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META-ANALYSIS

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Effects of different corticosteroid therapy on severe COVID-19 patients: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: To assess the efficacy and safety of corticosteroids in COVID-19 patients compared with standard care or placebo.

Methods: Electronic databases were searched to identify relevant studies. The mortality, adverse events, and other data from studies were pooled for statistical analysis.

Results: Ten randomized clinical trials were eligible for inclusion. Corticosteroid treatment in COVID-19 patients did not significantly reduce the risk of death (RR: 0.93; CI: 0.82, 1.05) and the need for mechanical ventilation (RR: 0.82; CI: 0.62, 1.08). No mortality reduction was also observed in the subgroup of patients requiring mechanical ventilation (RR: 0.90; CI: 0.79–1.03). The use of corticosteroids increased mortality in the subgroup of patients not requiring oxygen support (RR: 1.24; CI: 1.00–1.55). The survival benefit was observed in a low dosage of corticosteroids (RR: 0.90; CI: 0.84–0.97) and dexamethasone (RR: 0.90; 95% CI: 0.79–1.04). There was no difference in the rates of adverse events (RR: 1.13; CI: 0.58, 2.20) and secondary infections (RR: 0.87; CI: 0.66, 1.15).

Conclusion: Corticosteroid treatment did not convincingly improve survival in severe COVID-19 patients. Low-dose dexamethasone could be considered as a drug for the treatment of COVID-19 patients. More high-quality trials are needed to further verify this conclusion.

Expert Opinion: The effect of corticosteroids on patient survival highly depended on the selection of the right dosage and type and in a specific subgroup of patients. This meta-analysis, which included more RCTs, evaluated the safety and efficacy in severe COVID-19 patients and analyzed the effects of different types of corticosteroid treatments. Corticosteroid treatment did not convincingly improve survival in severe COVID-19 patients. But the low dose dexamethasone appear to have a role in the management of severe COVID-19 patients.

1. Introduction

Since December 2019, coronavirus disease 2019 (COVID-19), a novel infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has affected the world [1,2]. Severe pulmonary or extrapulmonary symptoms and even death may present in different populations [3,4]. Up to July 2021, the SARS-COV-2 pandemic had resulted in approximately 4 million deaths worldwide [5], and the number is still rising. Nevertheless, there is currently no definitive and effective antiviral treatment for COVID-19 [6]. Therefore, it is of utmost urgency to determine drug treatment plans to address this severe disease.

Corticosteroids have been confirmed to have an excellent inhibitory effect on the expression of cytokines involved in the inflammatory response and are used as adjuvant drugs to treat viral pneumonia [7,8]. However, the value of corticoids in the treatment of COVID-19 has been widely

debated with conflicting results [9–11]. Several trials have revealed that COVID-19 patients treated with corticosteroids had lower all-cause mortality than those not treated with corticosteroids [12,13]. Meanwhile, other randomized controlled trials (RCTs) showed no significant difference in all-cause mortality between COVID-19 patients treated with corticosteroids and those not treated with corticosteroids [10,14]. Previous meta-analyses mainly focused on the association between corticosteroids and COVID-19, and few of them explored the dose, the type of corticosteroids, and the disease severity of patients. In addition, most of the studies included in previous meta-analyses were retrospective or observational studies, or fewer RCTs, which provide low evidence grades to draw a scientific conclusion on the systemic use of corticosteroids in COVID-19 patients [15]. Our meta-analysis, which included more RCTs, aimed to evaluate the safety and efficacy in severe COVID-19 patients

to provide a high level of evidence for clinical decision-making in treating severe COVID-19 patients.

2. Methods

This study-level systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The PROSPERO registration ID is CRD42021229507.

2.1. Search strategy

An extensive search was conducted from December 2019 to 15 July 2021, in PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wan Fang Data without language restriction. The search terms were 'COVID-19', '2019 novel coronavirus disease', 'SARS-CoV-2 infection', 'COVID-19 virus disease', '2019 novel coronavirus infection', '2019-nCoV infection', 'coronavirus disease 2019', '2019-nCoV disease', 'corticosteroids', 'steroids', 'prednisolone', 'prednisone', 'dexamethasone', 'cortisol', 'hydrocortisone', 'glucocorticoid', 'methylprednisolone'. The reference lists from trials, review articles, and reports were also screened to identify additional eligible studies. The clinicaltrials.gov website was searched for RCTs that were also registered as completed but not yet published.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1)age>18 years; (2) hospitalized patients diagnosed with COVID-19; (3) patients treated with corticosteroids; (4) RCTs; (5) patients with SpO_2 ≤ 94% at room air or the use of supplementary oxygen or mechanical ventilation; and (6) all languages available. The exclusion criteria were as follows: (1) lack of placebo or control group; (2) studies with missing data or outliers; (3) lack of dose control group or no fixed-dose strategery; and (4) repeated publication of literature or research using similar data.

2.3. Outcomes

The primary outcomes of this study included mortality and adverse events. The secondary outcomes included the need for invasive mechanical ventilation (for patients not intubated at inclusion) and secondary infections.

2.4. Data extraction

The two authors (Jiayuan T and Tian X) who screened studies according to the inclusion and exclusion criteria also independently extracted data from the included studies. Any differences were resolved by a third reviewer (Yun Liu) or by consensus. The extracted information included the first author, study design, median age, sex, intervention (including the type and dosage of corticosteroids), control, primary outcomes, and secondary outcomes.

2.5. Quality assessment

Two other reviewers independently assessed the quality of the RCTs with the Cochrane risk of bias tool, which contains seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias [17]. A third reviewer arbitrated any disagreements.

2.6. Statistical analysis

The data were analyzed using Review Manager 5.4. We derived risk ratios (RRs) and their 95% confidence intervals (CIs) for dichotomous outcomes. Depending on the presence of statistical heterogeneity, we used either fixed-effect or random-effects models. We quantified inconsistencies in associations among the trials using the I^2 statistic and derived P values for heterogeneity using the Cochran Q statistic. $P < 0.05$ was considered statistically significant. Sensitivity analysis was conducted to assess the stability of the combined results.

3. Results

3.1. Study selection and characteristics

A total of 1647 articles were identified by searching the electronic databases. After the duplicates were removed, 1058 articles remained. A total of 573 articles were excluded after the title and abstract screening. After assessing the remaining 16 articles, six were excluded because they either did not report corticosteroid treatment or were not RCTs. Finally, 10 articles were included (Figure 1) [10,11,14,18–24].

The main characteristics of the included studies are shown in Table 1. The studies originated from Brazil, Iran, the United Kingdom, China, Spain, and France with international cooperation, with varied sample sizes ranging from 50 to 6425 patients. The median ages of the patients in the enrolled studies ranged from 54 to 73 years, and the patients were predominantly male (46.5% to 72%). Clinical heterogeneity is mainly due to inclusion criteria, mechanical ventilation, type of corticosteroid, dosage and duration of administration, accompanying antiviral or anti-inflammatory drugs.

3.2. Risk of bias

The risk of bias was assessed in all ten trials: 9 were deemed to have a moderate risk of bias [11,14,18–24], and 1 was deemed to have a low risk of bias [10]. Three trials were double-blind, randomized clinical trials [10,14,22], 3 trial was single-blinded [19,23,24], and 4 trials were open-label [11,18,20,21]. There was no evidence of reporting bias. The risk of bias for the studies is shown in Figure 2.

3.3. Outcomes

3.3.1. Mortality

A total of 12,473 participants in 10 studies were included in our meta-analysis [10,11,14,18–24]. A total of 1135 of 4354
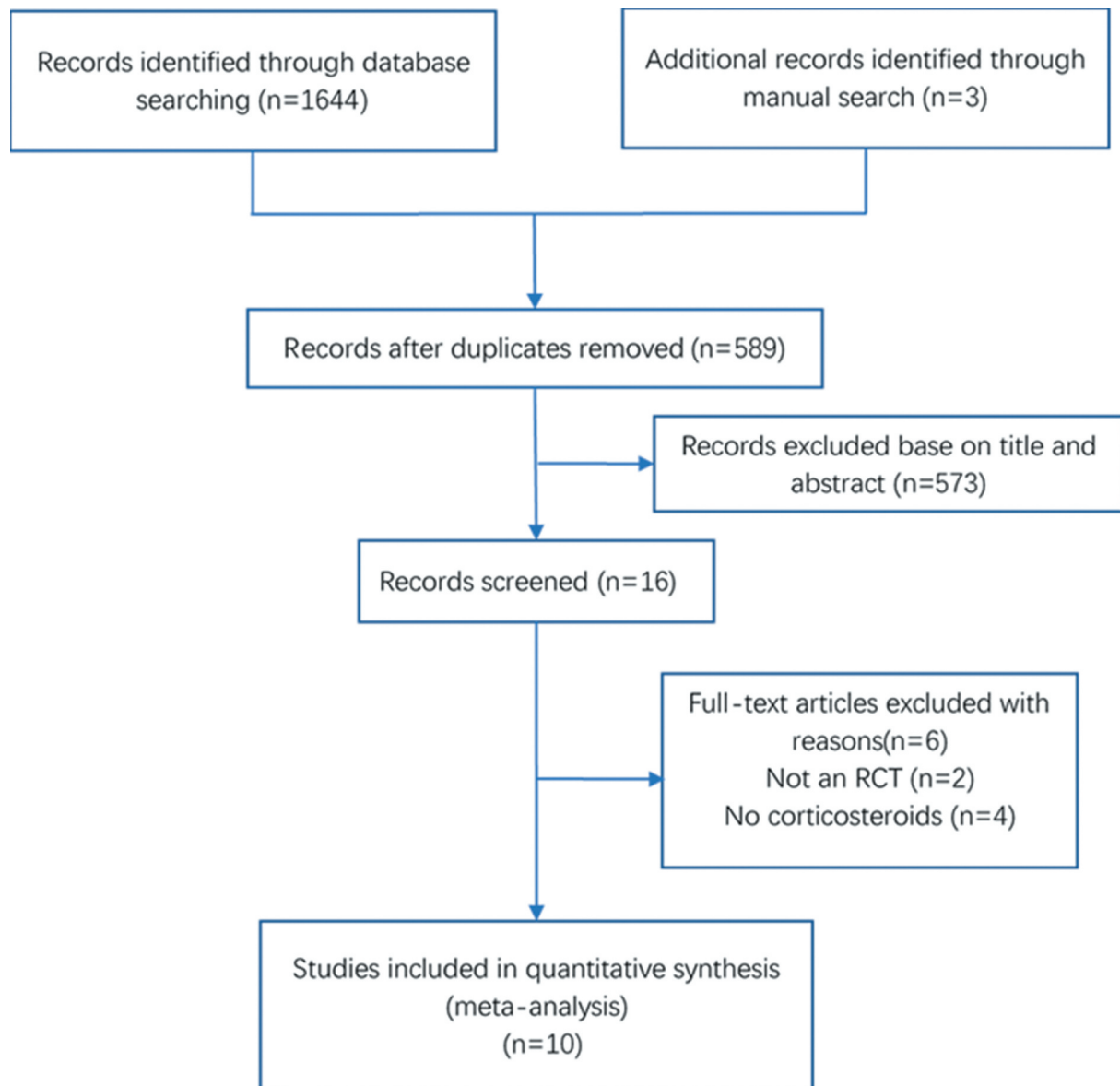
Figure 1. Flow diagram of the selection of studies for systematic review and meta-analysis.

patients died in the corticosteroid treatment group, and 2153 of 8119 patients died in the usual care or placebo group, which showed that corticosteroid did not significantly reduce the risk of death (RR: 0.93; CI: 0.82, 1.05; P = 0.26; I^2 = 52%, Figure 3). To address the heterogeneity, we conducted subgroup analyses. No reduction in mortality also was observed in the subgroup of patients who required mechanical ventilation (355 of 815 [43.6%] in the corticosteroids group vs. 657 of 1441 [45.6%] in the control group, RR: 0.90; CI: 0.79–1.03; P = 0.13, I^2 = 56%, Figure 4). However, the use of corticosteroids increased mortality in the subgroup of patients who do not require oxygen support, with results confirmed at sensitivity analyses (RR: 1.24; 95% CI: 1.00–1.55; P = 0.05; I^2 = 0%, Figure 4). The benefit was observed in a low dosage of corticosteroids (RR: 0.90; 95% CI: 0.84–0.97; P = 0.007; I^2 = 0%, Figure 5). Patients

treated with dexamethasone had a significantly lower risk of mortality(RR: 0.90; 95% CI: 0.79–1.04; P = 0.14; I^2 = 0%, Figure 5). No difference in mortality was found in the subgroups of hydrocortisone and methylprednisolone. However, these results were not stable, and if the RECOVERY trial was excluded [11], such survival benefit was absent.

3.3.2. Adverse events
A total of 3050 participants in 7 studies reported adverse events [10,18–21,23,24], including pulmonary embolism, edema, shock, intracranial hemorrhage, thrombocytopenia, ventricular tachycardia, and hypoglycemia, and so on. The incidence of adverse events was similar in both arms (7.0% vs 5.9%). There was no association between corticosteroids and adverse events (RR: 1.13; CI: 0.58, 2.20; P = 0.72; I^2 = 41%, Figure 6), with results confirmed at sensitivity analyses.

Table 1. Characteristics of included randomized clinical trials.

Study	Country	Patients, total n	Male sex n(%)	Age, years	Intervention	Control	Primary outcomes	Secondary outcomes
Corral-Gudino L, et al	Spain	64(35vs 29)	23(66) vs 16(55)	73 (11) vs 66 (12)	MP 40 mg bid for 3 Days and then 20 mg bid for 3 more days	Standard of care	All-cause mortality; escalation to ICU admission; progression of respiratory insufficiency that required noninvasive ventilation (NIV)	Adverse events; laboratory biomarkers; individual components of the composite endpoint
Dequin PF., et al	France	149(76vs 73)	54 (71.1) vs 50 (68.5)	63.1(51.5–70.8) vs 66.3 (53.5–72.7)	"continuous intravenous infusion of hydrocortisone at an initial dose of 200 mg/duntil day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days"	Placebo (saline)	Treatment failure on day 21, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy	The use of tracheal intubation (for patients not intubated at inclusion use of prone position; extracorporealmembrane oxygenation or inhaled nitric oxide; the PaO2:FIO2 ratio; nosocomial infections; adverse events
Edalatifard M., et al	Iranian	62(34 vs 28)	24 (70.6%) vs 15 (53 . 5%)	55.8 (16.35) vs 61.7 (16.62)	Standard care with methylprednisolone pulse (intravenous injection, 250 mg/day for 3 days)	Standard care alone	Discharge; mortality rate; time to improvement time; survival time	Clinical signs BORG score; Laboratory test results; Adverse events
Jamaati H, et al	Iran	50(25 vs 25)	18 (72%) vs 18 (72%)	62(14.07) vs 62 (10.37)	Intravenous dexamethasone at a dose of 20 mg/day from day 1–5 and then at 10 mg/day from day 6–10	Not receive dexamethasone treatment	The need for invasive mechanical ventilation and death rate	Duration of clinical improvement; length of hospital stay; and radiological changes in the computed tomography (CT) scan.
Jeronimo CMP., et al	Brazil	393(194 vs 199)	126 (64.9) vs 128 (64.3)	54(15) vs 57 (15)	Intravenous sodium succinate Methylprednisolone (0.5 mg/kg) twice daily for 5 days	Placebo (saline solution) twice daily for 5 days	28-day mortality	Early mortality (Days 7 and 14); the need for orotracheal intubation by Day 7; the proportion of patients with an oxygenation index (PaO2 /FiO2) < 100 by Day 7
RECOVERY	United Kingdom	6425 (2104 vs 4321)	1338 (64) vs 2749 (64)	66.9(15.4) vs 65.8(15)	The usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days (or until hospital discharge if sooner)	The usual standard of care alone	All-cause mortality within 28 days	The time until discharge from the hospital; patients not receiving invasive mechanical ventilation at the time of randomization subsequent receipt of invasive mechanical ventilation or death; cause-specific mortality

(Continued)

Table 1. (Continued).

| Study	Country	Patients, total n	Male sex n(%)	Age, years	Intervention	Control	Primary outcomes	Secondary outcomes
RECOVERY2	United Kingdom	4716 (1561 vs 3155)	960(61.5) vs 1974 (62.6)	65.2(15.2) vs 65.4 (15.4)	Patients received hydroxychloroquine sulfate in a loading dose of four tablets (total dose, 800 mg) at baseline and at 6 hours, which was followed by two tablets (total dose, 400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge	Usual care	all-Cause mortality within 28 days; further analyses were specified at 6 months	The time until discharge from the hospital and a composite of the initiation of invasive mechanical ventilation including extracorporeal membrane oxygenation or death among patients who were not receiving invasive mechanical ventilation at the time of randomization.
REMAP-CAP	Australia, Canada et al	238(137 vs 101)	98 (71.5) vs 72 (71.3)	60.4 (11.6) vs 59.9 (14.6)	A fixed dose of intravenous hydrocortisone, 50 mg, every 6 hours for 7 days.	No hydrocortisone	Respiratory and cardiovascular organ support–free days up to day 21; death	In-hospital mortality; ICU and hospital length of stay; respiratory support–free days; cardiovascular organ support–free days; a composite outcome of progression to invasive mechanical ventilation; extracorporeal membrane oxygenation (ECMO) or death among those not ventilated at baseline; the WHO ordinal scale; Adverse Events
Tang X, et al	China	86(43 vs 43)	21 (48.8) vs 20 (46.5)	57(13.33) vs 55(20)	1 mg/kg per day of methylprednisolone (produced by Pfizer Manufacturing Belgium NV) dissolved in 100 mL 0.9% normal saline was administered intravenously for 7 days	100 mL 0.9% normal saline	The incidence of clinical deterioration 14 days after randomization	The incidence of clinical cure 14 days; the incidence of intensive care unit (ICU) admission; in-hospital mortality; the time from randomization to clinical cure; the time from the onset to virus shedding of SARS-CoV-2 in respiratory tract samples; hospitalization duration; complications including blood glucose abnormal; stress ulcer; secondary infections.
Tomazini BM., et al	Brazil	299(151 vs 148)	90 (59.6) vs 97 (65.6)	60.1 (15.8) vs 62.7 (13.1)	Dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first, plus standard care.	Standard care only	Days alive and ventilator free at 28 d	6-Point ordinal scale at day 15; 28-Day results; SOFA score; Serious adverse events; a New diagnosis of infection until day 28; Ventilator-associated pneumonia; Catheter-related bloodstream infection; Catheter-associated urinary tract infections; Other Bacteremia Insulin use for hyperglycemia
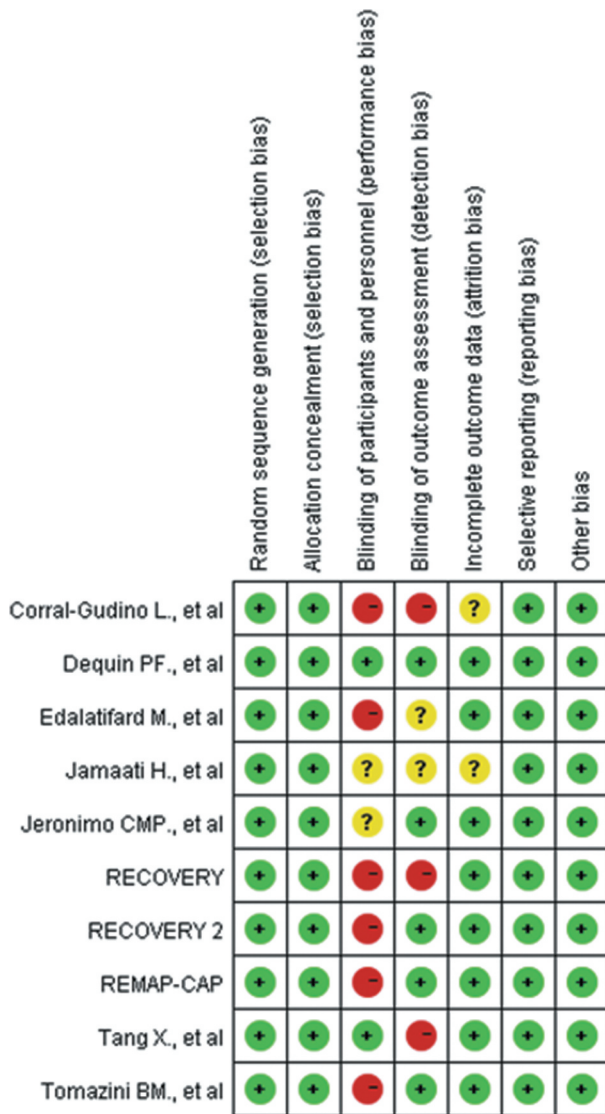
corticosteroid group and 595(9.2%) patients in the control group required subsequent mechanical ventilation. There was no significant between-group difference (RR: 0.82; CI: 0.62, 1.08; P = 0.16; I^2 = 71%, Figure 7). However, this result was not confirmed in the sensitivity analysis. If the RECOVERY2 trial excluded [24], there was a lower risk of the need for mechanical ventilation with corticosteroids in COVID-19 patients than with no corticosteroids or placebo treatment (RR: 0.74; CI: 0.58, 0.96; P = 0.02; I^2 = 43%).

3.3.4. Secondary infections
Four studies with 567 participants who reported secondary infection were included in this meta-analysis [10,19–21]. The incidence of nosocomial infections was similar in both arms (22.8% vs 26.7%), and no significant differences were found among the studies (RR: 0.87; CI: 0.66, 1.15; P = 0.32; I^2 = 0%, Figure 8). Sensitivity analysis showed that the result was stable.

4. Discussion

In this study, a meta-analysis of 10 randomized clinical trials with a total of 12,473 severe COVID-19 patients showed corticosteroids treatment did not significantly reduce mortality. However, the subgroup analysis found the survival benefit was observed in both patients treated with a low dosage of corticosteroids and patients treated with dexamethasone. No increased risk of the need for mechanical ventilation, adverse events, or secondary infections were found. However, due to the great heterogeneity between trials, clear conclusions remain a challenge.

COVID-19 is an emerging infectious disease, and there is currently no optimal treatment [8]. Based on its in vitro SARS-CoV-2 antiviral activity and data from observational researches that effectively reduce viral load, corticosteroids have been widely used in severe COVID-19 patients [24], Whether the efficacy of this strategy has been controversial. Several meta-analysis studies have evaluated the efficacy of corticosteroids in COVID-19 patients with inconsistent results. In a meta-analysis based on retrospective studies, Pei et al. [25] reported that corticosteroids treatment might increase the risk of death (OR: 2.43; 95% CI: 1.44–4.1; P = 0.0001). Another meta-analysis

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

3.3.3. Need for mechanical ventilation
Seven studies with 9771 participants were included in our meta-analysis [10,11,14.18,19,22,24]. 295(8.9%) patients in the
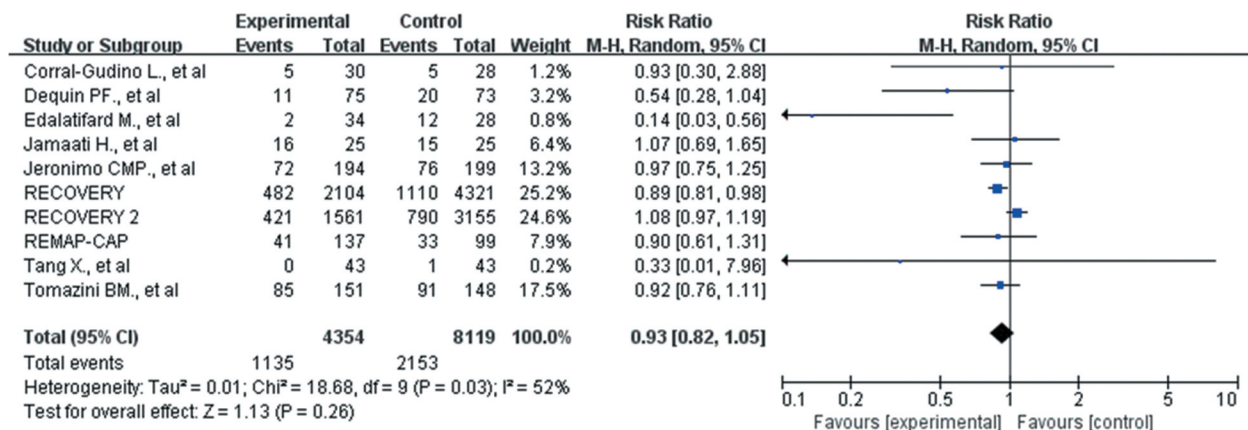
Figure 3. Forest plot of comparison: corticosteroids versus standard care or placebo, outcome: all-cause death.
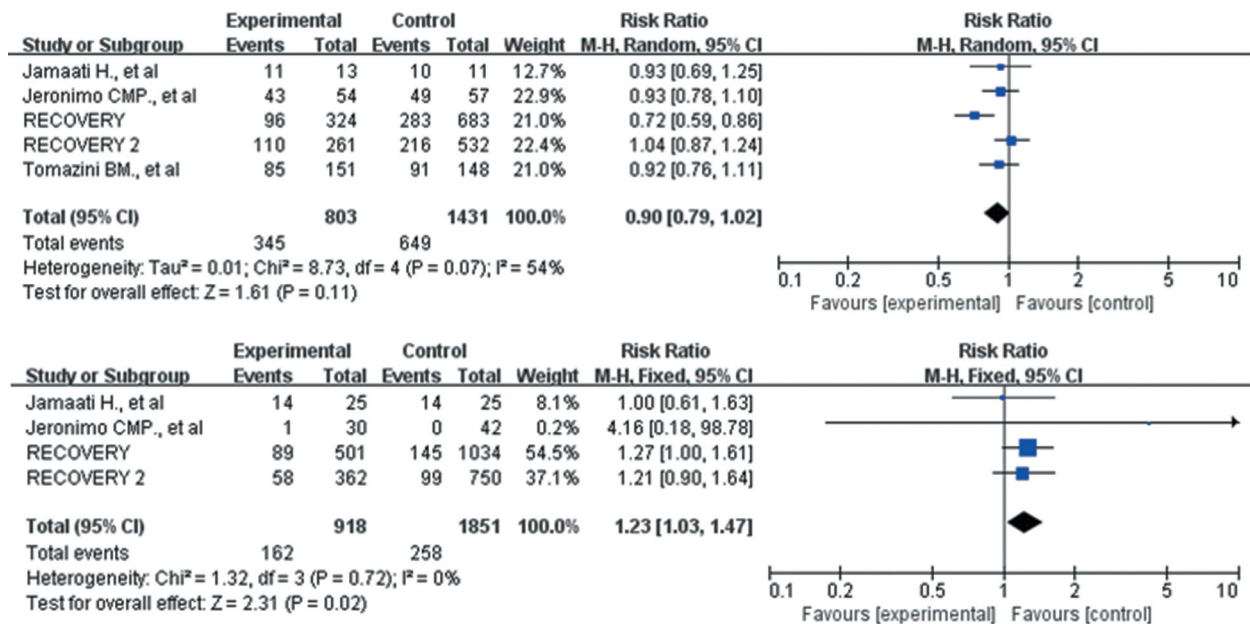
Figure 4. Forest plot of comparison: corticosteroids versus standard care or placebo, outcome: mortality in the subgroups of patients who required mechanical ventilation and patients who do not require oxygen support.
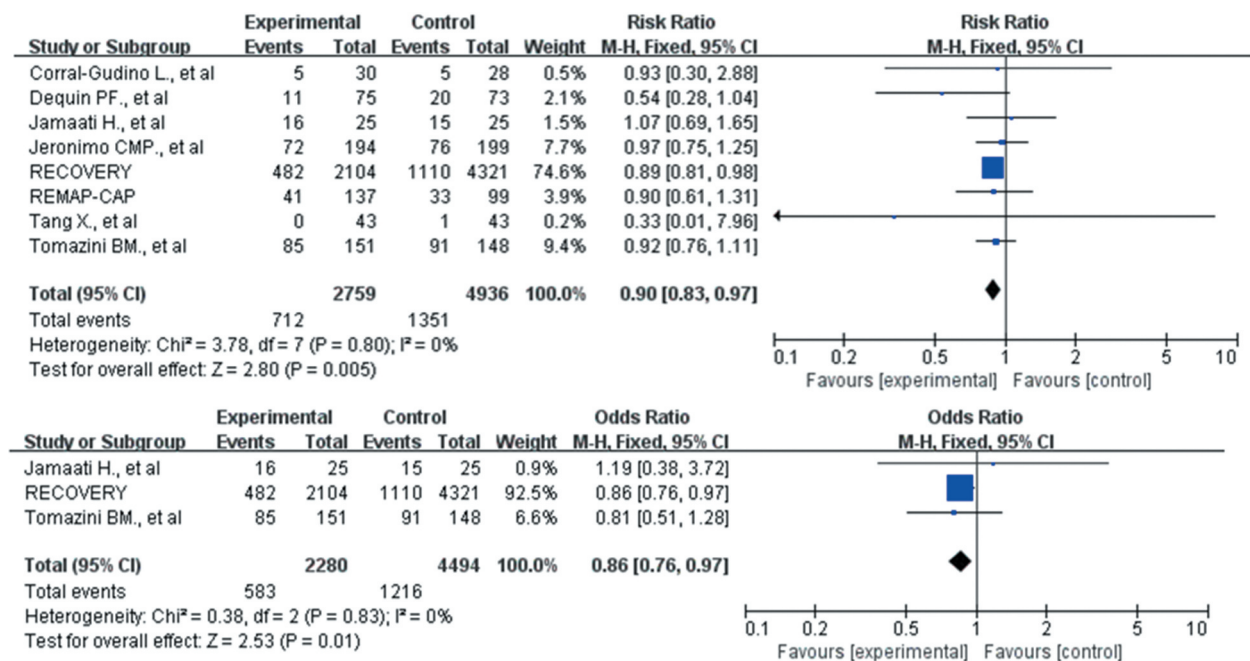

Figure 5. Forest plot of comparison: corticosteroids versus standard care or placebo, outcome: mortality in the subgroups of patients receiving low-dose corticosteroids and Patients treated with dexamethasone.

of cohort studies shared a similar conclusion that corticosteroids were ineffective in reducing mortality, shortening the duration of symptoms, or virus clearance time [26]. However, both of these meta-analyses include non-RCTs, which may be biased and reduce the quality of conclusions. Conversely, Some recent meta-analyses of RCTs showed a mortality benefit in severe COVID-19 patients treated with corticosteroids [27,28]. Our meta-analysis included more RCTs and reached

the different conclusions that 1135 (26.2%) patients died in the corticosteroid treatment group, 2153 (26.5%) patients died in the usual care or placebo group, corticosteroids did not significantly reduce the risk of death. But due to the different inclusion criteria, type of corticosteroid, dosage, this conclusion had great heterogeneity.

The effect of corticosteroids on patient survival highly depended on the selection of the right dosage and type
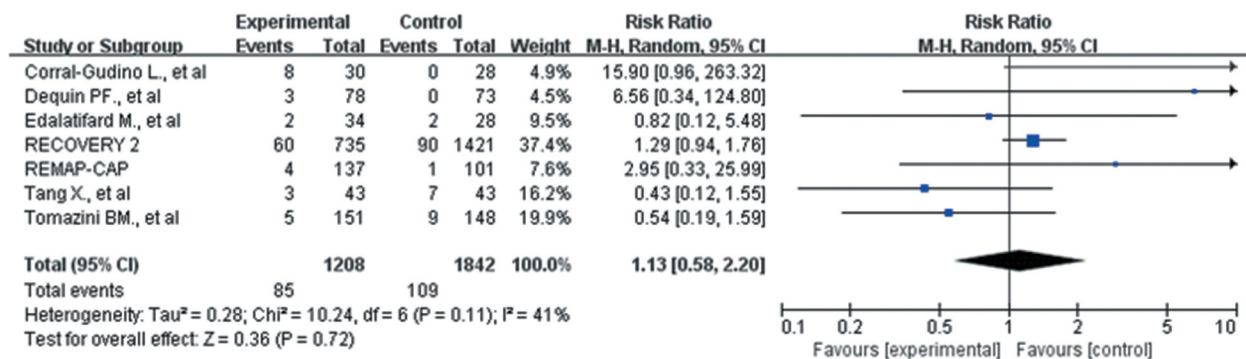
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Corral-Gudino L., et al	8	30	0	28	4.9%	15.90 [0.96, 263.32]
Dequin PF., et al	3	78	0	73	4.5%	6.56 [0.34, 124.80]
Edalatifard M., et al	2	34	2	28	9.5%	0.82 [0.12, 5.48]
RECOVERY 2	60	735	90	1421	37.4%	1.29 [0.94, 1.76]
REMAP-CAP	4	137	1	101	7.6%	2.95 [0.33, 25.99]
Tang X., et al	3	43	7	43	16.2%	0.43 [0.12, 1.55]
Tomazini BM., et al	5	151	9	148	19.9%	0.54 [0.19, 1.59]
Total (95% CI)		1208		1842	100.0%	1.13 [0.58, 2.20]
Total events	85		109			

Heterogeneity: Tau² = 0.28; Chi² = 10.24, df = 6 (P = 0.11); I² = 41%
Test for overall effect: Z = 0.36 (P = 0.72)

Figure 6. Forest plot of comparison: corticosteroids versus standard care or placebo, outcome: adverse events.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dequin PF., et al	8	16	12	16	12.1%	0.67 [0.38, 1.17]
Edalatifard M., et al	3	34	9	28	4.4%	0.27 [0.08, 0.92]
Jamaati H., et al	13	25	11	25	11.8%	1.18 [0.66, 2.11]
Jeronimo CMP., et al	18	93	16	95	11.2%	1.15 [0.62, 2.11]
RECOVERY	102	1780	285	3638	21.1%	0.73 [0.59, 0.91]
RECOVERY 2	128	1300	225	2623	21.4%	1.15 [0.93, 1.41]
REMAP-CAP	23	50	37	48	17.9%	0.60 [0.43, 0.84]
Total (95% CI)		3298		6473	100.0%	0.82 [0.62, 1.08]
Total events	295		595			

Heterogeneity: Tau² = 0.08; Chi² = 20.42, df = 6 (P = 0.002); I² = 71%
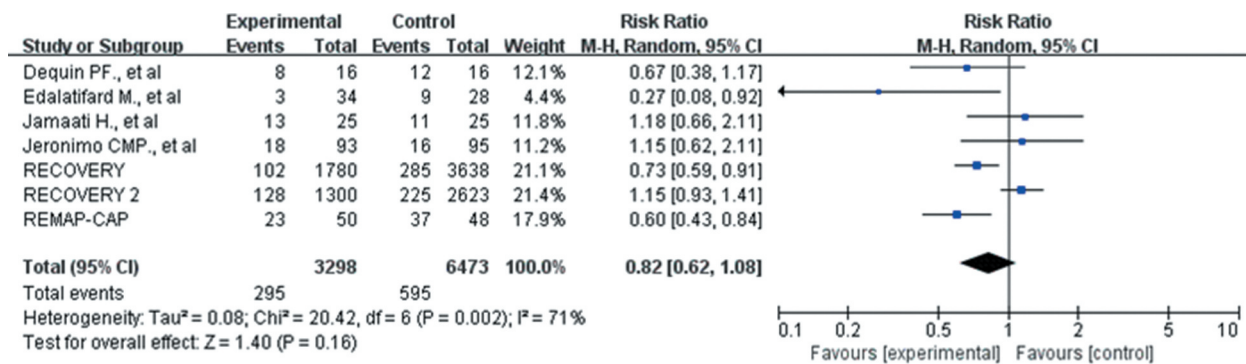Test for overall effect: Z = 1.40 (P = 0.16)

Figure 7. Forest plot of comparison: corticosteroids versus standard care or placebo, outcome: invasive mechanical ventilation.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corral-Gudino L., et al	4	30	1	28	1.4%	3.73 [0.44, 31.41]
Dequin PF., et al	28	75	30	73	40.3%	0.91 [0.61, 1.36]
Edalatifard M., et al	1	34	0	28	0.7%	2.49 [0.11, 58.74]
Tomazini BM., et al	33	151	43	148	57.6%	0.75 [0.51, 1.11]
Total (95% CI)		290		277	100.0%	0.87 [0.66, 1.15]
Total events	66		74			

Heterogeneity: Chi² = 2.79, df = 3 (P = 0.43); I² = 0%
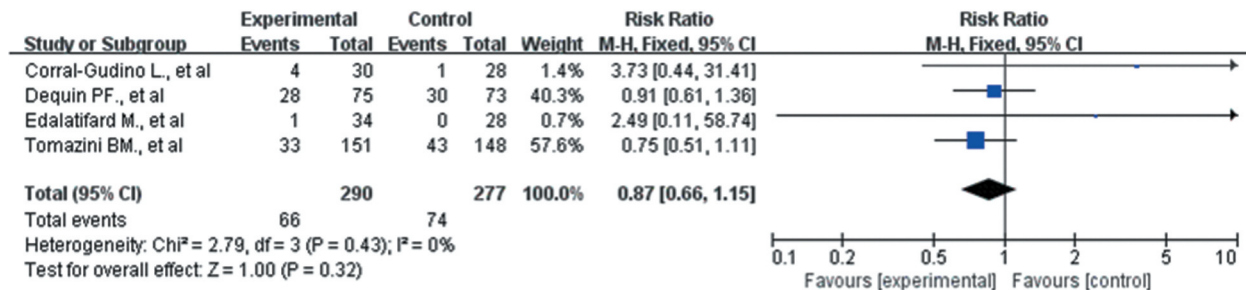Test for overall effect: Z = 1.00 (P = 0.32)

Figure 8. Forest plot of comparison: corticosteroids versus standard care or placebo, outcome: secondary infections.

and in a specific subgroup of patients [27]. Pasin et al. [29] found a reduction in mortality was observed in the subgroup of patients who required mechanical ventilation. It was recommended that severe patients could consider corticosteroids therapy. In our meta-analysis, the survival benefit of corticosteroid therapy was not observed in the subgroup of patients requiring mechanical ventilation. Evidence was mainly obtained from 5 trials, of which four trials showed no survival benefit [14,20,22,24]. One trial indicated that the use of dexamethasone reduced the 28-day mortality among those receiving either mechanical ventilation or oxygen alone [11]. Remarkably, our study found patients who have not received oxygen had a trend toward increased mortality when using corticosteroids. Jeronimo et al. [14] proposed a possible explanation that early use of corticosteroids in COVID-19 patients could lead to an increase in viral load, which needs to be confirmed by further studies. Therefore, caution is needed in the use of corticosteroids in mild subjects not receiving oxygen therapy. In addition, Patients over 60 years old receiving corticosteroids therapy had a lower mortality rate, while patients under 60 years old had a higher mortality rate [14]. However, Corral-Gudino et al. [21] found no evidence of interaction between treatment and patient age; corticosteroids have similar beneficial effects in the treatment of young and old patients.

Subgroup analyses of different dosages and types of corticosteroids were performed in our meta-analysis. The survival benefit was observed in a low dosage of corticosteroids but not in high-dose corticosteroids. Similar to Ma et al.'s findings [27]. 8 studies used low-dose corticosteroids (25–150 mg/d, methylprednisolone) and 2 studies used high-dose corticosteroids(>150 mg/d, methylprednisolone) [30]. Edalatifard et al. [19] used a higher dose of

methylprednisolone(250 mg/d), and the results suggest it could be an efficient therapeutic agent for COVID-19 patients. On the contrary, Horby et al. [24] used 1200 mg/d hydroxychloroquine (equivalent dose was 240 mg/d methylprednisolone), and results suggest it had a longer duration of hospitalization and a higher risk of invasive mechanical ventilation or death. In previous research, the mortality rate was extremely high among COVID-19 patients treated with high-dose corticosteroids [31]. However, due to limited trials and great clinical heterogeneity, more data are required to elucidate the underlying clinical significance.

The survival benefit was also observed in treatment with dexamethasone. In our study, the main types of corticosteroids were hydrocortisone, dexamethasone, and methylprednisolone. No difference in mortality was found in the subgroups of hydrocortisone and methylprednisolone. A retrospective quasi-experimental study showed that dexamethasone is more effective in improving the PO2/FiO2 ratio of COVID-19 patients than methylprednisolone [32]. Another study also provided evidence that dexamethasone and betamethasone are effective for COVID-19 treatment because of their potential to inhibit the proteolytic activity of Mpro (a cysteine protease that plays a vital role in polyprotein processing and virus maturation) by comparing molecular docking studies of six corticosteroids (cortisone, hydrocortisone, prednisolone, methylprednisolone, betamethasone, and dexamethasone) and two repurposed drugs (darunavir and lopinavir) [33–36]. However, these survival benefits depended largely on the RECOVERY trial [11], which consisted of approximately 83.5% and 94.8%of the total number of patients in the analysis. if the RECOVERY trial excluded [11], these survival benefits were absent, more RCTs are needed in the future to draw definite conclusions.

The safety of corticosteroids in COVID-19 still is debated. Corticosteroid therapy attenuates the immune response, which increased the chance of infection and other adverse events [37]. In our study, seven studies reported the incidence rate of adverse events in COVID-19 patients (corticosteroid:7.0% vs control:5.9%) [10,18–21,23,24]. Four studies reported the incidence rate of nosocomial infections (corticosteroid:22.8% vs control:26.7%) [10,19–21]. There was no difference in the rates of adverse events and nosocomial infections between the corticosteroids group and the control group. One of 7 studies (GLUCOCOVID) showed that hyperglycemia (>180 mg/dl) was more frequent in the corticosteroid group in the ICU, with a significant difference [21]. Tomazini et al. [20] also reported unspecified hyperglycemia. Except for hyperglycemia, the incidence of adverse events was similar in either group. Similarly, a systematic review including peer-reviewed studies of any design reported that hyperglycemia was the most common adverse effect [38]. Therefore, when corticosteroids are used in clinical treatment, we need to pay more attention to blood sugar levels.

5. Limitations

The study has several limitations. First, only ten trials were included, and we were unable to obtain data for the ongoing unfinished studies, which may cause selection bias. Second, the presence of confounding variables (age, severity of disease, corticosteroids type, dosage, treatment duration, and so on) led to significant clinical heterogeneity and weakened the results of this meta-analysis. Therefore, the summary results need to be interpreted carefully. Third, the mortality rates in different periods were reported by multiple studies; 5 trials reported mortality at 28 days, 2 trials reported mortality at 21 days, 1 trial reported mortality at 14 days, and 1 trial did not mention the time of death, potentially leading to inconsistent experimental results. Fourth, Except for the RECOVERY trial and RECOVERY2 trial, most of the included studies have small sample sizes and may be biased. Small studies might have lower quality and a high risk of bias, which might contribute to the exaggerated intervention effects compared with large studies, so further exploration is needed [39,40].

6. Conclusions

In this meta-analysis of 10 RCTs and 12473 severe COVID-19 patients, pooled results suggested that corticosteroid therapy did not convincingly improve survival and reduce the need for mechanical ventilation in severe patients with COVID-19, and it is not recommended for patients who do not require oxygen support. A low dosage of dexamethasone could be considered as a drug for the treatment of COVID-19 patients. Due to significant clinical heterogeneity, more high-quality clinical trials are needed to further verify this conclusion.

Declaration of interest

Ethics approval and consent to participate

Not applicable. The PROSPERO registration ID is CRD42021229507.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JY. Tu and T Xie conducted the literature search and selected studies. XQ. Mo and XD. Zhang assessed the methodologic quality of the studies. J Xie, Y Liu, and XS. Chen extracted data. JY. Tun conceived and planned the review, assessed the methodologic quality of the studies, verified the data, and drafted and revised the manuscript. T Xie provided methodologic advice, content expertise, and revised the manuscript. All authors contributed to writing the protocol. All authors read and approved the final manuscript.

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