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

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Research

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Abstract

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

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 (OS) that examined the corticosteroid use in COVID-19 patients. The primary outcome was in-hospital mortality, while the secondary outcome was the need for mechanical ventilation (MV) and serious adverse events.

Results: 11 RCTs and 46 OS involving 7,893 and 4,1696 COVID-19 patients were included in the study. Corticosteroid use was associated with lower COVID-19 mortality in RCTs, but was not statistically significant (OR, 0.88; 95% CI, 0.74–1.05; I^2=66.9%). The subgroup analysis of severe COVID-19 patients, corticosteroid type and dose also showed no survival benefit statistically. However, the corticosteroid use may reduce the MV need (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 OS showed that the pulse dose (OR, 0.52; 95% CI, 0.39–0.70) and methylprednisolone use (OR, 0.69; 95% CI, 0.52–0.92; I^2=66.7%) may lower the mortality in COVID-19 patients.

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 COVID-19 patients and restrict serious adverse events. Additionally, the pulse dose of methylprednisolone may be a good treatment choice for COVID-19 patients.

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 COVID-19 virus is a novel β-coronavirus having 96% similarity with 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 (MERS-CoV) that appeared in the 21st century [3, 4]. According to statistics, there have been 133,552,774 confirmed infections and 2,894,295 deaths worldwide by April 10, 2021 (https://www.who.int/data#reports). However, no drugs with curative effects on COVID-19 have been found so far.

Corticosteroid administration is an important adjuvant treatment for severe viral infections because of its powerful anti-inflammatory effects [5]. During the SARS epidemic, corticosteroids were widely used in critically ill patients [6, 7]. Corticosteroid therapy is advisable for COVID-19 patients because it was used to treat severe SARS patients earlier, and the COVID-19 virus shares 79.6% of sequence identity with SARS-CoV [8]. A large number of COVID-19 RCTs were registered to research the corticosteroid effect on COVID-19 patients. Three recently published RCTs [9–11] demonstrated that corticosteroid use does not lower COVID-19 mortality; however, dexamethasone administration does have short-term survival benefits for COVID-19 patients requiring respiratory support [12]. A prospective meta-analysis published in the JAMA showed that corticosteroid use could reduce the short-term all-cause mortality [13]. The World Health Organization (WHO) strongly recommended corticosteroid therapy in critical COVID-19 patients recently. (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1).

Nevertheless, corticosteroid use in COVID-19 patients remains controversial. This meta-analysis reviewed the RCTs and OS literature comprehensively to establish a relationship between corticosteroid use and COVID-19 mortality. It aimed to explore the beneficial effect of corticosteroids, if any, on COVID-19 patients. The conclusions of this study may assist a doctor in clinical decision-making.

Methods

The meta-analysis (CRD42021242739) followed the PRISMA reporting guidelines [14] , and was enrolled at PROSPERO (http://www.crd.york.ac.uk/PROSPERO). 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. Table S2 gives the retrieval strategy in detail. EndNote X9 software performed 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.

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) COVID-19 patients with or without corticosteroid therapy (low dose corticosteroid meant that patients were treated with less than 15 mg dexamethasone or equivalent per day; high dose corticosteroid meant that patients were treated with more than 15 mg dexamethasone or equivalent per day); 3) corticosteroid- and non-corticosteroid-treated patients’ mortality, need for MV and safety were measured; and 4) RCTs or OS. Studies were excluded if they lacked patients’ outcome data or were animal researches.

Studies Selection and Data Extraction

Available data were independently extracted based on the eligibility criteria mentioned in the earlier section. The primary outcomes were the risk odds ratios (ORs) of mortality, and the secondary outcomes were the need for MV and safety of COVID-19 patients, with or without corticosteroid use. The data of each study were listed as follows: the study including first author and publication year, study design, period of inclusion, sample size, corticosteroid type and daily

dose, 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 based on original numerical values provided in the literature.

Bias Risk Assessment

Cochrane Collaboration [15] and Newcastle-Ottawa Scale (NOS) [16] was performed for RCTs and OS to assess the bias risk of outcomes, 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 was assessed as high risk, the study was considered to have a high-risk 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 to be high quality. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criterion was used to estimate and summarize the quality of the RCT evidence and grade the collected data based on evidence [17].

Statistical Analysis

Statistical analyses were conducted by 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 based on corticosteroid type and its dose and severity in COVID-19 patients. 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 6,717 articles from the three databases. Three RCTs 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 [13] to obtain the prospective data; the other two unpublished records [18, 19] were identified by medRxiv website. There were 4,508 records left after removing the duplicates. Furthermore, we identified 106 studies after preliminary screening by title or abstract. Two OS [20, 21] were not in the range of 95% CIs after sensitivity analysis, and so the two articles were deleted. Finally, our meta-analysis included 11 RCTs and 46 OS enrolling 7,893 and 4,1696 patients (Figure 1).

Study Characteristics

There were 11 RCTs [9-12, 22-25] (DEXA-COVID 19, NCT04325061; COVID STEROID, NCT04348305; Steroids-SARI, NCT04244591) and 46 OS [18, 19, 26-69] that reported an association between COVID-19 patients' mortality and corticosteroid therapy. There were five RCTs [10, 22, 23] (DEXA-COVID 19, NCT04325061; COVID STEROID, NCT04348305; Steroids-SARI, NCT04244591) and 10 OS [30, 36, 42, 43, 45, 51, 53, 55, 59, 60] that used high doses of corticosteroid (>15 mg/d De), and 6 OS [33, 34, 36, 56-58] that administered pulse dose corticosteroid. There were two RCTs [9, 11] and 20 OS [18, 19, 32, 35, 39, 43, 44, 48, 49, 52, 54, 55, 57, 59, 61, 64, 66-69] that included severe or critical COVID-19 patients. Table 1 and Table S3 present the characteristics of literature included.

Risk of Bias Assessment

Figure S1 presents the RCTs of the Cochrane Collaboration bias risk evaluation tool. Four RCTs [10, 12, 22, 25] were high-risk bias because of performance bias. Three RCTs [9, 11, 24] were low-risk bias, and one trial [23] had unclear risk bias. According to the NOS, all 46 eligible OS [18, 19, 26-69] were greater than or equal to seven points, indicating a low-risk bias. Table S4 reports the specific contents of risk bias in the included OS.

Corticosteroid Effects 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, 0.88; 95% CI, 0.74–1.05; I^2=66.9%; evidence rank, moderate). Considering the effect of confounding factors on mortality of OS, we listed the adjusted and unadjusted OR separately in the forest plot. The adjusted or unadjusted OS results were consistent with the RCTs (OR, 0.91; 95% CI, 0.74–1.11; I^2=85.3%) (Figure S2). Figures 3 and S3 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 COVID-19 patients.

Subgroup Analysis with Mortality

We analyzed subgroups to explore the sources of high heterogeneity, according to severe or critical COVID-19 patients and corticosteroid type and dose. Figures S4 and S5 show that corticosteroid therapy did not result in a significantly lower hospital mortality in severe COVID-19 patients (RCT: OR, 0.66; 95% CI, 0.39–1.13; I^2=28.9%; OS: OR, 1.09; 95% CI, 0.73–1.63; I^2=88.8%). We also did a subgroup analysis on patients with corticosteroid dose. It was found that the low- or high-dose corticosteroids therapy was not associated with any significant positive impact on hospital mortality (low: OR, 0.91; 95% CI, 0.78–1.06; I^2=63.4%; high: OR, 0.90; 95% CI, 0.43–1.89; I^2=74.7%) (Figure S6). We also analyzed the effect of corticosteroid types on mortality (De: OR, 0.97; 95% CI, 0.77–

1.23; I^2=43.6%; Hy: OR, 0.82; 95% CI, 0.37–1.82; I^2=58.6%; Me: OR, 0.64; 95% CI, 0.27–1.52; I^2=85.2%) (Figure S7). We found that the pulse dose corticosteroid treatment improved survival in OS (pulse: OR, 0.52; 95% CI, 0.39–0.70; I^2=2.7%; low: OR, 0.86; 95% CI, 0.71–1.06; I^2=63.2%; high: OR, 1.37; 95% CI, 0.80–2.33; I^2=82.2%) (Figure 4). The methylprednisolone use also lowered the mortality (Me: OR, 0.69; 95% CI, 0.52–0.92; I^2=66.7%; Pre: OR, 0.94; 95% CI, 0.54–1.65; I^2<0.01%; Hy: OR, 1.36; 95% CI, 0.93–1.99; I^2<0.01%; De: OR, 0.49; 95% CI, 0.15–1.53; I^2=93.0%) (Figure 5).

Sensitivity Analyses

Due to 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 these RCTs and OS results were robust and reliable (Figures S8 A and B).

Publication Bias Assessment

We performed funnel plots (Figures S9 A and B) and Begg's regression tests to examine the publication bias of the included studies. There was no significant publication bias in RCTs (P=0.876) and OS (P=0.425).

Discussion

The meta-analysis identified 11 RCTs (7,893 patients) and 46 OS (4,1696 patients) on corticosteroid and COVID-19. The results of RCTs demonstrated that corticosteroid use had little survival benefits, but its use lowered the need for MV without significantly increasing the serious adverse events. Additionally, the OS analysis showed that the pulse dose and methylprednisolone use caused a significant decrease in mortality.

There are no specific effective drugs to treat COVID-19 at present. The genes of COVID-19 and SARS-CoV-2 viruses are homologous, and the patients infected with these two viruses exhibit similar clinical features. Corticosteroids were widely used in severe SARS because of their pathological changes, such as structural destruction of alveoli and mucus exudation, similar to acute respiratory distress syndrome (ARDS) [6, 70]. However, it must be noted that besides their strong anti-inflammatory effect and activity, corticosteroids can also damage the body's resistance and lead to adverse reactions such as the spread of infection. A systematic review of SARS-CoV patients found that the use of corticosteroids may cause severe adverse effects and even possible harm [71]. Also, corticosteroids treatment does not significantly reduce critically ill MERS patients' mortality [72, 73]. The SARS-CoV's primary immune escape strategy lies in inhibiting the corticosteroid stress response of its host. Corticosteroid therapy provides the required amount of corticosteroid necessary for fighting infection to improve prognosis [74]. Corticosteroids also downregulate the production of pro-inflammatory lymphokines, leading to improvements in SARS-CoV infection prognosis [75]. This difference may be due to the different pathogenic mechanisms of the three viruses: SARS-CoV and SARS-CoV-2 mainly infect humans using angiotensin-converting enzyme 2 (ACE2) as a receptor [76, 77], while MERS-CoV uses dipeptidyl peptide 4 (DPP4) [78, 79]. These mechanisms may lead to differences in benefits among the three viral infections treated with glucocorticoid. Earlier studies on the efficacy and safety of corticosteroid therapy in severe pneumonia [80] indicated a significant association between corticosteroid use and ARDS-risk reduction, the hospital- and ICU stay-length, but did not reduce the 28-day mortality of septic shock [81]. Nevertheless, the use of corticosteroids for treating COVID-19 patients remains controversial. In early April 2020, meta-analysis studies [82, 83] highlighted the limited effect of corticosteroids on COVID-19 patients, but they included only retrospective observational studies. Another review published in Lancet did not recommend corticosteroid use in COVID-19 patients [84]. However, three recent high-quality meta-analyses [13, 85, 86] included RCTs and have shown a significant mortality advantage in corticosteroid-treated COVID-19 patients, in particular severely ill COVID-19 patients. The *Guidelines on the Management of Critically Ill Adults with COVID-19* recommends against the routine application of systemic corticosteroids (weak recommendation, low-quality evidence) in COVID-19 infected patients with respiratory failure (without ARDS), but suggests using systemic corticosteroids (weak recommendation, low-quality evidence) in COVID-19 infected patients with ARDS [87] .

This meta-analysis had several advantages. The study included the largest number of published RCTs and OS, including manually searched meta-analysis and unpublished literature, available to date. The study included the most recent meta-analysis based on six RCTs and the observation that corticosteroids administration could lower 28-day mortality in critically ill COVID-19 patients [13]. Therefore, our study had the most comprehensive inclusion of articles. The GRADE and NOS were performed to assess the evidence quality and bias risk. We included 46 OS, consisting of varying COVID-19 severities, to avoid any selection bias. The sensitivity analysis validated the study results to be robust and reliable and suggested that corticosteroids might be more suitable for severe COVID-19 patients.

The study had a few limitations. Only 11 RCTs were included in this study, even though we searched all relevant literature; however, the enrolled sample size of 7,893 COVID-19 patients was quite large. Our result was limited by high heterogeneity, possibly due to very few original studies that could determine the source of heterogeneity. The included COVID-19 patients may have individual differences and different genotypes, and therefore larger sample studies are needed to verify. However, the GRADE assessment showed that our conclusions were 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. However, corticosteroid administration might have very little effect on the survival of COVID-19 patients. Additionally, the study also concluded that the pulse dose of methylprednisolone might have the potential for COVID-19 treatment.

Declarations

Consent for publication

Not applicable.

Author Contributions

All the authors contributed substantially to the work presented in this article. TWS and 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.

Availability of Data and Materials

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

Ethical Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Tables

Table 1. A summary of included RCTs studies.

Study	Period of inclusion	Sample size	Critical or severe	Cor type and daily dose	Disease severity Mean (SD) (Cor/ Non- Cor use)	Cor use No. (deaths)	Non- Cor use No. (deaths)	Follow up	Adjusted OR (95% CI)	MV No. (Cor/ Non- Cor use)	Adver events No. (Cor/ Non- Cor use)
Angus 2020	2020/3/9-2020/6/17	379	severe	IV Hy, 50 mg, every 6 hours × 7 d; while in shock for up to 28 days; fixed-dose of 100 mg every 6 hours × 7 d (2 patients)	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
Dequin 2020	2020/3/7-2020/6/1	149	critical	IV Hy at an initial dose of 200mg/d; continued at 200mg/d × 7d and then decreased to 100 mg/d × 4 d and 50 mg/d × 3 d, for a total of 14 d. If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200mg/d × 4 d, followed by 100mg/d ×2 d and then 50 mg/d × the next 2 d, for a total of 8 d.	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
Edalatifard 2020	2020/4/20-2020/6/20	62	NA	24-48 hours after hospitalization receive Me pulse (IV injection, 250mg/d × 3 d).		34(2)	28(12)	in-hospital	0.293(0.154-0.556)		2/2
Horby 2020	2020/5/9-2020/6/8	6425	NA	oral or IV De (6 mg/d) × 10 d (or until hospital discharge if sooner)		2104(482)	4321(1110)	28-day	0.83(0.75-0.93)	95/283	
Jamaati 2021	2020/3	50	NA	IV De 20 mg/d from day 1–5 and then at 10 mg/d from day 6–10		25(16)	25(10)	28-day	2.68(0.85-8.37)	13/11	

Jeronimo 2020	2020/4/18-2020/6/16	647	NA	IV Me (0.5 mg/kg), twice daily× 5 d	PaO_2:FiO_2 160 (118-200)/ 156 (120-227)	194(72)	199(76)	28-day	1.14(0.76-1.71)	53/57	
Tang 2021	2020/2/14-2020/3/31	86	NA	1 mg/kg/d of IV Me ×7 d	SOFA 2 (1–2) /1 (0–2)	43(0)	43(1)	in-hospital	0.977 (0.933–1.023)		
Tomazini 2020	2020/4/17-2020/6/13	299	NA	IV De 20 mg/d × 5 d, followed by 10 mg/d for additional 5 days or until ICU discharge	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
COVID STEROID		29		IV Hy 200 mg/d ×7 d (continuous or bolus dosing every 6 h)	SOFA 9 (7-10.5) /8 (7-11)	15(6)	14(2)	28-day	4(0.65-24.66)		1/0
Steroids-SARI		47		40 mg IV Me every 12h × 5 d		24(13)	23(13)	28-day	0.91(0.29-2.87)		23/23
DEXA-COVID 19		19		20 mg/d IV De × 5 d and then 10 mg/d × 5 d		7 (2)	12(2)	28-day	2(0.21-18.69)		3/11

Abbreviations:

Figures

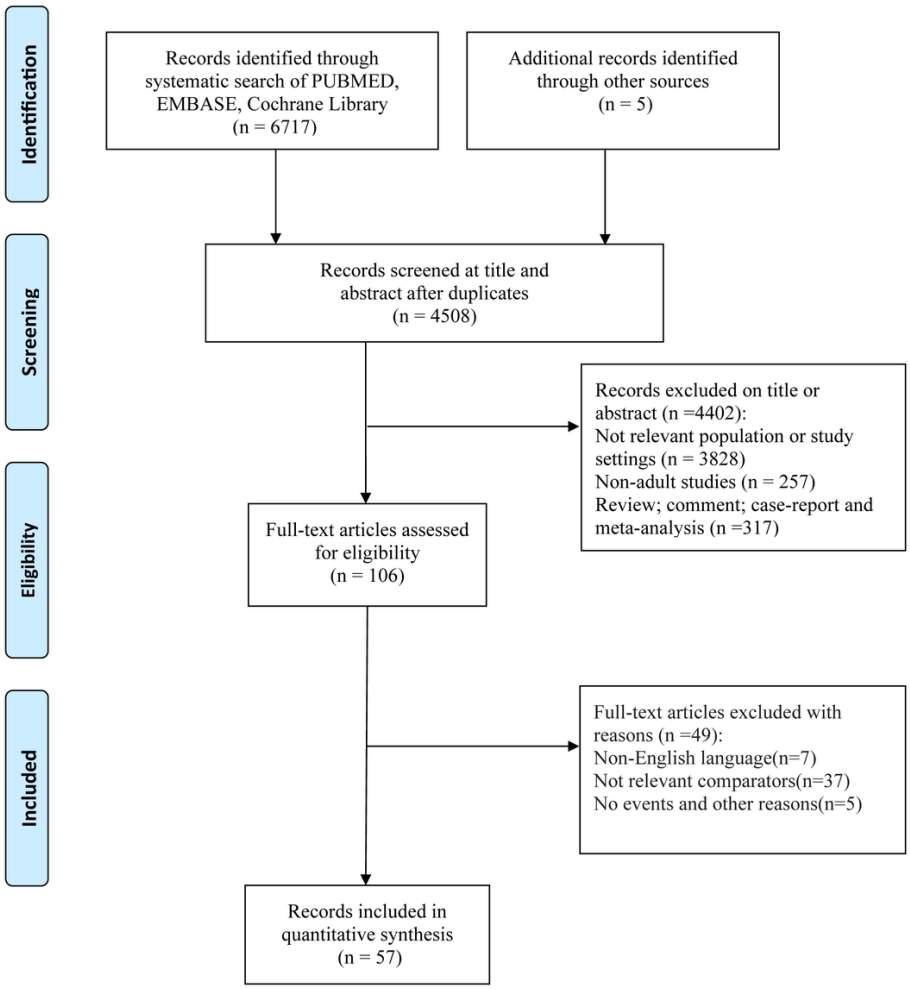

Figure 1

The flow-process diagram of the study selection.

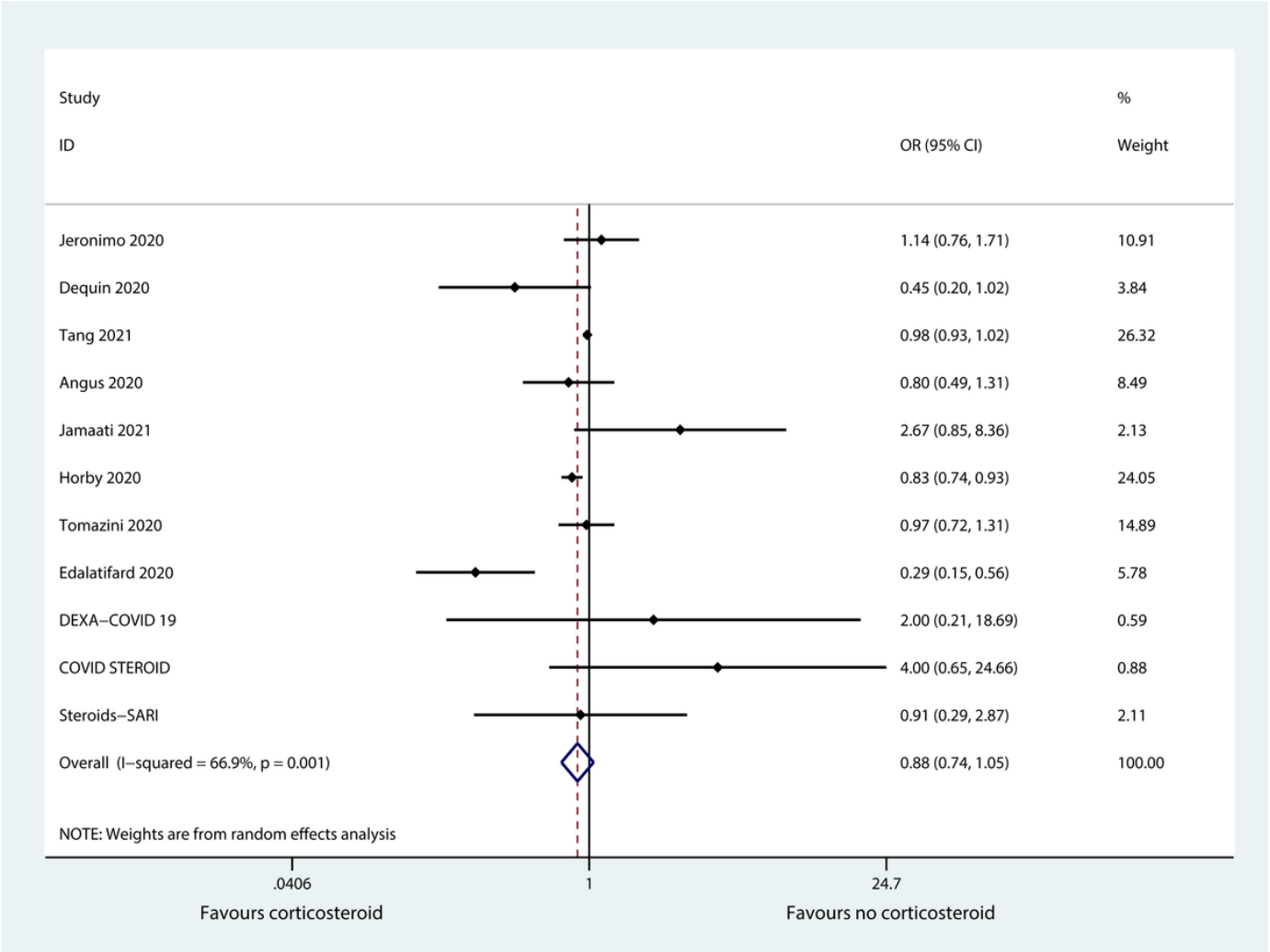

Figure 2

A forest plot showing the association between corticosteroid use and COVID-19 mortality in RCTs using the random-effects model.

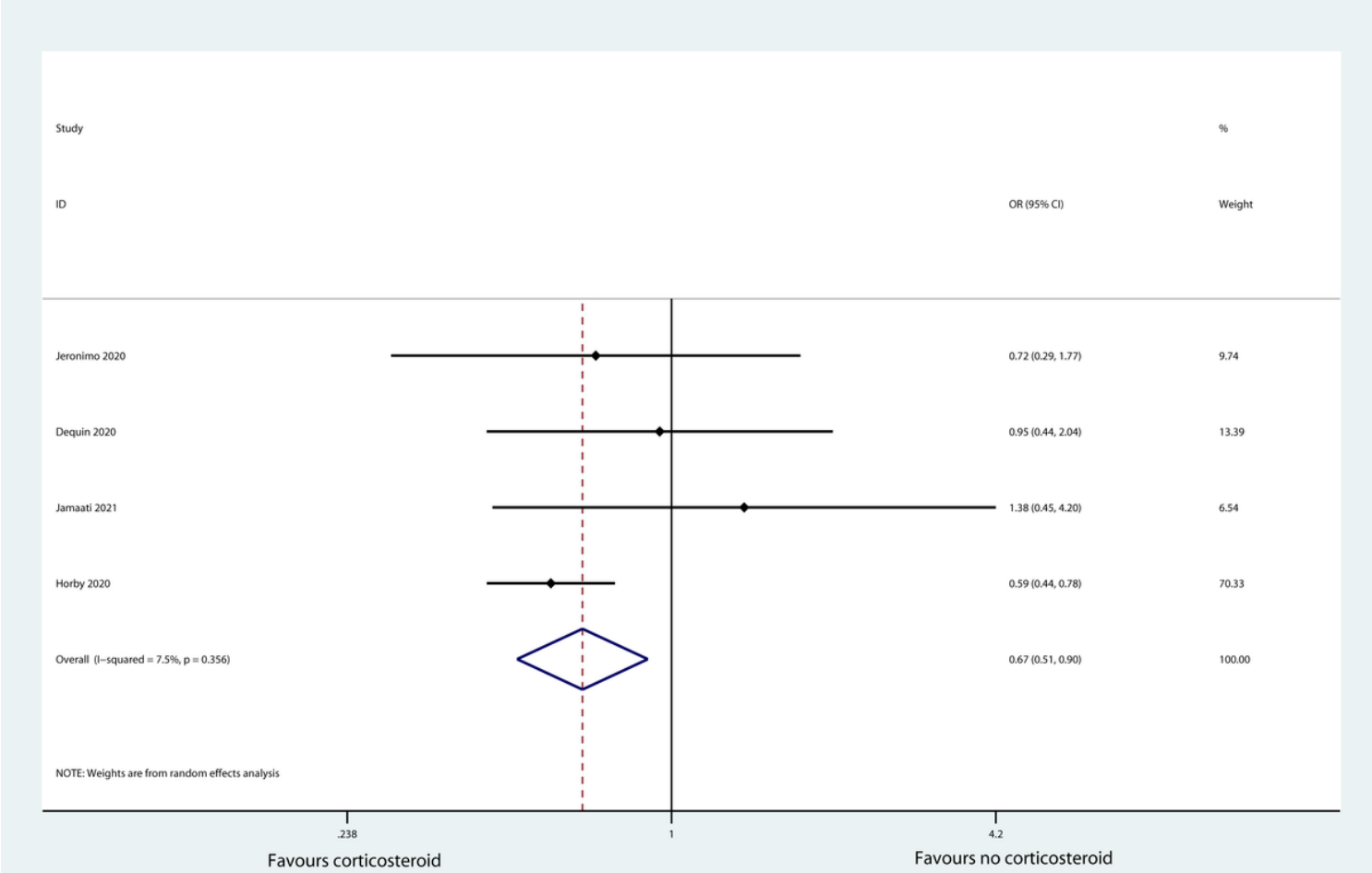

Figure 3

A forest plot showing the association between corticosteroid use and the need for MV in RCTs using the random-effects model.

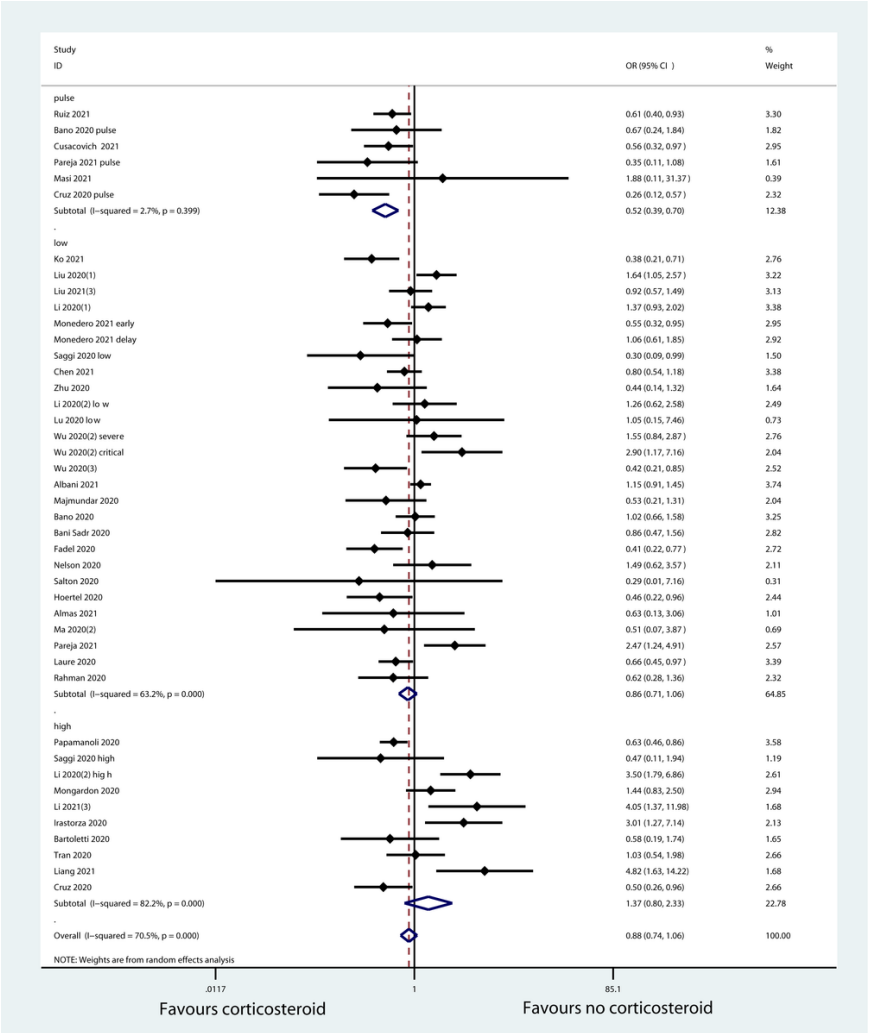

Figure 4

A forest plot showing the association between low, high, or pulse dose corticosteroid use and COVID-19 mortality in OS using the random-effects model.

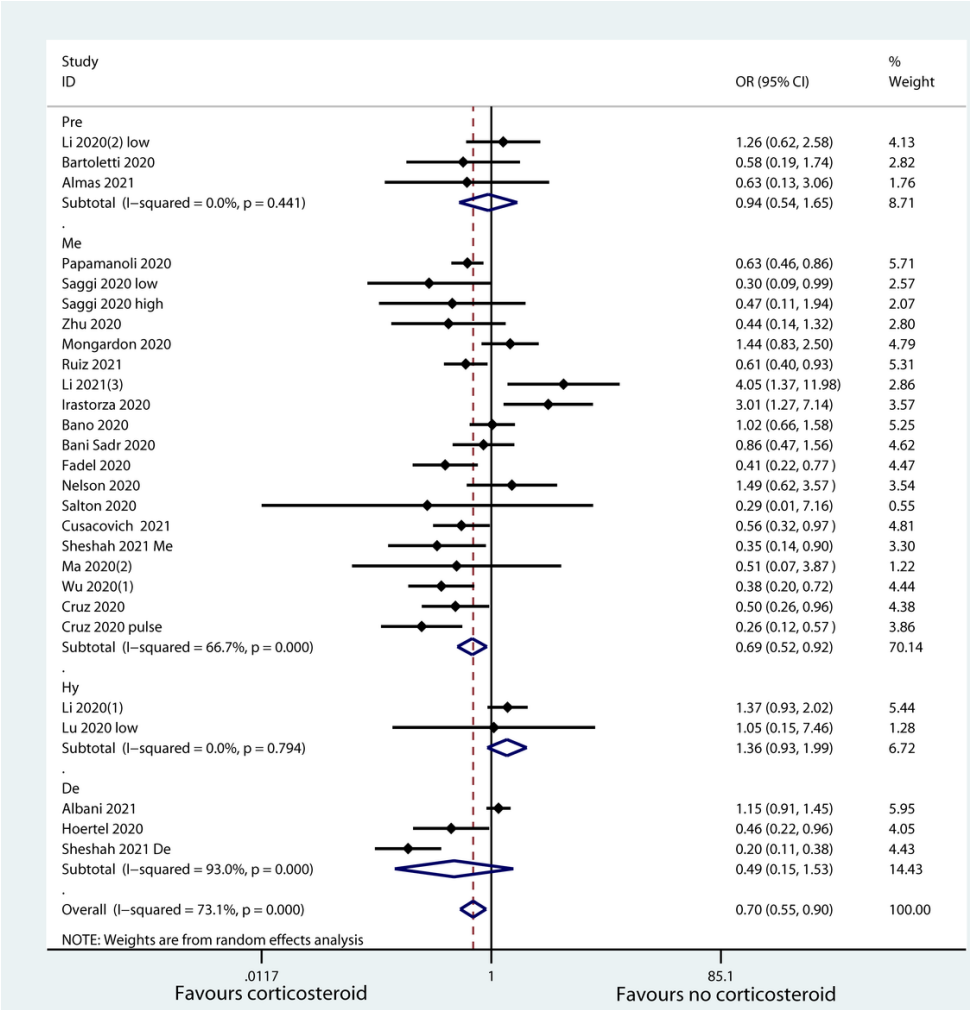

Figure 5

A forest plot showing the association between different types of corticosteroid use and COVID-19 mortality in OS using the random-effects model.

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