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Steroid therapy for COVID-19: A systematic review and meta-analysis of randomized controlled trials

Tarun Krishna Boppana, Saurabh Mittal, Karan Madan, Anant Mohan, Vijay Hadda, Pawan Tiwari, Randeep Guleria

Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Abstract

There is an urgent need for effective treatment modalities for coronavirus disease 2019 (COVID-19). Data for the use of steroids in COVID-19 is emerging. We conducted this systematic review and meta-analysis to estimate the effectiveness of steroid administration in mortality reduction due to COVID-19 compared to the control group. A systematic search of the PubMed and Embase databases was performed to extract randomized controlled trials (RCTs) regarding the use of steroid therapy for COVID-19. An overall and subgroup (based upon the type of steroid) pooled mortality analysis was performed, and odds ratios were reported. Cochrane risk of bias assessment tool was used to assess the risk of bias. Heterogeneity was assessed using the I^2 statistic. Six RCTs, including 7707 patients, were selected for review. Three trials reported 28-day mortality, and two trials reported 21-day mortality, and one trial reported in-hospital mortality. There were 730 deaths among 2837 participants in the steroid group while 1342 deaths among 4870 patients randomized to the control group (odds ratio 0.76, 95% confidence interval 0.58-1.00, p=0.05). The effect was significant in patients on oxygen or mechanical ventilation. There was no difference in the various preparations and doses of the steroids. There was heterogeneity among the trials as the I^2 value was 53%, with a p-value of 0.06. There was no indication of increased serious adverse events. This meta-analysis of RCTs demonstrated that the use of systemic corticosteroids is associated with a reduction in all-cause mortality in patients with COVID-19 on oxygen or mechanical ventilation.

Correspondence: Dr Saurabh Mittal, Assistant Professor, Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi 110029, India.
Tel. +91.11.26546346.
E-mail: saurabh_kgmu@yahoo.co.in; saurabh.aiims@aiims.edu

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Introduction

Coronavirus disease 2019 (COVID-19) has affected the world over the last year and is associated with significant morbidity and mortality [1]. The initial attempts for disease containment failed, and it has now affected almost all countries globally [2-4]. This disease has killed more humans in a short period than many other infectious diseases, and there has been differential spread to various parts of the world [5,6]. Since the onset of the pandemic, there have been attempts to find a remedy for this disease. The repurposing of drugs for COVID-19 is being tried. Almost all classes of drugs are under investigations, including antibiotics, antihelminthic, antivirals, and anti-inflammatory agents [7,8]. Certain other strategies such as awake proning are also being employed widely to improve hypoxemia in patients with COVID-19 [9-12]. To date, no definite medical management against COVID-19 is available; however, the Food and Drug Administration recently approved remdesivir for COVID-19 [13]. Steroid therapy has been tried for community-acquired pneumonia, and the evidence remains uncertain [14]. The use of steroids for COVID-19 also has been tried, and multiple randomized controlled trials (RCTs) and retrospective cohort studies are available [15-25]. There has been conflicting evidence, although most RCTs tend to show benefit while retrospective studies do not. Multiple meta-analyses of cohort studies have been conducted but are limited by a high risk of bias in the included studies [26]. The largest RCT available on this topic is the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial which demonstrated mortality benefit with the use of low-dose dexamethasone [15]. A recently published meta-analysis by the World Health Organisation (WHO) Rapid evidence Appraisal for COVID-19 Therapies (REACT) working group has demonstrated the mortality benefit of using systemic

steroids in critically ill patients with COVID-19 [27]. However, this meta-analysis included ongoing trials, and the number of patients was small. Since this meta-analysis, some RCTs have been completed, and a few others have also been published. Hence, we conducted this systematic review and meta-analysis to analyze the current evidence for the efficacy of systemic steroid therapy in reducing mortality in patients with COVID-19. There is also emerging evidence for the use of steroid therapy for post-COVID-19 sequelae, which is out of the scope of this review.

Methods

The report of this systematic review was made according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28].

Eligibility criteria

We included randomized controlled trials involving adults with COVID-19 wherein systemic steroids were used in comparison to placebo or usual care. We excluded all single-arm studies and non-randomised prospective and retrospective studies involving systemic as well as inhalational steroids. The mortality reporting was essential for the trial to be included in the meta-analysis.

Search strategy and initial review

Two authors (SM and TKB) performed a systematic search of the two databases PubMed and EMBASE to identify the original, peer-reviewed, full-length, human subject articles describing the use of steroids for the treatment of COVID-19. The following database-specific Boolean search strategy was used. Free text search terms were: (COVID OR coronavirus disease) AND ("steroid" OR "corticosteroid" OR "prednisolone" OR "prednisone" OR "dexamethasone" OR "methylprednisolone" OR "hydrocortisone" OR "deflazacort").

The study protocol was registered and made available on the PROSPERO database (CRD42020213300) on October 15th, 2020. The retrieved studies were imported into reference management software, and duplicate citations were removed. The initial screening of the studies was performed by title and abstract. Full texts of the articles were downloaded for review, wherever required. The reference lists of the extracted articles were also reviewed to look for potential studies. The finally selected studies were independently screened by two authors (SM and TKB). We included only original articles describing the results of a randomized controlled trial regarding steroids in COVID-19 and reporting mortality outcomes.

Data abstraction

Data from the finally selected studies were extracted on the data extraction form. The following information was retrieved after a thorough review of the full text – (a) author, (b) year, (c) number of patients, (d) sex, (e) study country, (f) age, (g) oxygenation status at randomization (h) proportion of patients on mechanical ventilation, (i) type of steroid (j) dose and duration of steroid k) mortality in each group l) any other secondary outcome as reported in the trial. The systematic review methodology is summarized in Figure 1.

The primary outcome analyzed was the mortality between the two groups. We also performed a subgroup analysis to assess the differences between different preparation and dose of steroids. The other outcomes assessed during the review were the duration of hospital stay and discharge rate at 28 days. Safety outcome included the incidence of serious adverse events.

Risk of bias assessment

We used the Cochrane Risk of Bias Assessment tool to assess the risk of bias in each trial (reported as low risk, high risk or unclear risk). The following criteria were used to assess the risk of bias: i) The generation of randomization sequence and allocation concealment; ii) blinding; iii) completeness of the data and reporting of outcomes. Two authors (SM and TKB) completed these assessments independently, and disagreements were resolved by mutual discussion.

Statistical analysis

Statistical analyses were performed using the STATA statistical analysis software (StataCorp. 2017. Stata Statistical Software: Release 15; College Station, TX, USA), and forest plots were generated using Revman 5.0. The primary analysis was done by the inverse-variance method with a random-effects model reporting the odds ratio for overall mortality. A subgroup analysis, based on the drug and the dose used in the trial, was also performed. For this, the trials were classified based on the steroid dose used by them, with low dose defined as up to 15 mg/d of dexamethasone, 400 mg/d of hydrocortisone, and 1mg/kg of methylprednisolone. A pre-planned subgroup analysis of patients on oxygen or ventilator support was also performed. Random-effects model analysis, as well as risk ratio analysis, was also done. The impact of heterogeneity on the pooled estimates of the outcome was assessed using the I^2 statistic, and p values were generated using the Cochran Q statistic. Publication bias was assessed by funnel plot and Egger's test (statistically significant publication bias when $p<0.1$) [29].

Results

The initial literature search yielded 2797 articles, and 2442 results were obtained after duplicate removal, from which six published randomized controlled trials were selected for data abstraction and included in the meta-analysis. The flow diagram depicting the identification of eligible trials for the meta-analysis is shown in Figure 1. The included studies were conducted in the United States of America, the United Kingdom, Brazil, Iran and France [15-20]. Among the included trials, two studies reported the use of hydrocortisone [17,18], two studies reported the use of methylprednisolone [19,20], and two studies reported using dexamethasone [15,16]. One study reported methylprednisolone pulse [19] while four used low dose steroids [15,17,18,20], and one used high dose steroids [16]. The basic details of the included trials are summarized in Table 1.

The COVID-19 dexamethasone trial (CODEX) included only

patients with moderate to severe ARDS on mechanical ventilation [16]. RECOVERY trial included patients with all severity, although we included patients on oxygen or mechanical ventilation for mortality analysis separately [15]. REMAP-CAP trial included patients with severe COVID-19 admitted to intensive care unit (ICU) [17]. The CAPE-COVID trial included COVID-19 patients requiring at least 6 l/min of oxygen [18]. The METCOVID trial included patients with oxygen saturation less than 94% or requiring supplemental oxygen or invasive mechanical ventilation [20]. The study by Edalatifard *et al*. included patients with oxygen saturation less than 90% with evidence of cytokine storm and excluded patients on mechanical ventilation or room air saturation less than 75% [19].

The total number of patients randomized in the six trials were 7707 (2837 to steroid group and 4870 to placebo or standard of care). RECOVERY trial randomized patients in a 1:2 ratio to steroid verœus placebo, contributing to a larger number of patients in the control group. Among these, 65.97% were males, and the mean age varied from 55 years to 66.1 years. The number of patients on invasive mechanical ventilation was 1767 out of 7707 (22.9%). The mean PaO_2:FiO_2 ratio was available in four trials and varied from 130-158 [16-18,20]. One study had provided data on mean pulse oxygen saturation as 82.7±5.3 % 19.

Study outcomes

The outcome measures from individual trials are summarized in Table 2. There were 730 deaths among 2837 participants randomized to steroid therapy (25.73%), while in the control group, 1342 participants died among 4870 randomized (27.55%). Based on a random-effect meta-analysis, the summary odds ratio was 0.76 (95% confidence interval 0.58-1.00, p=0.05) for all-cause mortality comparing corticosteroids with placebo or usual care (Figure 2). The summary OR using a fixed-effect model for meta-analysis was 0.84 (95% CI, 0.75-0.93).

The overall inverse variance-weighted fixed-effect risk ratio was 0.88 (95% CI, 0.81-0.95, p=0.001) for all-cause mortality among all randomized patients. When excluding patients with mild disease (not on oxygen or mechanical ventilation) from the RECOVERY trial, the inverse variance-weighted fixed-effect risk ratio 0.84 (95% CI, 0.77-0.91, p<0.001). This translates into a 16% absolute reduction in the mortality risk in patients receiving steroids. On subgroup analysis based on whether patients received oxygen (or mechanical ventilation) or not, the summary OR for on oxygen/MV group was 0.74 (95% CI, 0.57-0.97) while for no oxy-

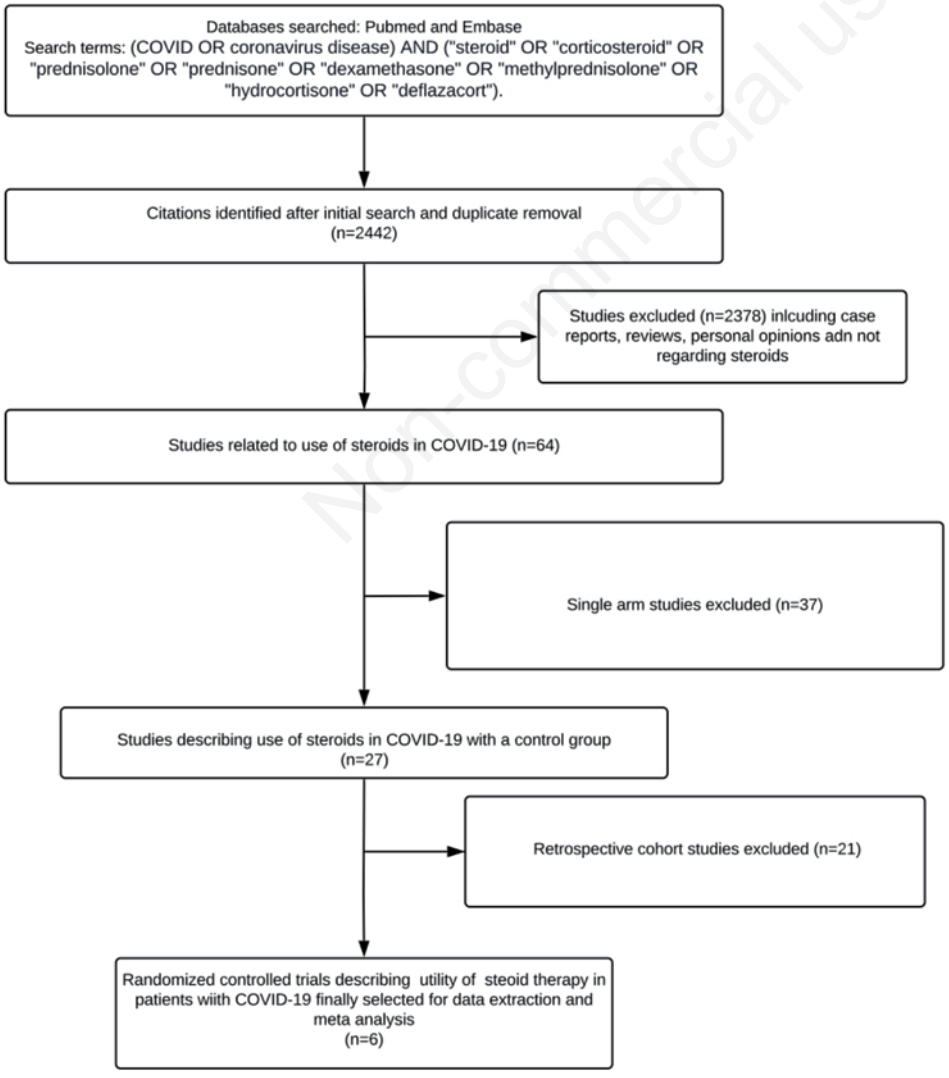

Figure 1. Flow diagram describing the process of systematic review and selection of relevant studies for meta-analysis.

gen group was 1.32 (95% CI, 0.99-1.77) with a significant between-group difference (p=0.004) (Figure 3). The GRADE assessment of the certainty of evidence from this meta-analysis was considered moderate because of concerns regarding bias due to non-blinding and heterogeneity (Figure 4).

There was some degree of heterogeneity among the trials as the I^2 value was 53%, with a p-value of 0.06. There was no evidence of publication bias on the visual inspection of the funnel plot as well as by Egger's test (p=0.20) (Supplementary Figure 1).

For the two trials using dexamethasone, the summary OR using the random-effect model was 0.86 (95% CI, 076-0.96, p=0.01) while RR was 0.90 (95% CI, 0.82-0.97), suggesting a 10% reduction in mortality in the dexamethasone group. Similarly, from the two trials reporting the use of hydrocortisone, the summary OR was 0.69 (95% CI, 0.45-1.04, p=0.08, fixed-effect), and summary RR was 0.76 (95% CI, 0.56-1.03, p=0.07,

Table 1. The basic details of the trials included in the meta-analysis.

Author and year	Trial Acronym	Number of subjects	Main inclusion criteria	Steroid: Type and dosage	Dose category	Control arm	Primary outcome	Mortality outcome	Place of study	Age and Sex	Number (%) on mechanical ventilation	Mean PaO_2: FiO_2
Angus *et al.* 2020	REMAP-CAP	379	Severe COVID-19 admitted to ICU for respiratory (NIV, MV, HFNC with more than 30 l/min flow and 40% FiO_2) or cardiac support	Hydrocortisone; 50 mg six hourly for seven days (Group 1) or till shock (Group 2)	Low	Standard of care	Composite mortality and 21-day organ support free days	Day 21	USA	Mean age 59.5-60.4 years; Males 72.03%	213 (56.2%)	137-149
Dequin *et al.* 2020	CAPE-COVID	149	COVID-19 with any of the following: Need for mechanical ventilation; PaO_2: FiO_2 <300; Pulmonary severity index >130	Hydrocortisone; 200 mg per day for 7 days	Low	Placebo	Treatment failure at day 21	Day 21	France	Mean age 62.2 years; Males 69.8%	116 (77.8%)	130-133
Edalatifard *et al.* 2020	None	62	COVID-19 with SpO_2 <90% with raised CRP and Il-6. Patients on MV excluded	Methylprednisolone; 250 mg per day for three days	High	Standard of care	Time of clinical improvement and discharge from the hospital or death	In-hospital	Iran	Mean age 58.5±16.6 years; Males 62.9%	0 (0 %)	PaO_2: FiO_2 not reported; Mean SpO_2 82.7%±5.3
Horby *et al.* 2020	RECOVERY	6425	Hospitalized COVID-19 patients of all severity	Dexamethasone; 6 mg once daily up to 10 days	Low	Standard of care	28 Day Mortality	Day 28	UK	Mean age 66.1±15.7 years; Males 64%	1006 (15.67%)	Not available
Jeronimo *et al.* 2020	METCOVID	393	COVID-19 with SpO_2 ≤94% at room air OR need of supplementary oxygen OR on IM	Methylprednisolone; 0.5 mg/kg twice daily for 5 days	Low	Placebo	28 Day Mortality	Day 28	Brazil	Mean age 55±15 years; Males 64.6%	133 (33.8%)	158 (120-213)
Tomazini *et al.* 2020	CODEX	299	COVID-19 patients on MV having moderate to severe ARDS with P:F ratio <200	Dexamethasone; 20 mg per day for five days followed by 10 mg per day for five days	High	Standard of care	Ventilator free days at day 28	Day 28	Brazil	Mean age 60.1-62.7 years; Males 62.5%	299 (100%)	131.1-132.6

fixed effect). There was no evidence of any difference in the sub-groups based upon the type of steroid used (Figure 2). On sub-group analysis based on steroid dose, the OR for low dose steroids was 0.85(95% CI, 0.76-0.95) while for high dose, it was 0.30 (95% CI, 0.03-2.74) with no significant between-group difference (p=0.35) (Figure 5).

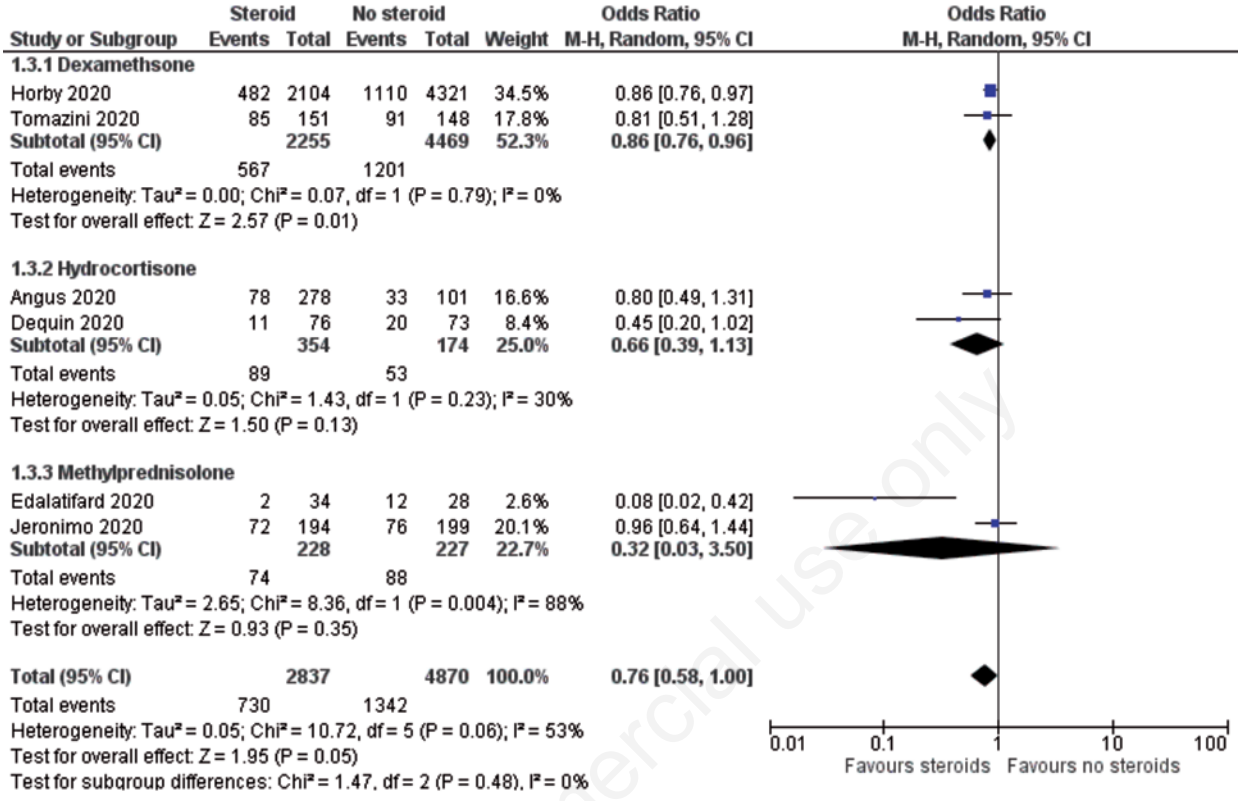

Figure 2. The all-cause mortality in each trial along with sub-group analysis bases upon the drug used drug.

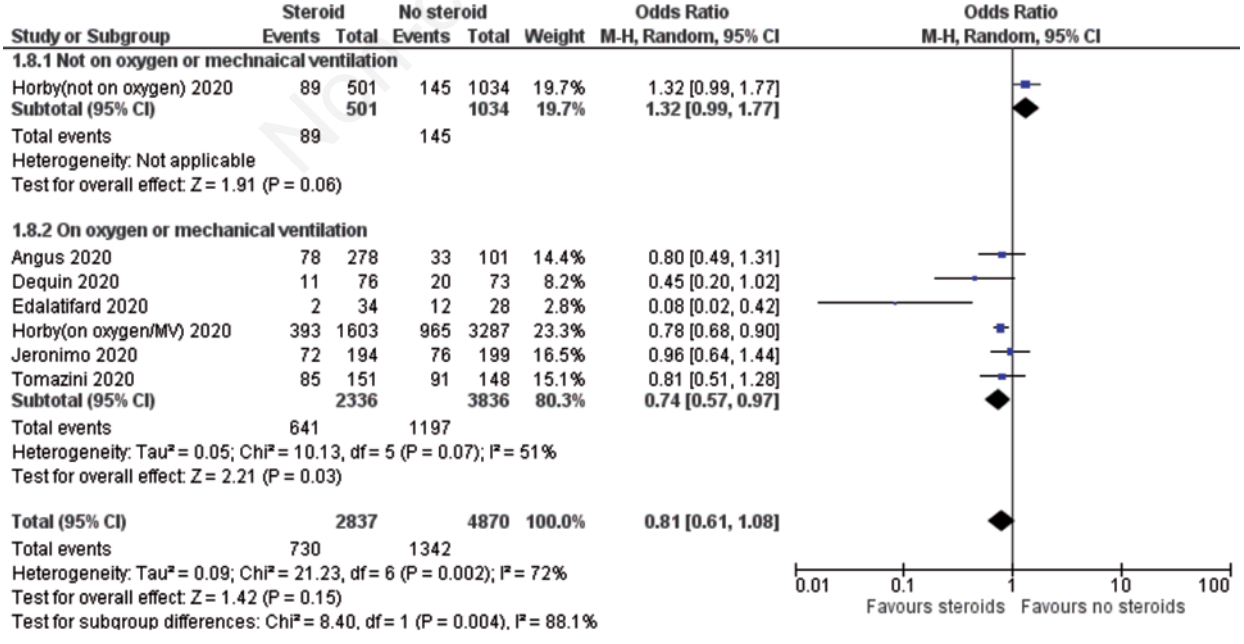

Figure 3. The sub-group analysis for the all-cause mortality based upon disease severity (the need for oxygen or mechanical ventilation).

Safety assessment

Regarding serious adverse events, there was no indication of increased serious adverse events in any of the trials (Table 2). Increased requirement of insulin for hyperglycemia was reported in the METCOVID trial. RECOVERY trial did not report adverse events in its initial available manuscript.

Discussion

In this systematic review and meta-analysis of six randomized controlled trials, including 7707 patients with COVID-19 from various countries, we found that the administration of steroids was associated with a reduction in all-cause mortality compared to placebo or usual care. The effect was evident in patients who required oxygen or mechanical ventilation; while there was no benefit among those not on oxygen. The odds ratio for dexamethasone was better than that for hydrocortisone, although there was no between-group difference statistically.

This meta-analysis included all the published randomized controlled trials to date regarding any corticosteroid regimen used for COVID-19; however, the large effect size of the RECOVERY trial was responsible for the majority of the conclusions. Since the publication of the RECOVERY trial, it seems reasonable to use dexamethasone therapy for critically ill individuals with COVID-19. However, this meta-analysis found that rather than the drug effect of dexamethasone, it seems a class effect of steroids. Although steroids have long been used for individuals with acute respiratory distress syndrome, there has been no strong evidence for their use [30]. We performed a comparison of low vs high dose of steroid

Figure 4. The risk of bias assessment summary using Cochrane Risk of Bias Assessment tool. +, low risk of bias; -, high risk of bias.

Table 2. The reported efficacy and safety outcomes from the included trials.

Author and year	Mortality outcome	Other relevant outcomes	Serious adverse events
Angus *et al.* 2020	Steroid: 78/278 (28%), Control: 33/101 (32.67%)	The median organ support–free days: 0 (IQR, –1 to 15), 0 (IQR, –1 to 13), and 0 (–1 to 11) days in the fixed-dose steroid, shock-dose steroid and control group, respectively	9 in steroid group (3.2%) and 1 in placebo (0.99%)
Dequin *et al.* 2020	Steroid: 11/76 (14.47%), Control: 20/73 (27.39%)	Treatment failure at day 21: Steroid group: 32/76 (42.1%) Control group: 37/73 (50.6%)	3 events, none related to drug
Edalatifard *et al.* 2020	Steroid: 2/34 (5.88%), Control: 12/28 (42.85%)	Time to improvement: Steroid group: 11.84 ± 4.88 days Control group: 16.44 ± 6.93 days	Two patients (5.8%) in the methylprednisolone group and two patients (7.1%) in the standard care group
Horby *et al.* 2020	Overall:Steroid: 482/2104 (22.9%), Control: 1110/4321 (25.68%) On oxygen or MV: Steroid: 393/1603 (24.51%), Control: 965/3287 (29.35%)	28-day discharge: Steroid group: 1413/2104 (67.15%) Control group: 2745/4321 (63.52%)	Not reported
Jeronimo *et al.* 2020	Steroid: 72/194 (37.11%), Control: 76/199 (38.19%)	Length of hospital stay: Steroid group: 9 (7 - 12) days Control group: 10 (7 - 13) days	No increased sepsis; higher insulin requirement
Tomazini *et al.* 2020	Steroid: 85/151 (56.29%), Control: 91/148 (61.48%)	Ventilator-free days: Steroid group: 6.6 (5.0 to 8.2) Control group: 4.0 (2.9 to 5.4) (p=0.02) Duration of mechanical ventilation: Steroid group: 12.5 (11.2 to 13.8) days Control group: 13.9 (12.7 to 15.1) days	Steroid group: 5 (3.3%) Control: 9 (6.1%)

with no efficacy difference; however, as only one study used high dose steroids and the other one used pulse steroids with a small sample size, this result needs further validation. However, it can be safely concluded that low dose steroids work well for preventing mortality in patients with moderate to severe COVID-19. One study used pulse methylprednisolone and demonstrated significant improvement in mortality [19]. This study was of a small sample size, and we need more data to assess the benefit of pulse steroid therapy with or without background low dose steroids. The initial enthusiasm for the use of pulse steroids came from the use of tocilizumab in cytokine storm syndrome, and it was postulated that pulse steroid therapy might work the same way. However, currently, there is emerging evidence that tocilizumab therapy may not help in preventing mortality in severe COVID-19 [31].

Due to the non-availability of individual patient data, subgroup analysis based upon age, gender, or timing of steroid initiation could not be performed. All these parameters may affect individual patient outcomes. The definitions used during different trials varied, and baseline severity scores such as SOFA (Sequential Organ Failure Assessment) or APACHE (Acute Physiology and Chronic Health Evaluation) were not available for all studies. Due to this, it was not possible to further categorize the trial patients based upon disease severity (other than the need for oxygen or ventilator support).

The findings of this meta-analysis suggest that the use of steroids is associated with reduced mortality in COVID-19, which contrasts with the findings for patients with influenza-related ARDS, where it has been seen that mortality and nosocomial infections may be increased with the use of steroid therapy [32]. We were not able to analyze the adverse effects of the therapy due to the non-availability of complete data; however, issues of worsening hyperglycemia and critical illness weakness remain major concerns with steroid use [33,34]. The studies by Tomazini *et al.* [16] and Edalatifard *et al.* [19] used significantly higher doses as compared to others and it is important to understand that the complications in the form of hyperglycemia, and secondary infections should always be looked for in such patients.

This meta-analysis of randomized controlled trials is the most extensive analysis to date regarding the benefit of corticosteroid therapy in COVID-19. The trials were conducted in various geographic areas and provide generalizable evidence. The protocol for the analysis was published publically on the PROSPERO database before initiation to avoid post-search bias.

This analysis has several limitations, as well. We only included the published randomized controlled trials, and ongoing partially completed trials were not included, which were included by the WHO REACT group. We did not include any unpublished data as well as available online preprints for the meta-analysis. We did not assess the side-effect profile of steroid therapy in these patients; however, severe adverse events were assessed. All the trials included adult individuals; the effectiveness of steroid therapy in children with severe COVID-19 remains unknown. One trial reported in-hospital mortality while the other two reported 21-day mortality, potentially leading to inconsistency and under-reporting as delayed deaths due to severe COVID-19 or its sequelae are well reported. Moreover, the results of this meta-analysis were highly driven by the RECOVERY trial due to its large sample size; however, other trial results were also not significantly different.

Conclusions

This meta-analysis of randomized controlled clinical trials of administration of systemic corticosteroids compared to placebo or usual care demonstrated a reduction in mortality. However, all except one trial included patients with moderate to severe COVID-19 suggesting this subgroup is likely to benefit most from the therapy.

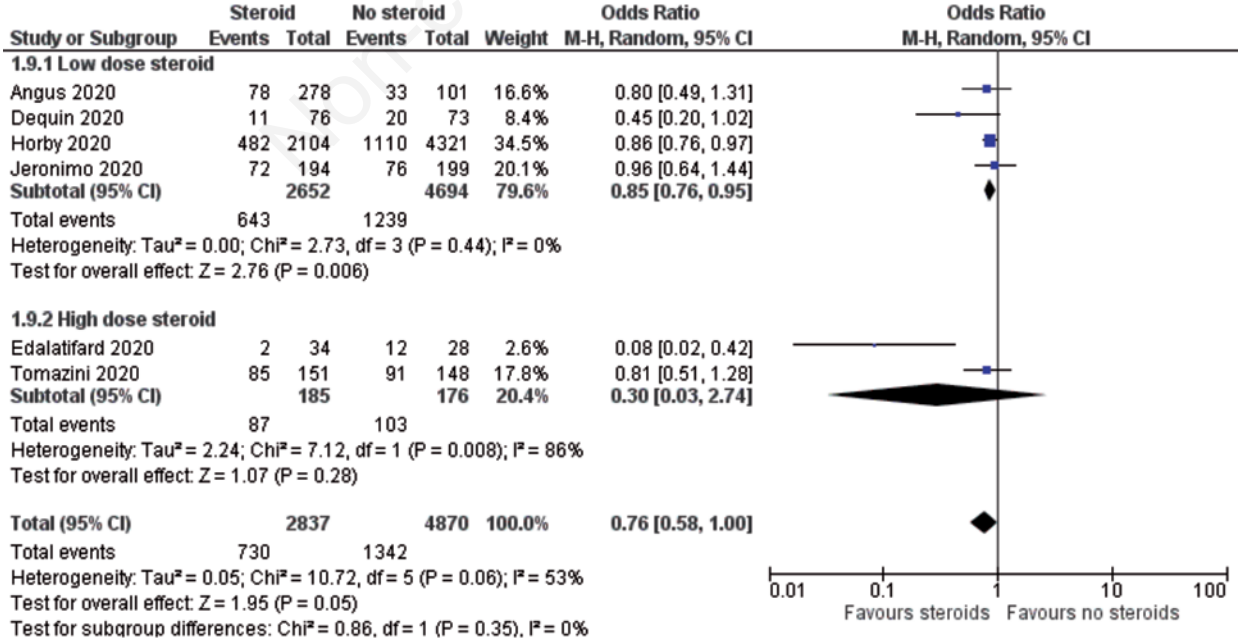

Figure 5. The sub-group analysis for the all-cause mortality based upon the steroid dosage (low *versus* high).

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