.45–0.80; I^2 = 0%) had a beneficial effect on survival. It was especially significant when the duration of pulse methylprednisolone use was less than 7 days (OR 0.59, 95% CI 0.43–0.80; I^2 = 0%).

Conclusions: This meta-analysis indicated that corticosteroid use might cause a slight reduction in COVID-19 mortality. However, it could significantly reduce the MV requirement in patients with COVID-19 and restrict serious adverse events. Additionally, the pulse dose of methylprednisolone for less than 7 days may be a good treatment choice for patients with COVID-19.

Keywords: Corticosteroid use; COVID-19; Mortality; MV; Adverse events; Meta-analysis

Yuqing Cui, Yali Sun, and Junyi Sun contributed equally to this work.

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Key Summary Points

Corticosteroid use might cause a slight reduction in COVID-19 mortality.

Corticosteroid use could reduce the Mechanical Ventiilation (MV) requirement and restrict serious adverse events in patients with COVID-19.

The pulse dose of methylprednisolone for less than 7 days may be a good treatment choice for patients with COVID-19.

INTRODUCTION

The rapid worldwide spread of coronavirus infections disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has threatened global health seriously [1]. The virus causing COVID-19 is a novel betacoronavirus with 96% similarity to the bat coronavirus genome [2]. It is the third most highly transmissible and pathogenic coronavirus after the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) that appeared in the twenty-first century [3, 4]. Statistically, there have been 133,552,774 confirmed infections and 2,894,295 deaths worldwide by April 10, 2021 (https://www.who.int/data#reports).

There are some drugs, such as low molecular weight heparin, remdesivir, and convalescent plasma, that attracted people's attention during the COVID-19 epidemic. However, the results of recent large-scale, high-quality randomized controlled trials (RCTs) showed that there is no significant difference in the efficacy of convalescent plasma or remdesivir treatment between the control group and patients with COVID-19 [5, 6]. Corticosteroid administration is an important adjuvant treatment for severe viral infections because of its powerful anti-inflammatory effects [7]. During the SARS epidemic, corticosteroids were widely used in critically ill patients [8, 9]. Corticosteroid therapy is a rational option for patients with COVID-19 because it was previously used to treat patients with severe SARS [10]. Many COVID-19 RCTs have been registered to research the effect of corticosteroids on patients with COVID-19. Three recently published RCTs [11–13] demonstrated that corticosteroid use does not lower COVID-19 mortality; however, dexamethasone administration does have short-term survival benefits for patients with COVID-19 requiring respiratory support [14]. A prospective meta-analysis published in *JAMA* showed that corticosteroid use could reduce short-term all-cause mortality [15]. Corticosteroid treatment probably reduced mortality in patients with COVID-19 and non-COVID-19 acute respiratory distress syndrome (ARDS) [16]. The World Health Organization (WHO) also strongly recommended corticosteroid therapy in critically ill patients with COVID-19 recently (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1).

Despite there being several recent meta-analyses, the optimal corticosteroid type, dose, and duration in patients with COVID-19 remains unclear. This meta-analysis reviewed the RCT and OS literature comprehensively to establish a relationship between corticosteroid use and COVID-19 mortality. It aimed to explore the beneficial effect of corticosteroids, particularly in pulse methylprednisolone use in patients with COVID-19.

METHODS

The meta-analysis (CRD42021242739) followed the PRISMA reporting guidelines [17], and was enrolled at PROSPERO (http://www.crd.york.ac.uk/PROSPERO). Supplementary Material Table S1 provides the PRISMA 2009 checklist. English articles were searched in PUBMED (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (www.embase.com), and Cochrane CENTRAL (www.cochranelibrary.com/central) databases since their inception to March 13, 2021. We used "SARS-CoV-2", "COVID-19", "COVID2019", "severe acute respiratory syndrome coronavirus 2", "adrenal cortex

hormones", "steroids", "corticosteroid", "glucocorticoid," and other terms to search the database. Supplementary Material Table S2 gives the retrieval strategy in detail. EndNote X9 software was used to perform the literature screening process. Furthermore, we also looked up available references and searched the medRxiv website (https://www.medrxiv.org/) for relevant unpublished articles. The authors Yuqing Cui and Yali Sun searched the literature independently. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

The studies were included in the meta-analysis based on the following population, intervention, comparison, outcome, and study design (PICOS) criteria: (1) adult patients with COVID-19; (2) patients with COVID-19 with or without corticosteroid therapy (low-dose corticosteroid, < 15 mg dexamethasone or equivalent per day; high-dose corticosteroid, > 15 mg dexamethasone or equivalent per day; and pulse dose corticosteroid—pulse dose was explicitly mentioned in the original studies); (3) corticosteroid- and non-corticosteroid-treated patients' mortality, need for MV, and safety were measured; and (4) RCTs or OSs were excluded if they lacked patients' outcome data or were animal research.

Studies Selection and Data Extraction

Available data were independently extracted on the basis of the afore mentioned eligibility criteria. The primary outcomes were the risk odds ratios (ORs) of mortality, and the secondary outcomes were the need for MV and safety of patients with COVID-19, with or without corticosteroid use. The data of each study were listed as follows: the study including first author and publication year, country, study design, gender, age, period of inclusion, sample size, corticosteroid type, daily dose and duration, disease severity, number of corticosteroid and non-corticosteroid use (deaths), follow-up, and the data of primary and secondary outcome. If ORs were missing, they were computed on the basis of original numerical values provided in the literature.

Bias Risk Assessment

Cochrane Collaboration bias risk evaluation tool [18] and Newcastle–Ottawa scale (NOS) [19] were used to assess the bias risk of outcomes in RCTs and OSs, respectively. The selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases were used to assess the risk of an RCT. If any of these items were assessed as high risk, the study was considered to have a high risk of bias. Additionally, according to the OS selection (four points at most), the comparability of OS design and analysis (two points at most), and the adequacy of outcome measures (three points at most), a maximum of nine points could be awarded; seven to nine points were considered as high quality. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria were used to estimate and summarize the quality of the RCT evidence and grade the collected data on the basis of evidence [20].

Statistical Analysis

Statistical analyses were conducted with STATA 14.0 (College Station, Texas, 77845, USA, Serial number 401406267051) and Review Manager (RevMan), version 5.3 (Cochrane Collaboration). Inverse variance random-effects meta-analyses were used for the included studies, and the pooled effect of each outcome was measured. The OR and 95% CI from each included study were either calculated or directly extracted from the data. I^2 estimated the heterogeneity of the included studies, where heterogeneity, not sampling error, resulted in variability. The heterogeneity was recorded as moderate when I^2 equaled 51–74% and was recorded as high when I^2 was more than 74%. Subgroup analyses were conducted on the basis of corticosteroid type and its dose and severity in patients with COVID-19. The stability of outcomes was verified by sensitivity analysis.

Funnel plots and Begg's linear regression were performed to evaluate the publication bias.

RESULTS

Study Selection

In total, we identified 6717 articles from the three databases. Three RCT records [DEXA-COVID 19 (The efficacy of dexamethasone treatment for patients with ARDS caused by COVID-19; NCT04325061); COVID STEROID (The hydrocortisone for COVID-19 and severe hypoxia; NCT04348305); Steroids-SARI (Glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure; NCT04244591)] were searched by related meta-analysis [15] to obtain the prospective data; the other two unpublished records [21, 22] were identified by searching the *medRxiv* website. There were 4508 records left after removing the duplicates. Furthermore, we identified 106 studies after a preliminary screening by title or abstract. Finally, our meta-analysis included 11 RCTs and 44 OSs enrolling 7893 and 41,164 patients (Fig. 1).

Study Characteristics

There were 11 RCTs [11–14, 23–26] (DEXA-COVID 19, NCT04325061; COVID STEROID, NCT04348305; Steroids-SARI, NCT04244591) and 44 OSs [21, 22, 27–68] that reported an association between mortality and corticosteroid therapy in patients with COVID-19. There were only one RCT [23] and eight OSs [33, 34, 46, 49, 55–58] that used pulse dose of corticosteroid. The OSs were included to further explore the corticosteroid type and pulse dose duration that were beneficial to patients with COVID-19. Table 1 and Supplementary Material Table S3 present the characteristics of literature included.

Risk of Bias Assessment

Supplementary Material Fig. S1 presents the RCTs of the Cochrane Collaboration bias risk evaluation tool. Four RCTs [12, 14, 23, 26] were at high risk of bias because of performance bias. Three RCTs [11, 13, 25] were at low risk of bias, and one trial [24] had unclear risk bias. According to the NOS, all 44 eligible OSs [21, 22, 27–68] scored greater than or equal to seven points, indicating a low risk of bias. Supplementary Material Table S4 reports the specific contents of risk bias in the included OSs.

Effects of Corticosteroids on Outcomes

Figure 2 shows the preliminary results of RCTs. The results showed that the corticosteroid use did not reduce the in-hospital mortality significantly (OR 0.91, 95% CI 0.77–1.07; I^2 = 63.4%; evidence rank, moderate). The association between corticosteroid and COVID-19 mortality was also not statistically significant in OSs (OR 0.89, 95% CI 0.74–1.08; I^2 = 83.3%) (Supplementary Material Fig. S2). Supplementary Material Figs. S3 and S4 show the secondary outcomes of the RCTs. Corticosteroid administration did reduce the need for MV (OR 0.67, 95% CI 0.51–0.90; I^2 = 7.5%; evidence rank, moderate) and did not statistically increase the serious adverse events (OR 0.84, 95% CI 0.30–2.37; I^2 = 33.3%; evidence rank, moderate) among patients with COVID-19.

Subgroup Analysis and Effect on Mortality

We analyzed subgroups to explore the sources of high heterogeneity, according to corticosteroid type and dose. We found that the pulse dose corticosteroid treatment improved survival in one RCT (pulse: OR 0.29, 95% CI 0.15–0.56; low: OR 0.93, 95% CI 0.81–1.07; high: OR 1.34, 95% CI 0.66–2.69) (Fig. 2) and OSs (pulse: OR 0.66, 95% CI 0.45–0.95; I^2 = 30.8%; low: OR 0.86, 95% CI 0.69–1.06; high: OR 1.03, 95% CI 0.66–1.61) (Fig. 3). Furthermore, we found that the pulse dose of methylprednisolone (pulse Me: OR 0.60, 95% CI 0.45–0.80; Hy: OR 3.28, 95% CI 0.98–10.99) significantly lowered the hospital mortality in patients with COVID-19 (Fig. 4), particularly in patients with a duration less than 7 days (pulse methylprednisolone less

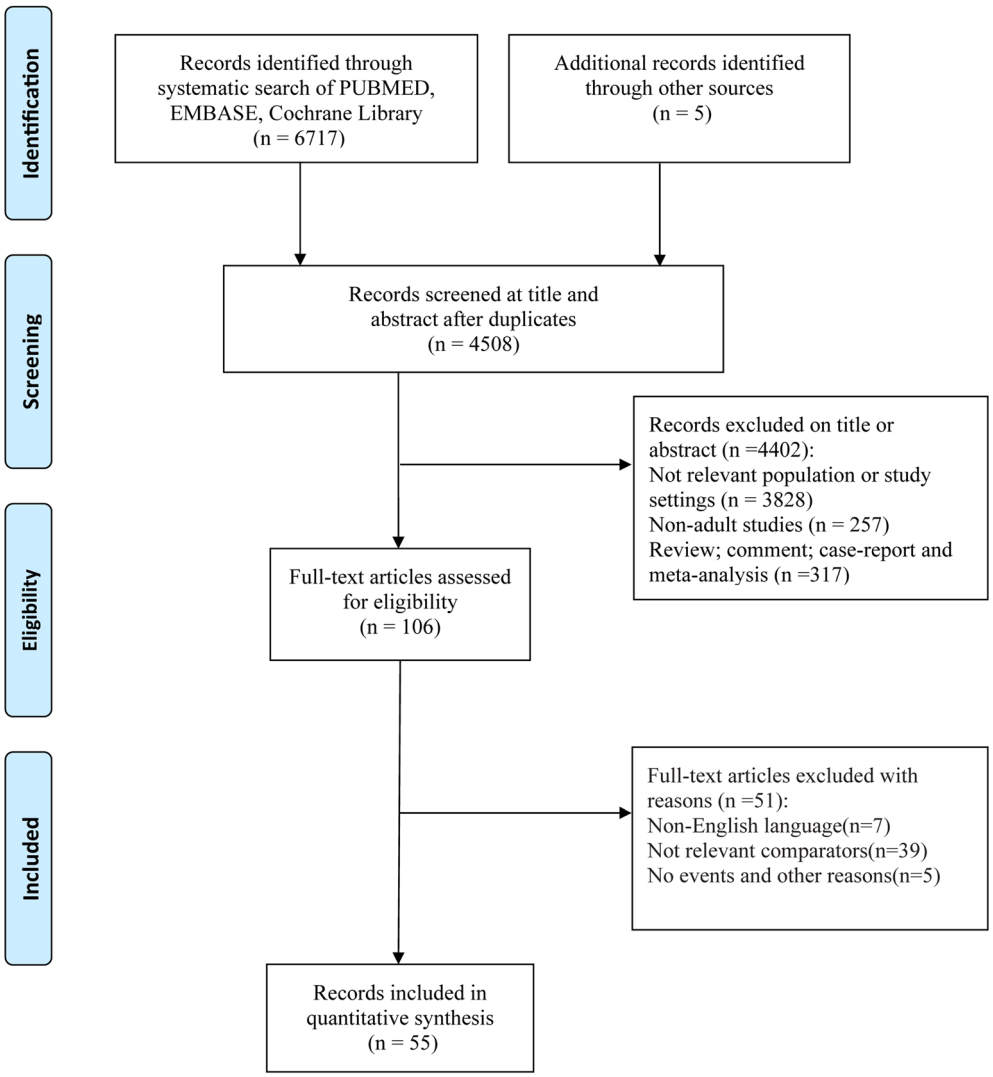

Fig. 1 Flow diagram of the study selection

than 7 days: OR 0.59, 95% CI 0.43–0.80; more than 7 days: OR 1.08, 95% CI 0.27–4.40) (Fig. 5).

Sensitivity Analyses

As a result of the high heterogeneity of our results, we conducted a sensitivity analysis to evaluate the impact of any single study on the pooled OR and 95% CI by omitting one study at a time. We found that the results of these RCTs and OSs were robust and reliable (Supplementary Material Figs. S5 A and B).

Publication Bias Assessment

We generated funnel plots (Supplementary Material Figs. S6 A and B) and performed Begg's regression tests to examine the publication bias of the included studies. There was no significant publication bias in RCTs ($P = 0.732$) and OSs ($P = 0.659$).

DISCUSSION

The meta-analysis identified 11 RCTs (7893 patients) and 44 OSs (41,164 patients) based on

Table 1 Summary of included RCTs

Study	Country	Period of inclusion	Sample size	Female/male (cor/non-cor use)	Age (mean ± SD/) (cor/non-cor use)	Critical or severe	Cor type and daily dose
Angus 2020	USA	2020/3/9–2020/6/17	379	Fixed-dose[a] 39/98; shock-dependent[b] 43/103; non-Cor[c] 29/72	Fixed-dose 20.4 ± 11.6; Shock-dependent 59.5 ± 12.7; Non-Cor 59.9 ± 14.6	Severe	IV Hy, 50 mg, every 6 h × 7 days; while in shock for up to 28 days; fixed-dose of 100 mg every 6 h × 7 days
Dequin 2020	France	2020/3/7–2020/6/1	149	22/54 23/50	63.1 (51.5–70.8) 66.3 (53.5–72.7)	Critical	IV Hy 200 mg/day; continued at 200 mg/day × 7 days and then decreased to 100 mg/day × 4 days and 50 mg/day × 3 days, for a total of 14 days. If sufficiently improved by day 4, 200 mg/day × 4 days, followed by 100 mg/day × 2 days and then 50 mg/day × the next 2 days, for a total of 8 days
Edalatifard 2020	Iran	2020/4/20–2020/6/20	62	10/24 13/15	55.8 ± 16.35 61.7 ± 16.62	Severe	24–48 h after hospitalization receive Me pulse (IV injection, 250 mg/day × 3 days)
Horby 2020	UK	2020/5/9–2020/6/8	6425	766/1338 1572/2749	66.9 ± 15.4 65.8 ± 15.8	Overall	Oral or IV De (6 mg/day) × 10 days (or until hospital discharge if sooner)
Jamaati 2021	Iran	2020/3	50	NA	NA	Overall	IV De 20 mg/day from day 1 to day 5 and then at 10 mg/day from day 6 to day 10
Jeronimo 2020	USA	2020/4/18–2020/6/16	647	68/194 71/199	54 ± 15 57 ± 15	Overall	IV Me (0.5 mg/kg), twice daily × 5 days
Tang 2021	China	2020/2/14–2020/3/31	86	45/41 22/21	57 (49–67) 55 (38–65)	Non-severe	1 mg/kg/day of IV Me × 7 days
Tomazini 2020	Brazil	2020/4/17–2020/6/13	299	61/90 51/97	60.1 ± 15.8 62.7 ± 13.1	Severe	IV De 20 mg/day × 5 days, followed by 10 mg/day for additional 5 days or until ICU discharge

Table 1 continued

Study	Country	Period of inclusion	Sample size	Female/male (cor/non-cor use)	Age (mean ± SD/) (cor/non-cor use)	Critical or severe	Cor type and daily dose
COVID STEROID	Denmark		29	2/13 4/10	57 (52–75) 62 (51–71)	Severe	IV Hy 200 mg/day × 7 days (continuous or bolus dosing every 6 h)
Steroids-SARI	China		47	7/17 5/18	67 (61–74) 62 (54–68)	Severe	40 mg IV Me every 12 h × 5 days
DEXA-COVID 19	Spain		19	3/4 3/9	62 (48–68) 60 (52–69)	Severe	20 mg/day IV De × 5 days and then 10 mg/day × 5 days

Study	Disease severity mean (SD) (cor/non-cor use)	Cor use no. (deaths)	Non-cor use no. (deaths)	Follow-up	Unadjusted or adjusted OR (95% CI)	MV no. (cor/non-cor use)	Adverse events no. (cor/non-cor use)
Angus 2020	PaO_2/FiO_2 137 (74)/138 (78) APACHE 17 (12–24)/15 (12–21)	278 (78)	101 (33)	21-day	0.8 (0.49–1.31)		9/1[d]
Dequin 2020	PaO_2/FiO_2 130.0 (96.7–188.0)/133.0 (89.8–174.8) SOFA 6.0 (4.0–8.0)/6.0 (4.0–7.5)	76 (11)	73 (20)	21-day	0.45 (0.20–1.02)	17/17	3/0[e]
Edalatifard 2020		34 (2)	28 (12)	In-hospital	0.293 (0.154–0.556)		2/2
Horby 2020		2104 (482)	4321 (1110)	28-day	0.83 (0.75–0.93)	95/283	[f]
Jamaati 2021		25 (16)	25 (10)	28-day	2.68 (0.85–8.37)	13/11	
Jeronimo 2020	PaO_2/FiO_2 160 (118–200)/ 156 (120–227)	194 (72)	199 (76)	28-day	1.14 (0.76–1.71)	53/57	

Table 1 continued

Study	Disease severity mean (SD) (cor/non-cor use)	Cor use no. (deaths)	Non-cor use no. (deaths)	Follow-up	Unadjusted or adjusted OR (95% CI)	MV no. (cor/ non-cor use)	Adverse events no. (cor/non-cor use)
Tang 2021	SOFA 2 (1–2)/1 (0–2)	43 (0)	43 (1)	In-hospital	0.977 (0.933–1.023)		
Tomazini 2020	PaO_2/FiO_2 131.1 (46.2)/132.6 (45.7) SOFA 9 (7–10.5)/8 (7–11)	151 (85)	148 (91)	28-day	0.97 (0.72–1.31)		5/9[g]
COVID STEROID	SOFA 9 (7–10.5)/8 (7–11)	15 (6)	14 (2)	28-day	4 (0.65–24.66)		1/0[h]
Steroids-SARI		24 (13)	23 (13)	28-day	0.91 (0.29–2.87)		23/23[i]
DEXA-COVID 19		7 (2)	12 (2)	28-day	2 (0.21–18.69)		3/11[j]

Cor corticosteroid, *No.* number, *MV* mechanical ventilation, *OR* odds ratio, *CI* confidence interval, *RCT* randomized controlled trials, *overall* included severe and non-severe patients, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *Hy* hydrocortisone, *Me* methylprednisolone, *De* dexamethasone, *Pre* prednisone, *NA* not available, *COVID STEROID* hydrocortisone for COVID-19 and severe hypoxia, *DEXA-COVID 19* efficacy of dexamethasone treatment for patients with ARDS caused by COVID-19, *Steroids-SARI* glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure

[a] Using fixed dose of corticosteroid

[b] Using shock-dependent dose of corticosteroid

[c] Not using corticosteroid; serious adverse event definitions

[d] Per ICH good clinical practice guidelines (events not already captured as a trial end point, e.g., mortality); when the event may reasonably have occurred because of study participation

[e] Any; excluded some listed in protocol; excluded expected adverse events related to the patient's disease or comorbidity

[f] Cause-specific mortality; ventilation; dialysis; cardiac arrhythmia; (in a subset); other that were believed to be related to study treatment

[g] Mortality; infections; insulin use

[h] New episodes of septic shock (Sepsis-3 criteria); invasive fungal infection; clinically important gastrointestinal bleeding; anaphylaxis

[i] Secondary bacterial infections; barotrauma; severe hyperglycemia; gastrointestinal bleeding; requiring transfusion; acquired weakness

[j] Secondary infections of pneumonia, sepsis, or other similar; pulmonary embolism

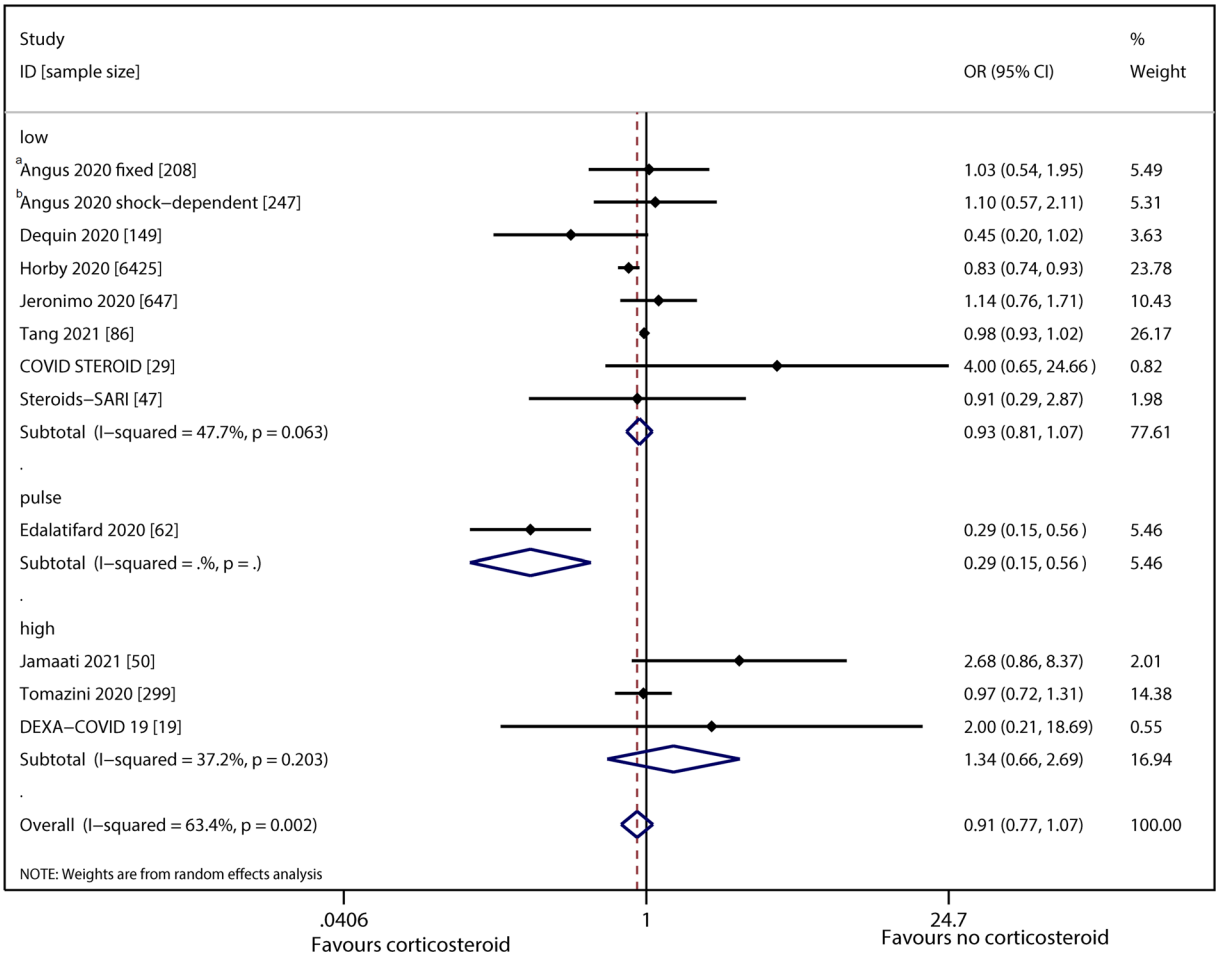

Fig. 2 Forest plot showing the association between corticosteroid dose and COVID-19 mortality in RCTs using the random-effects model. Low, using low dose of corticosteroid; high, using high dose of corticosteroid; pulse, using pulse dose of corticosteroid; using [a]fixed dose or [b]shock-dependent dose of corticosteroid

corticosteroid and COVID-19. The results of RCTs demonstrated that corticosteroid use had survival benefits, especially the pulse corticosteroid use. Furthermore, its use lowered the need for MV without significantly increasing the serious adverse events. Additionally, the OS analysis showed that the pulse dose of methylprednisolone for less than 7 days leads to a significant decrease in mortality.

The pathophysiology of COVID-19 includes host-mediated excessive inflammation and cytokine storm that causes severe endothelial and alveolar damage [69]. COVID-19-related death is mainly due to excessive inflammation and uncontrolled immune response [70]. Corticosteroids are well tolerated and widely used worldwide. They could reduce cytokine storm risk and inflammation in COVID-19 [71]. Moreover, they also could regulate inflammation-mediated lung injury, thereby reducing the progression of respiratory failure and death [14, 72]. Earlier studies on the efficacy and safety of corticosteroid therapy in severe pneumonia [73] indicated a significant association between corticosteroid use and reduction in ARDS risk as well as hospital and ICU length of stay [74]. Three recent high-quality meta-analyses [15, 75, 76] included RCTs and have shown a significant mortality advantage in corticosteroid-treated patients with COVID-19, in

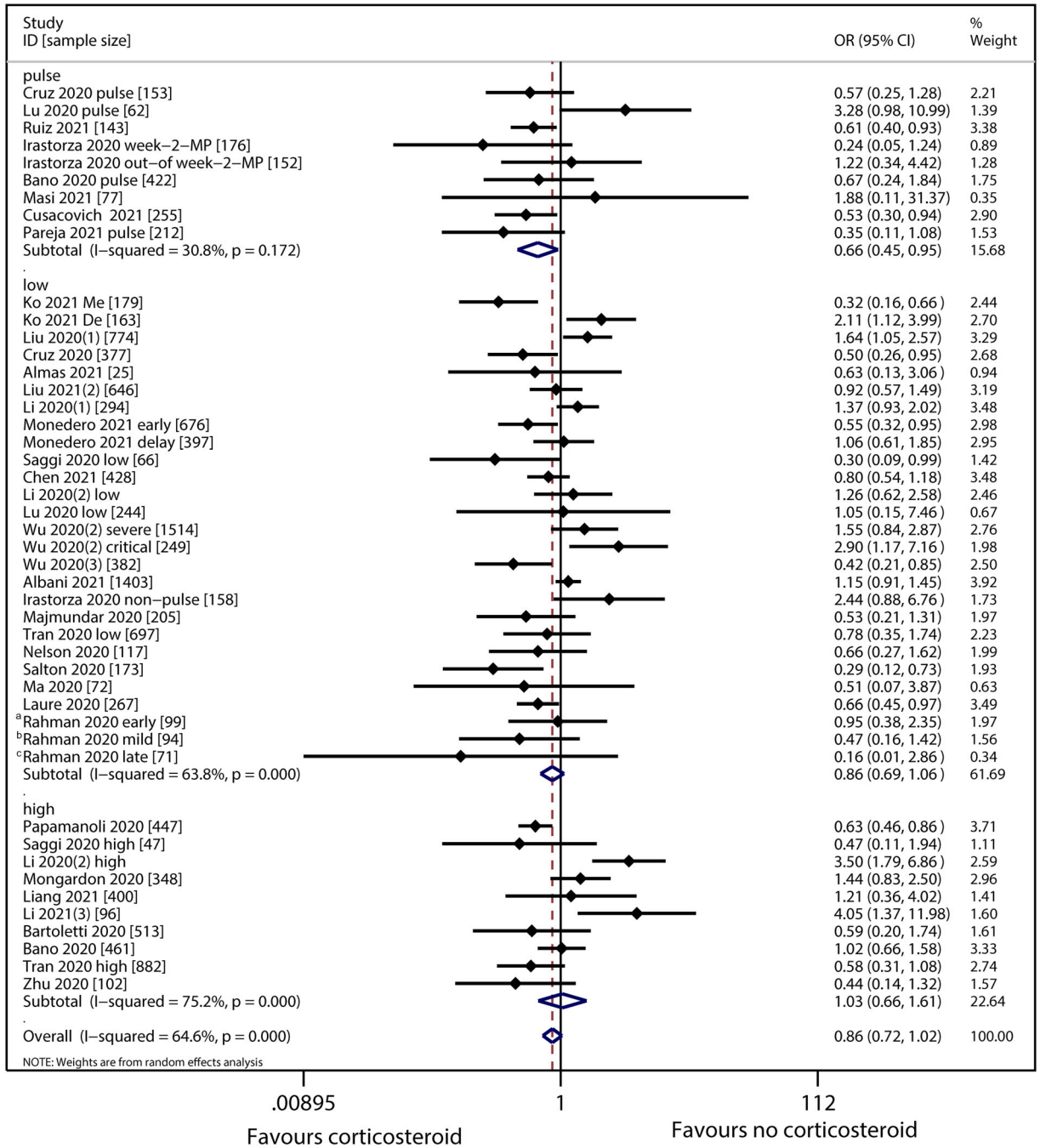

Fig. 3 Forest plot showing the association between corticosteroid dose and COVID-19 mortality in OSs using the random-effects model. Low, using low dose of corticosteroid; high, using high dose of corticosteroid; pulse, using pulse dose of corticosteroid; Me, methylprednisolone; De, dexamethasone; early, early use of corticosteroid; delay, delayed use of corticosteroid; severe, using corticosteroid in severe cases; critical, using corticosteroid in critical cases; out-of-week-2-MP, receiving pulse dose of methylprednisolone at week 1 or 3; week-2-MP, receiving pulse dose of methylprednisolone during week 2; non-pulse, receiving non-pulse dose of methylprednisolone. [a]Receiving steroids within 48 h of ICU admission; [b]receiving steroids between 48 h and 7 days from admission; [c]receiving their first dose of steroids more than 7 days after ICU admission

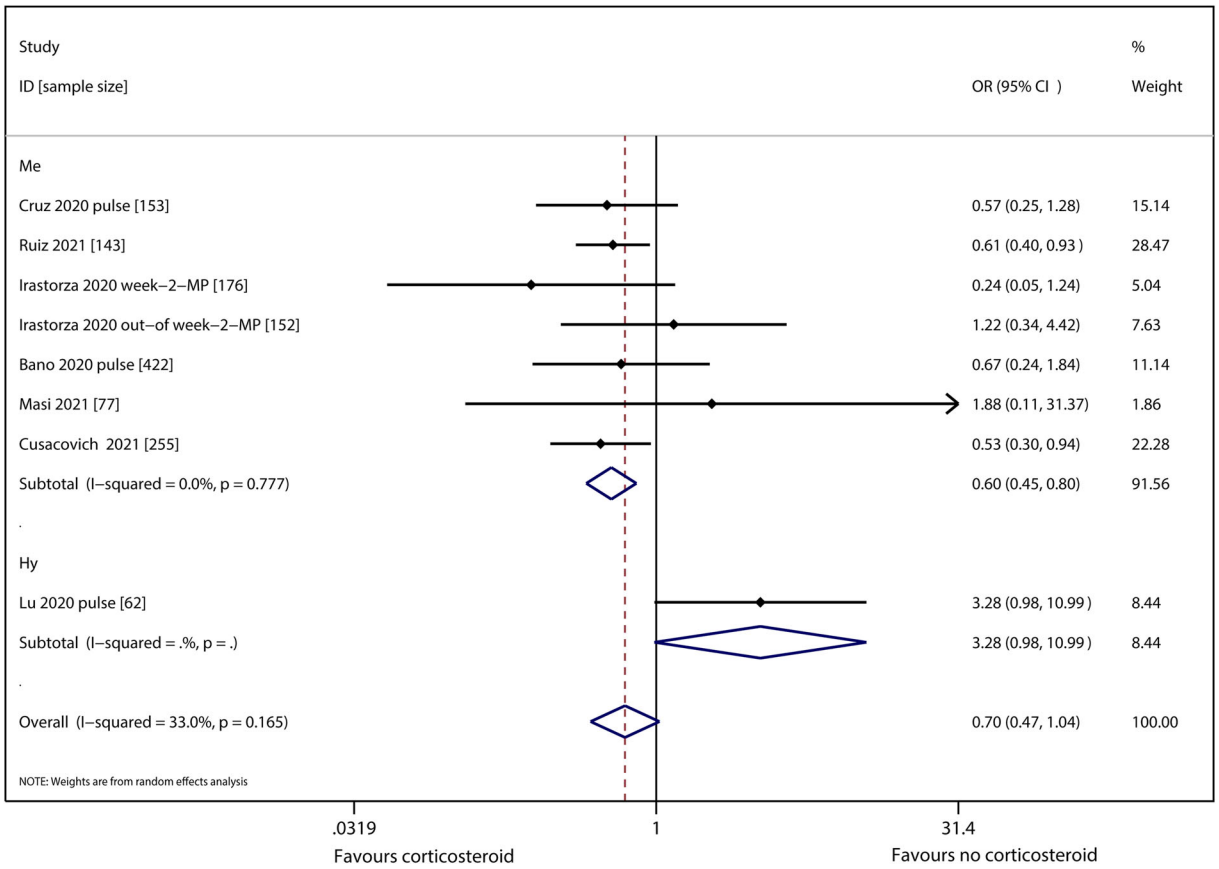

Fig. 4 Forest plot showing the association between pulse corticosteroid type and COVID-19 mortality in OSs using the random-effects model. Pulse, using pulse dose of corticosteroid; Me, methylprednisolone; Hy, hydrocortisone; out-of-week-2-MP, receiving pulse dose of methylprednisolone at week 1 or 3; week-2-MP, receiving pulse dose of methylprednisolone during week 2

particular severely ill patients with COVID-19. The latest guidelines strongly recommend the short application of systemic corticosteroids in patients with MV, no matter whether complicated with ARDS or not [77]. Corticosteroids alter inflammatory pathways at the genomic level or through rapid non-genomic pathways [78]. The genomic mechanism includes activation of cytosolic glucocorticoid receptors, thereby activating or inhibiting protein synthesis, including cytokines, chemokines, and adhesion molecules, which has a direct inhibitory effect on inflammatory cells [79]. Non-genomic mechanisms may play other roles in pulse therapy [80]. At present, the existing evidence supports the use of corticosteroid in patients with COVID-19, but the type, dosage, starting time, and duration need more research. Compared with dexamethasone, methylprednisolone had short half-life and high affinity for glucocorticoid receptor [81]. Pulse methylprednisolone use could quickly reach glucocorticoid receptor saturation to perform genomic and non-genomic functions [82]. Additionally, short-term corticosteroid treatment could minimize severe adverse effects, such as reduced excessive inflammation and exposure time, which may have obvious therapeutic effects.

This meta-analysis had several advantages. The study included the largest number of published RCTs and OSs, including manually searched meta-analysis and unpublished literature, available to date. Therefore, our study had the most comprehensive inclusion of articles. The GRADE and NOS were performed to assess the evidence quality and bias risk. The sensitivity

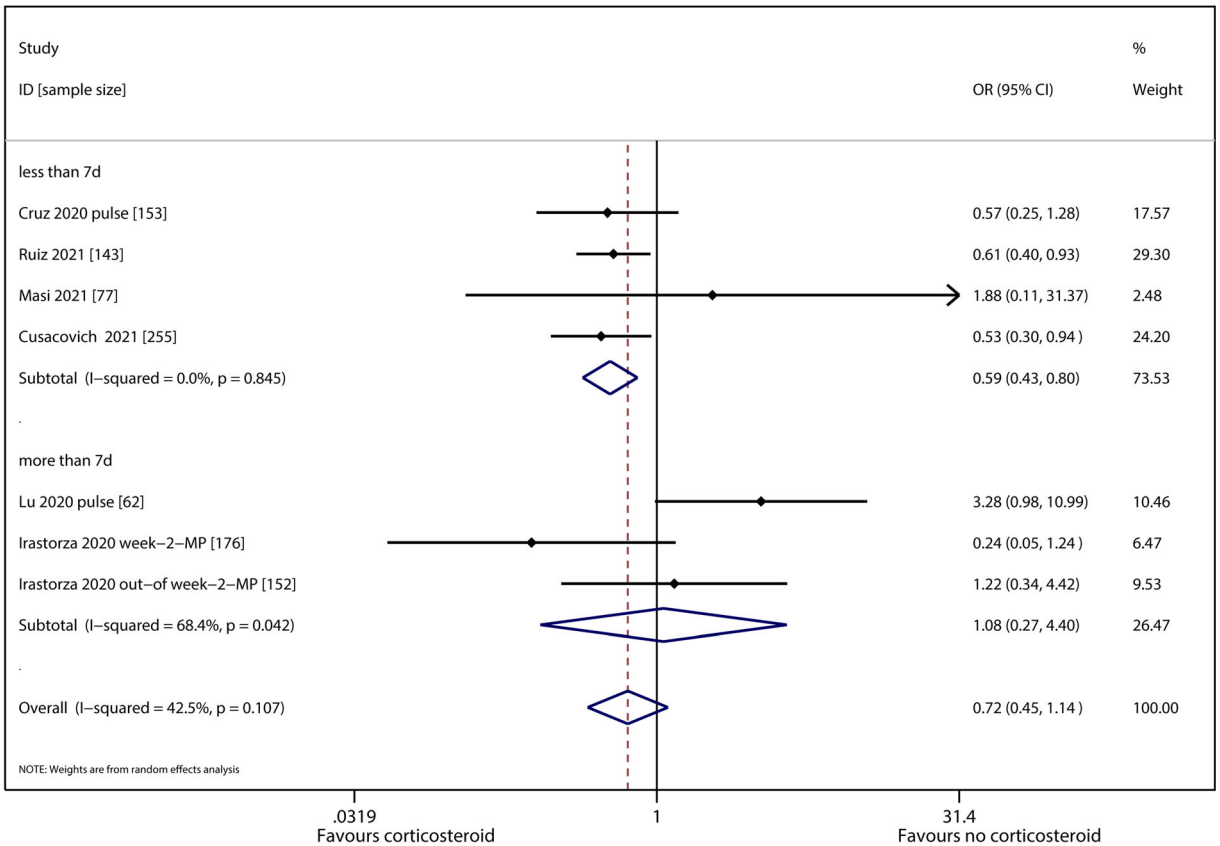

Fig. 5 Forest plot showing the association between duration of pulse methylprednisolone use and COVID-19 mortality in OSs using the random-effects model. Pulse, using pulse dose of corticosteroid; out-of-week-2-MP, receiving pulse dose of methylprednisolone at week 1 or 3; week-2-MP, receiving pulse dose of methylprednisolone during week 2

analysis validated the study results to be robust and reliable. The starting time of corticosteroid administration is inconsistent in included studies, and there are few further studies on the dosage and duration of corticosteroid use. In our meta-analysis, we used as comprehensive literature as possible to explore suitable corticosteroids types, dosage, and duration in patients with COVID-19.

The study had a few limitations. Only one RCT on pulse dose, even though we searched all relevant literature; however, eight OSs were included and also confirmed the protective effect of pulse dose corticosteroid in patients with COVID-19. Our result was limited by high heterogeneity, which may come from differences in the study population, medical conditions, disease severity, type of corticosteroid used, dose, duration, and so on. It suggested that patients with COVID-19 with individual differences and different genotypes may need different glucocorticoid treatment strategies, such as different dosage or duration of use, but further larger-sample clinical trials are needed to explore this. However, the GRADE assessment showed our conclusions to be convincing.

CONCLUSIONS

The meta-analysis indicated that corticosteroid administration might be safe for COVID-19 treatments and showed a statistically significant difference in reducing the need for MV. Moreover, pulse methylprednisolone administration might have a beneficial effect on the survival of

patients with COVID-19, especially with a duration less than 7 days.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author Contributions. All the authors contributed substantially to the work presented in this article. TWS conceived of the study. YQC, YLS and JYS contributed to the data interpretation. HYL, XFD, XYS and DW contributed to the study protocol. TWS revised the article. All authors have approved the final and submitted version of the manuscript.

Data Availability. The datasets used and/or analysed in the present study are available from the corresponding author on reasonable request.

Disclosures. Yuqing Cui, Yali Sun, Junyi Sun, Huoyan Liang, Xianfei Ding, Xueyi Sun, Dong Wang and Tongwen Sun have nothing to disclose.

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