Does methylprednisolone reduce the mortality risk in hospitalized COVID-19 patients? A meta-analysis of randomized control trials

Abstract

Objectives: The questions remained if mortality benefits with dexamethasone seen in patients with coronavirus disease 2019 (COVID-19) also extend to other systemic corticosteroids such as methylprednisolone. This article presents a meta-analysis of randomized controlled trials (RCTs) to ascertain if methylprednisolone can be recommended for use in patients with COVID-19 to prevent deaths.

Methods: Systematic literature search was performed in PubMed, Scopus, Cochrane Central Register of Controlled Trials, and preprint servers until 13th April 2021. The outcome of interest was all-cause mortality. The random-effects model for the meta-analysis was utilized to estimate the pooled odds ratio (OR) at 95% confidence intervals (CI).

Results: Five RCTs were included in the meta-analysis. The pooled OR for all-cause mortality was 0.64 (95% CI: 0.29 -1.43, n=652) comparing methylprednisolone with the control, indicating no mortality benefits. A similar finding was noted with a sub-group analysis including four trials that used low-dose methylprednisolone. However, the only trial that administered high doses of methylprednisolone indicated a statistically significant mortality benefit (OR 0.08, 95% CI: 0.02-0.42).

Conclusions: A short duration (3 to 5 days) pulse therapy of high-dose methylprednisolone can be a promising alternative to the low-dose dexamethasone therapy in severely ill patients with COVID-19 to prevent deaths.

Keywords: Coronavirus; corticosteroids; deaths; dexamethasone; methylprednisolone; pandemic; SARS-CoV-2

Article Highlights

- The pulsed high-dose methylprednisolone therapy may offer an alternative to low-dose dexamethasone in preventing deaths in severely ill COVID-19 patients.
- The optimal duration of methylprednisolone pulse therapy may be as short as 3 days to limit its exposure and minimize its impact on viral clearance.
- In determining equipotent doses for an acute short-course pulse therapy of corticosteroids, the biological half-life of steroids (short, intermediate, or long-acting) should also be accounted for besides the potency factor. The dose estimation based on potency alone is still suitable for long-term corticosteroids use in chronic conditions.

1. Introduction

In the early days of the coronavirus disease 2019 (COVID-19) pandemic, the use of systemic corticosteroids was raised as a cause of concerns in patients with COVID-19 due to the possibility for delayed viral clearance, inferred from the findings in patients with severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [1,2]. However, the RECOVERY trial [3] provided evidence in favour of corticosteroids use and demonstrated a significantly lower risk of mortality compared to usual care (rate ratio = 0.83; 95% confidence interval: 0.75 to 0.93) in critically ill COVID-19 patients.

Nevertheless, the questions remained if mortality benefits also extend to other systemic corticosteroids including methylprednisolone. The meta-analysis [4] by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group reported an overall significantly lower risk of all-cause mortality with systemic corticosteroids, however, subgroup analysis revealed mortality benefits with the dexamethasone only but not with methylprednisolone. It can be argued that a potential mortality benefit associated with methylprednisolone use may have been masked due to inadequate sample size.

A retrospective study by Ko et al. [5] compared the effectiveness between methylprednisolone and dexamethasone in patients with COVID-19 in an attempt to establish if comparative efficacy of methylprednisolone to dexamethasone in critically ill covid-19 patients. The aforementioned study reported that intravenous pulse methylprednisolone was significantly associated with a lower risk of all-cause mortality compared to usual care (16.4% versus 41.3%; $P<0.01$), and even compared to dexamethasone (16.4% versus 26.5%; $p<0.01$). Nevertheless, confounding bias cannot be entirely ruled out due to the retrospective nature of this study. Therefore, it was necessary to assess the findings from all qualifying randomized controlled trials to ascertain if methylprednisolone can be recommended for use in severely ill patients with COVID-19 to prevent deaths.

2. Methods

We performed a systematic literature search in electronic databases including PubMed, Scopus, Cochrane Central Register of Controlled Trials, and preprint servers (medRxiv, Research Square, SSRN) with no language restriction for eligible studies published up until 13th April 2021. The search strategy was built based on the following keywords and MeSH terms: “COVID-19”, “SARS-CoV-2”, “randomized controlled trials”, and “methylprednisolone”. Two investigators (CSK and SSH) independently performed the literature screening to identify eligible studies. The reference lists of relevant articles were also reviewed

to identify potential studies. The eligibility criteria for inclusion of studies were the randomized controlled trials which reported mortality outcomes with methylprednisolone compared to placebo and/or standard-of-care in patients with COVID-19. We excluded studies with observational design, non-randomized trials, single-arm trials, and trials that did not report mortality outcomes.

The outcome of interest was all-cause mortality. Each included trial was independently evaluated by two investigators (CSK and SSH) who also extracted the study characteristics. Data collected included author(s), trial design, country, patients' age, a regimen of methylprednisolone, and mortality outcomes. Furthermore, two investigators (CSK and SSH) assessed the risk of bias of the trials included with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [6], which is a standardized method used to evaluate potential bias in reports of randomized trials. Essentially, RoB 2 is structured into a fixed set of domains of bias, for instance, different aspects of trial design, conduct, and reporting. We classified the included studies according to the dose of methylprednisolone used (i.e., low dose or high dose) based on the cutoff of 240 mg/day of methylprednisolone [7]. The random-effects model for the meta-analysis was utilized to estimate the pooled odds ratio at 95% confidence intervals. Subsequently, the heterogeneity among the included studies was examined using the I^2 statistics and the derived *p* values for heterogeneity using the Cochran Q statistic. Meta-analysis was performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

3. Results

Our search yielded 310 unique records. After an initial screening of the title and abstract, 7 studies were selected for a full review (**Figure 1**). Based on inclusion and exclusion criteria, 2 studies were excluded. The remainder of 5 trials, comprising 652 patients, was included in this meta-analysis. Two trials [4,8] originated from China, while the remaining three trials originated from Brazil [9], Spain [10], and Iran [11], respectively. Only one trial [11] administered a high dose of methylprednisolone, while the remaining four trials [4,8-10] administered low doses of methylprednisolone. Details of the included trials and the overall risk of bias assessed by RoB 2 are summarized in **Table 1**.

Only the trial by Jeronimo et al. [9] had an overall low risk of bias. The risk of bias was assessed as "high" for the two trials [10,11]; the trial by Edalatifard et al. [11] had a high risk of bias for the domains of 'deviations from intervention' and 'missing outcome data' due to imbalanced deviations between the two arms where 6 patients in the control group (17% of the control group) received the intervention drug and were excluded from the analysis of mortality, while the domain of 'randomization' expressed some

concerns because no information provided on allocation concealment; the trial by Corral-Gudino et al. [10] had a high risk of bias for the domain of 'randomization' due to the possibility that allocation sequence was not concealed and inadequate generation of the randomization sequence, while the domain of 'deviations from intervention' expressed some concerns due to open-label trial design. Risk of bias was assessed as 'some concerns' for the remaining two trials [4,8]; both the Steroids-SARI trial (NCT04244591) [4] and the trial by Tang et al. [8] had some concerns for the domain of 'randomization', due to the usage of a fixed-randomization block size within centers and the usage of text messages to implement randomization allocations for the former trial [4] and no information provided on allocation concealment for the latter trial [8].

Based on a random-effect meta-analysis, the pooled odds ratio was 0.64 (95% confidence interval: 0.29 to 1.43) for all-cause mortality comparing methylprednisolone with control (**Figure 2**), indicating inadequate evidence against the model hypothesis of 'no significant difference' with the current sample size. Similarly, in trials [4,8-10] that administered low doses of methylprednisolone, the overall random-effect pooled odds ratio was 0.96 (**Figure 2**; 95% confidence interval 0.66 to 1.38), and therefore inadequate evidence to reject the hypothesis 'no significant difference' with the current sample size. However, in the only trial [11] that administered high doses of methylprednisolone, the odds ratio was 0.08 (**Figure 2**; 95% confidence interval 0.02 to 0.42), hence indicated a statistically significant mortality benefit. Due to higher mortality observed in the Steroids SARI Trial than that in the other four trials and concerns about internal analysis of the data from Steroids SARI, we recalculated the pooled OR after excluding Steroid SARI data from our analysis and found a pooled odds ratio of 0.53 (95% confidence interval: 0.17 to 1.63, Q=8.90, p=0.03, I2=66%) for all-cause mortality comparing methylprednisolone with control.

4. Discussion

The findings of our meta-analysis of randomized controlled trials corroborated the findings from the retrospective study by Ko et al. [5] that high-dose intravenous methylprednisolone was significantly associated with a lower risk of all-cause mortality compared to control in patients with COVID-19. Taken together, the higher anti-inflammatory potency with high-dose methylprednisolone could confer mortality benefits beyond that of the low-dose methylprednisolone, and the optimal duration may be as short as 3 days to limit its exposure, since longer exposure may cause delayed viral clearance or pronounced hyperglycemia hence jeopardizing the mortality benefits [12]. This complies with the mortality benefit seen with a 3-day short-course of high-dose methylprednisolone (250 mg/day) in the

trial by Edalatifard et al. [11]. Indeed, the intention for the pulse intravenous methylprednisolone therapy with intermittent administration of supraphysiological quantities of the drug is to enhance its therapeutic effects while keeping the side effects to a minimum [13]. Indeed, a recent triple-blinded, randomized controlled trial [14] confirmed that there was no difference in the risk of mortality in patients with COVID-19 between high-dose intravenous methylprednisolone and the low-dose dexamethasone.

Moreover, the time to initiate corticosteroid therapy in patients with COVID-19 is an important consideration for the mortality benefits. The trial by Edalatifard et al. [11] administered methylprednisolone at a mean of 8 days from symptom onset while both the trials by Jeronimo et al. [9] and Corral-Gudino et al. [10] respectively, administered methylprednisolone at a median of 12-13 days from symptom onset. We are still learning the optimal time for the initiation of corticosteroids in patients with COVID-19, which is also largely confounded by inter-subject variability, an ongoing trial (NCT04530409) may provide invaluable insights on early vs. late administration of corticosteroids on mortality in patients with COVID-19 [15]. In the meantime, it may be best to administer methylprednisolone approximately 8 days upon symptom onset (following the approach by Edalatifard et al. [11]), which is also in line with the recommendations from the RECOVERY trial where dexamethasone was administered a median of 8 days since symptom onset. In addition, the observational study by Bahl et al. [16] indicated that mortality benefit was observed only in patients with more than 7 days of symptom onset to initiation of corticosteroids. Extrapolated from SARS patients, early initiation of corticosteroids is attributed to delayed viral clearance [17].

The conclusions from this manuscript may be limited by the inclusion of the trials with a high risk of bias; besides, there was only one trial [11] thus far which evaluated the effect of high-dose methylprednisolone. It should be noted that the included trials either determined 28-day mortality or in-hospital mortality and therefore the effect of methylprednisolone on long-term prognosis (beyond 28 days of hospitalization) is still unclear in patients with COVID-19. Therefore, appropriately designed large-scale randomized trials are still needed to confirm these findings. Moreover, a head-to-head comparison of the effectiveness between methylprednisolone and dexamethasone in patients with COVID-19 is still awaited and findings from the MEDEAS trial (methylprednisolone vs. dexamethasone in COVID-19 Pneumonia, NCT04636671) are likely to provide interesting insights [18].

5. Expert opinion

An aggressive treatment strategy was needed to address the high mortality seen in COVID-19 associated inflammatory complications and the RECOVERY trial confirmed the use of low-dose dexamethasone in reducing the risk of mortality in patients with COVID-19 on respiratory support [3]. Systemic corticosteroid therapy since became part of the 'standard of care' for severely ill patients with COVID-19. To meet the demand for corticosteroids amid the COVID-19 pandemic, other corticosteroids have been subjected to clinical investigation in anticipation of the mortality benefit similar to dexamethasone. Methylprednisolone was an obvious choice due to its wider use in various chronic inflammatory diseases (low-dose) and acute inflammatory flare-ups (high-dose) [19].

Low-dose methylprednisolone was employed in most of the clinical trials included in this analysis (four out of five) for severely ill patients with COVID-19, perhaps to simulate the recommendations from the RECOVERY trial that confirmed the mortality benefit associated with low-dose dexamethasone (6 mg per day for up to 10 days). Dexamethasone is a high-potency corticosteroid, approximately 25 times more potent than hydrocortisone, whereas methylprednisolone potency is approximately 5 times the hydrocortisone and referred to as intermediate-potency corticosteroid. Dexamethasone is, therefore, approximately 5 times more potent than methylprednisolone [20]. A 6 mg per day course of dexamethasone from the RECOVERY trial, therefore, equate approximately 30 mg per day course of methylprednisolone after adjusting for potency and this seems in compliance with the dosage used in the four out of five clinical trials [4, 8-10] employed in this meta-analysis. However, these trials failed to exhibit any statistically or clinically significant mortality benefits.

Besides potency, it is worth noting that dexamethasone is a long-acting corticosteroid compared to methylprednisolone which is an intermediate-acting (biological half-life: 36-72 h versus 12-36 h, [19]), albeit having a similar elimination half-life (approx. 3 hours [21-22]). The duration of action for methylprednisolone is, therefore, approximately 2 to 3 times shorter than that of dexamethasone; hence, to simulate the dexamethasone pulse therapy, a further 2 to 3 times higher doses of methylprednisolone (post-potency adjustment) may be required to compensate for the shorter duration of action. The equipotent dose of methylprednisolone for the dexamethasone, i.e., 30 mg per day if compensated further for the differences in duration of action, the equivalent dose for methylprednisolone will be 60-90 mg per day.

Furthermore, the RECOVERY trial administered a short course of dexamethasone up to 10 days, hence an equivalent total dose of methylprednisolone can be estimated as 600-900 mg divided over 10 days (i.e., 60-90 mg per day x 10). A short course of 3 to 5 days high-dose methylprednisolone is usually recommended in acute inflammatory conditions [19,22]; therefore, a pulse therapy of methylprednisolone may equate to 200-300 mg per day for three days (600-900 mg divided over three days, **Figure 3**). The consideration of corticosteroids biological half-life coupled with potency can, therefore, explain why a relatively higher dose of methylprednisolone (250 mg per day methylprednisolone for three days) provided a significant mortality benefit in the trial by Edalatifard et al [11] which was not seen with the low-dose methylprednisolone therapy in the other four clinical trials [4,8-10] included in this meta-analysis. It is, therefore, recommended that the biological half-life of corticosteroids (duration of action) should also be accounted for while working out equipotent corticosteroids doses for acute short-pulse interventions. The dose estimation approach based on potency alone is still suitable for the long-term use of corticosteroids in chronic conditions.

In conclusion, a short duration (3 to 5 days) pulse therapy of high-dose methylprednisolone is a promising alternative to the low dose dexamethasone therapy in severely ill patients with COVID-19. Clinicians should, however, anticipate and manage the acute hyperglycemia associated with the administration of methylprednisolone which may adversely impact the mortality benefits of the methylprednisolone in patients with COVID-19 [12].

6. Declarations

Conflict of interest/Competing interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

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Authors' contribution

SSH, CSK, and HAM conceived the content, retrieved the data, wrote the manuscript, and approved the final version. SSH, CSK, and HAM reviewed the data and revised the manuscript.

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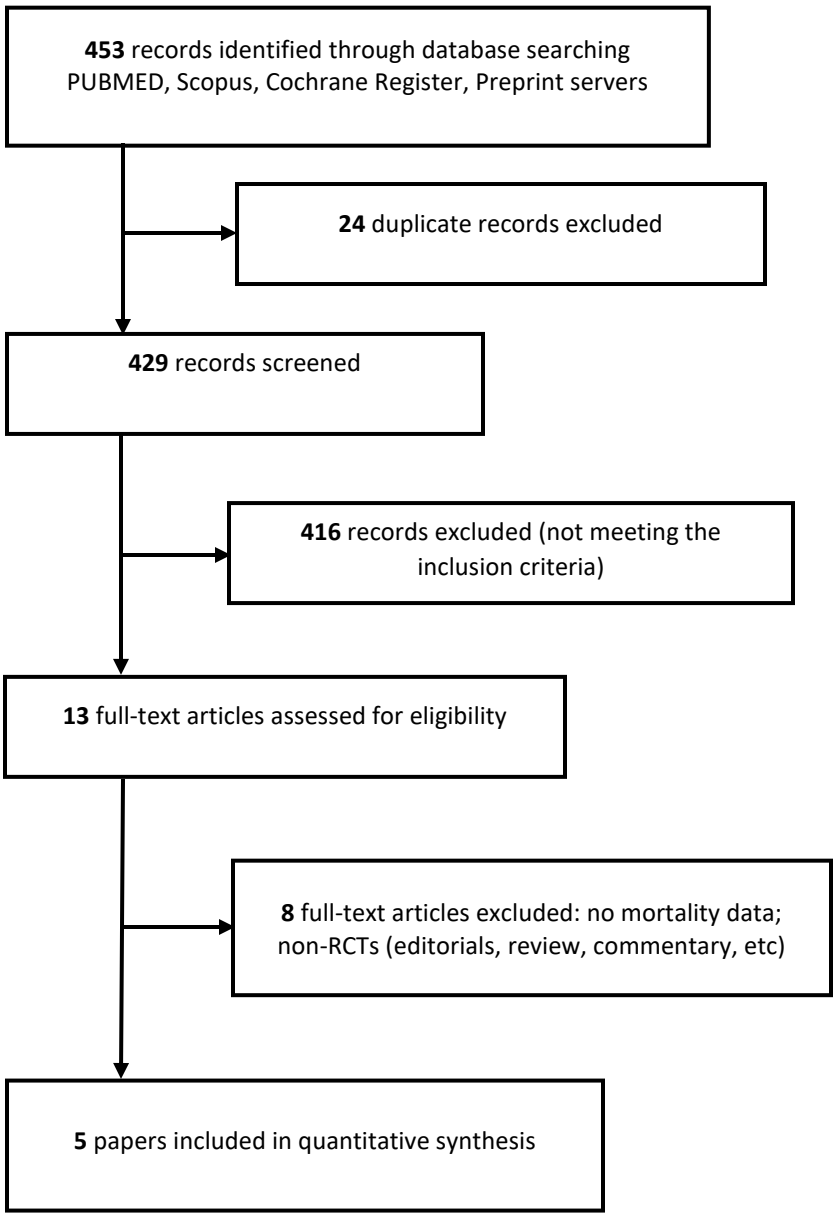

Figure 1: Study selection process (PRISMA)

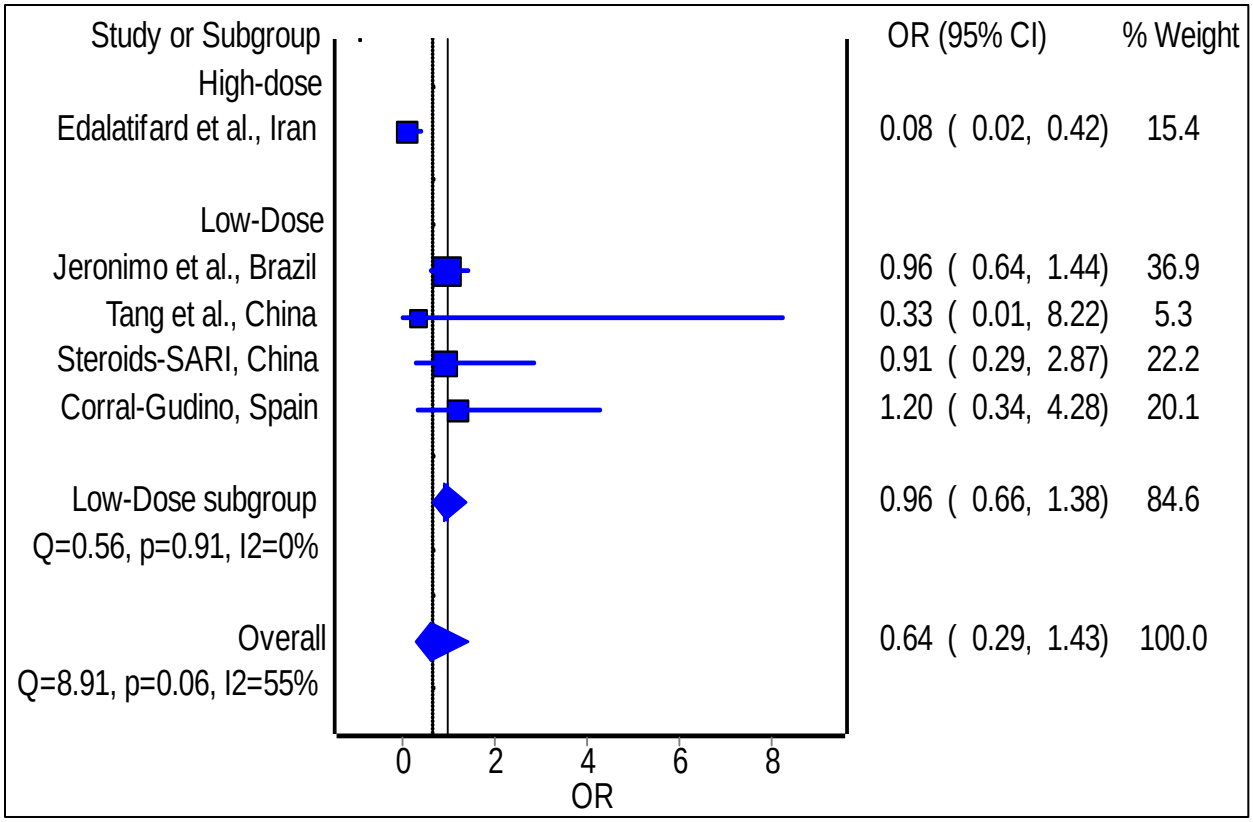

Figure 2: Pooled odds ratio of mortality with the use of methylprednisolone compared to non-use of methylprednisolone in patients with COVID-19

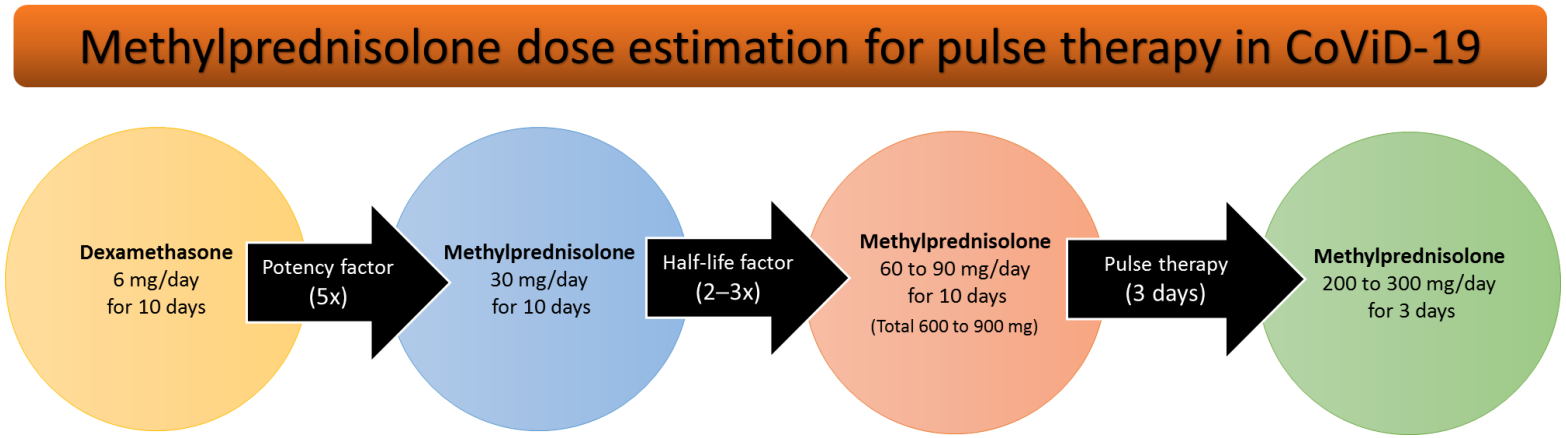

Figure 3: Dexamethasone equivalent dose estimation for methylprednisolone for corticosteroid pulse therapy in COVID-19 patients.

Table 1: Study characteristics of included trials

Study (trial registration number)	Study design	Country	Age (median/mean)	Disease severity	Dosage regimen of intravenous MeP in the intervention group	Regimen of comparative intervention in the controlled group	Median/Mean time from symptom onset to randomization (days)	28-day/In-hospital mortality		Risk of bias[1]
								MTP users (n/N; %)	Non-MTP users (n/N; %)	
Steroids-SARI [4] (NCT04244591)	Open label, randomized controlled trial	China	MeP users=67 Non-MeP users=62	All patients were admitted into intensive care unit with PaO_2/FiO_2 < 200 mmHg and required positive pressure ventilation or high flow oxygen therapy	40 mg twice daily for 5 days	Standard care	Unclear	28-day mortality: 13/24; 54.2	28-day mortality: 13/23; 56.5	Some concerns
Tang et al [8] (NCT04273321)	Randomized, single-blind, placebo-controlled Trial	China	MeP users=57 Non-MeP users=55	At randomization, 70.9% patients received oxygen therapy while 47.7% patients had hypoxemia respiratory failure	1 mg/kg per day for 7 days	Placebo (normal saline)	MeP users=8 Non-MeP users=11	In-hospital mortality: 0/43; 0	In-hospital mortality: 1/43; 2.3	Some concerns
Jeronimo et al. [9] (NCT04343729)	Randomized, double-blind, placebo-controlled trial	Brazil	MeP users=57 Non-MeP users=54	At baseline, 81.6% of patients required either invasive or non-invasive respiratory support	0.5 mg/kg twice daily for 5 days + standard care (intravenous ceftriaxone 1 g twice daily for 7 days and azithromycin 500 mg once daily for 5 days or clarithromycin 500 mg twice daily for 7 days)	Placebo (normal saline) + standard care	MeP users=13 Non-MeP users=13	28-day mortality: 72/194; 37.1	28-day mortality: 76/199; 38.2	Low
Corral-Gudino et al [10] (2020-001934-37)	Open label, randomized controlled trial	Spain	MeP users=73 Non-MeP users=66	All patients with moderate to severe disease:	40 mg twice daily for 3 days, followed by 20 mg twice daily for another 3 days +	Standard care	MeP users=12 Non-MeP users=12	28-day mortality: 7/35; 20.0	28-day mortality: 5/29; 17.2	High

				(a) PaO_2/FiO_2 < 300 or (b) SaO_2/FiO_2 < 400 or (c) at least two criteria of the BRESCIA-COVID Respiratory Severity Scale	standard care (acetaminophen, oxygen therapy, low-molecular-weight heparin, and antibiotics for co-infections)					
Edalatifard et al. [11] (IRCT20200404046947N1)	Randomized, single-blind, placebo-controlled trial	Iran	MeP users=67 Non-MeP users=62	At baseline, 100% of patients required oxygen therapy	250 mg per day for 3 days + standard care (hydroxychloroquine sulfate, lopinavir, and naproxen)	Standard care	MeP users=8-9 Non-MeP users=8-9	In-hospital mortality: 2/34; 5.9	In-hospital mortality: 12/28; 42.9	High

FiO_2 fraction of inspired oxygen MeP *methylprednisolone* PaO_2 *partial pressure of oxygen* SaO_2 *arterial oxygen saturation*

[1]Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.