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

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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 I² 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 I² 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.

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, anti-helminthic, 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 (S.M. and T.K.B.) 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: 1) The generation of randomization sequence and allocation concealment, 2) blinding, 3) 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: StataCorp LLC), 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 I² 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).

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. Among the included trials, two studies reported the use of hydrocortisone, two studies reported the use of methylprednisolone, and two studies reported using dexamethasone. One study reported methylprednisolone pulse while four used low dose steroids, and one used high dose steroids. 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. RECOVERY trial included patients with all severity, although we included patients on oxygen or mechanical ventilation for mortality analysis separately. REMAP-CAP trial included patients with severe COVID-19 admitted to intensive care unit (ICU). The CAPE-COVID trial included COVID-19 patients requiring at least 6 L/min of oxygen. The METCOVID trial included patients with oxygen saturation less than 94% or requiring supplemental oxygen or invasive mechanical ventilation. The study by Edalatiford 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%.

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 versus 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 PaO2: FiO2 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 oxygen 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 I² 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, fixed effect). There was no evidence of any difference in the subgroups based upon the type of steroid used (Figure 2). On subgroup 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).

**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. We performed a comparison of low vs high dose of steroid 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. 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. and Edalatiford et al. 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.

**Conclusion**

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.

**References**

1. Hussain MA, Yadav S, Hadda V, et al. Covid-19: a comprehensive review of a formidable foe and the road ahead. Expert Rev Respir Med 2020;14:869-79.
2. Mohan A, Tiwari P, Bhatnagar S, et al. Clinico-demographic profile & hospital outcomes of COVID-19 patients admitted at a tertiary care centre in north India. Indian J Med Res 2020;152:61–9.
3. Tyagi R, Mittal S, Madan K, et al. Assessment of the impact and reorganization of interventional pulmonology services at a tertiary care centre during nationwide lockdown for COVID-19 pandemic. Monaldi Arch Chest Dis 2021;91:1615.
4. Aggarwal N, Boppana TK, Mittal S. COVID-19 pandemic: The testing times for healthcare workers. Monaldi Arch Chest Dis 2021;91:1515.
5. Madan M, Pahuja S, Tyagi R, et al. Ambient temperature and COVID-19 outcomes. Adv Respir Med 2021;89:341-3.
6. Pahuja S, Madan M, Mittal S, et al. Weather parameters and COVID-19: A correlational analysis. J Occup Environ Med 2021;63:69-73.
7. Madan M, Mohan A, Madan K, et al. Timing of anti-viral therapy in COVID-19: Key to success. Adv Respir Med 2021;89:237-9.
8. Singh Sehgal I, Guleria R, Singh S, et al. A randomised trial of Mycobacterium w in critically ill patients with COVID-19 (ARMY-1). ERJ Open Res 2021;7:00059-2021.
9. Sryma PB, Mittal S, Madan K, et al. Reinventing the wheel in ARDS: Awake poning in COVID-19. Arch Bronconeumol 2020;56:747–9.
10. Mittal S, Pb S, Madan K, et al. Awake proning in COVID-19 - does CPAP make a difference? Adv Respir Med 2020;89:82.
11. Pb S, Mittal S, Madan K, et al. Awake prone positioning in non-intubated patients for the management of hypoxemia in COVID-19: A systematic review and meta-analysis. Monaldi Arch Chest Dis 2021;91:1623.
12. Sryma PB, Mittal S, Mohan A, et al. Effect of proning in patients with COVID-19 acute hypoxemic respiratory failure receiving noninvasive oxygen therapy. Lung India 2021;38:S6–10.

13. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - Final report. N Engl J Med 2020;383:1813-26.

14. Huang J, Guo J, Li H, et al. Efficacy and safety of adjunctive corticosteroids therapy for patients with severe community-acquired pneumonia: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e14636.

15. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - Preliminary report. N Engl J Med 2020;384:693-704.

16. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and cOVID-19: The CoDEX randomized clinical trial. JAMA 2020;324:1307-16.

17. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020;324:1317-29.

18. Dequin P-F, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: A randomized clinical trial. JAMA 2020;324:1298-306.

19. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J 2020;56:2002808.

20. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2020;72:e373-81.

21. Bani-Sadr F, Hentzien M, Pascard M, et al. Corticosteroid therapy for patients with COVID-19 pneumonia: a before-after study. Int J Antimicrob Agents 2020;56:106077.

22. Bartoletti M, Marconi L, Scudeller L, et al. Efficacy of corticosteroid treatment for hospitalized patients with severe COVID-19: a multicenter study. Clin Microbiol Infect 2020;27:105-11.

23. Cruz AF, Ruiz-Antorán B, Múñez Rubio E, et al. The right time for steroids in COVID-19. Clin Infect Dis 2020;72:1486-7.

24. Fadel R, Morrison AR, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020;71:2144-20.

25. Fang X, Mei Q, Yang T, et al. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19. J Infect 2020;81:147–78.

26. Sarkar S, Khanna P, Soni KD. Are the steroids a blanket solution for COVID-19? a systematic review and meta-analysis. J Med Virol 2021;93:1538-47.
27. Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA 2020;324:1330-41.
28. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
30. Khilnani GC, Hadda V. Corticosteroids and ARDS: A review of treatment and prevention evidence. Lung India 2011;28:114–9.
31. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020;383:233-44.
32. Lansbury LE, Rodrigo C, Leonard-Bee J, et al. Corticosteroids as adjunctive therapy in the treatment of influenza: An updated Cochrane systematic review and meta-analysis. Crit Care Med 2020;48:e98-106.
33. Mittal S, Madan K, Mohan A, et al. Diabetes in COVID-19: Steroid effect. J Med Virol 2021;93:4166.
34. Mittal S, Madan K, Mohan A. COVID-19 and steroid therapy: Impact on diabetes. Prim Care Diabetes 2020;14:568.
Figure 1. Flow diagram describing the process of systematic review and selection of relevant studies for meta-analysis.
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).

| Study or Subgroup | Steroid | No steroid | Odds Ratio | Odds Ratio |
|-------------------|---------|------------|------------|------------|
|                   | Events  | Total      | Weight     | M-H, Random, 95% CI |
| 1.8.1 Not on oxygen or mechanical ventilation | | | | |
| Hotbyron oxygen    | 89      | 145        | 1.32       | [0.92, 1.77] |
| Subtotal (95% CI)  | 501     | 1034       | 1.32       | [0.99, 1.77] |
| Total events       | 89      | 145        |            |             |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.81 (P = 0.08) |

#### 1.8.2 On oxygen or mechanical ventilation

| Study or Subgroup | Steroid | No steroid | Odds Ratio | Odds Ratio |
|-------------------|---------|------------|------------|------------|
|                   | Events  | Total      | Weight     | M-H, Random, 95% CI |
| Angus 2020        | 79      | 279        | 0.80       | [0.48, 1.31] |
| Dequin 2020       | 11      | 70         | 0.45       | [0.20, 1.02] |
| Edaleifford 2020  | 2       | 34         | 0.05       | [0.02, 0.42] |
| Hotbyron oxygen    | 383     | 1033       | 0.78       | [0.68, 0.89] |
| Iermonno 2020     | 72      | 194        | 0.96       | [0.64, 1.44] |
| Tomazin 2020      | 85      | 151        | 0.81       | [0.51, 1.28] |
| Subtotal (95% CI)  | 2336    | 3836       | 0.74       | [0.57, 0.97] |
| Total events       | 841     | 1197       |            |             |
| Heterogeneity: Tau^2 = 0.05; Chi^2 = 10.13; df = 5 (P = 0.07); P = 51% |
| Test for overall effect: Z = 2.21 (P = 0.03) |

| Study or Subgroup | Steroid | No steroid | Odds Ratio | Odds Ratio |
|-------------------|---------|------------|------------|------------|
|                   | Events  | Total      | Weight     | M-H, Random, 95% CI |
| Total (95% CI)     | 2837    | 4870       | 0.81       | [0.61, 1.09] |
| Total events       | 750     | 1342       |            |             |
| Heterogeneity: Tau^2 = 0.09; Chi^2 = 21.22; df = 6 (P = 0.002); P = 72% |
| Test for overall effect: Z = 1.42 (P = 0.16) |
| Test for subgroups: Chi^2 = 8.40; df = 1 (P = 0.004); P = 88.1% |
Figure 4. The risk of bias assessment summary using Cochrane Risk of Bias Assessment tool (the + sign indicates low risk of bias, and - indicates a high risk of bias).

|                | Tomazini 2020 | Jeronimo 2020 | Hotby 2020 | Edalafard 2020 | Dequin 2020 | Angus 2020 |
|----------------|---------------|---------------|------------|----------------|-------------|------------|
| Random sequence generation (selection bias) | +  | +  | +  | +  | +  | +  |
| Allocation concealment (selection bias) | +  | +  | -  | +  | +  | +  |
| Blinding of participants and personnel (performance bias) | -  | +  | +  | +  | +  | +  |
| Blinding of outcome assessment (detection bias) | -  | +  | +  | +  | +  | +  |
| Incomplete outcome data (attrition bias) | +  | +  | +  | +  | +  | +  |
| Selective reporting (reporting bias) | +  | +  | +  | +  | +  | +  |
| Other bias | +  | +  | +  | +  | +  | +  |
Figure 5. The sub-group analysis for the all-cause mortality based upon the steroid dosage (low versus high).
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 PaO2: FiO2 |
|-----------------|--------------|--------------------|-------------------------|--------------------------|---------------|-------------|----------------|----------------|---------------|------------|--------------------------------------|-----------------|
| Angus et al. 2020 | REMAP-CAP    | 379                | Severe COVID-19 admitted to ICU for respiratory (NIV, MV, HFNC with more than 30L/min flow and 40% FiO2) 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; PaO2: FiO2 <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 SpO2 <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 %)         | PaO2: FiO2 not reported; Mean SpO2 82.7% ± 5.3 |
| Horby et al. 2020 | RECOVRY     | 642                | 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 SpO2 ≤ 94% at room air OR need of supplementary oxygen OR on IMV | 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% (100%) | 299 | 131.1-132.6 |
Table 2. The reported efficacy and safety outcomes from the included trials.

| Author and year          | Mortality outcome                              | Other relevant outcomes                                                                 | Serious adverse events                                      |
|--------------------------|------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------|
| ngus 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%) | 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) | Steroid group: 5 (3.3%) Control: 9 (6.1%)                  |