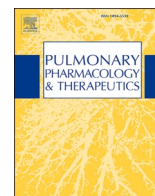




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Effects of corticosteroids on Covid-19 patients: A systematic review and meta-analysis on clinical outcomes

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ABSTRACT

Background: Covid-19 disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although corticosteroids have shown some promising results in Covid-19 patients, their effectiveness remains controversial. In this systematic review, we evaluated the effect of corticosteroids in mortality, Hospitalization, ICU admission, intubation, and mechanical ventilation in Covid-19 patients.

Methods: We searched major databases from March-2020 to Jan-2021. Twenty-nine studies were included after evaluating the eligibility of the literature. The extracted data for mortality, hospitalization, admission to the ICU, intubation, and mechanical ventilation were analyzed with RevMan® 5.4. Categorical variables are presented with odds ratios (OR), and numerical variables are shown with the mean difference.

Result: Corticosteroid treatment had no impact on mortality in 18,190 covid patients with OR = 1.12[0.83–1.50]. When we include the randomized controlled trials, corticosteroids reduced the mortality by 20% (OR = 0.80 [0.73, 0.88]; $P < 0.001$). Additionally, the risk of admission to the ICU, the need for endotracheal intubation, and mechanical ventilation were comparable between patients receiving corticosteroids and controls. The duration of hospitalization was also similar in the two groups.

Conclusion: Corticosteroid therapy may not be effective for reducing mortality, length of hospitalization, the likelihood of intubation and mechanical ventilation, and ICU admission in patients suffering from Covid-19 pneumonia.

1. Introduction

Coronavirus disease (Covid-19), caused by a novel coronavirus (SARS-CoV-2), was first reported in Wuhan, China, in December 2019. The virus infected millions of people when the World Health Organization announced coronavirus disease 2019 (Covid-19) as a pandemic on March 11, 2020 [1,2]. Since then, the Covid-19 disease has claimed millions of lives worldwide and plunged the global economy into a recession [3]. SARS-CoV-2 infections manifest with severe Covid-19 and excessive inflammatory responses, leading to fatal acute respiratory distress syndrome (ARDS) [4]. Corticosteroids have been used for their modulatory effects on the immune system, thereby treating patients with severe ARDS. However, the effectiveness of corticosteroids in the management of Covid-19 remains controversial.

Several clinical studies published that support the effectiveness of

corticosteroids in patients with Covid-19. A retrospective analysis by Wu et al. studied 201 Covid-19 patients and showed that the use of methylprednisolone notably reduced the risk of death (HR, 0.38; 95% CI, 0.20–0.72) [5]. Another meta-analysis reviewed 20,197 Covid-19 patients from 44 studies and showed a significant 28% mortality reduction in the corticosteroid group [6]. The analysis also reported a positive effect for the need and duration of mechanical ventilation in the corticosteroid group. All these findings seem to indicate the effectiveness of corticosteroids in the treatment of Covid-19.

In contrast, some clinical studies reported no differences or, even worse Covid-19 patients treated with corticosteroid [7]. In a systematic review and meta-analysis involving 4,451 patients, the use of corticosteroids was associated with a 2-fold increase in the relative risk of mortality and prolonged hospital length of stay (HLOS) by four days. In this study, there was no difference in the need for hospitalization,

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intubation, or mechanical ventilation [8].

Overall, the effectiveness of corticosteroids in Covid-19 patients remains inconclusive. In this study, we conducted a systematic review and meta-analysis of controlled trials including a large multinational RECOVERY trial to evaluate the impact of corticosteroids on the mortality rate, HLOS, ICU admission, intubation, and mechanical ventilation in Covid-19 patients with severe pneumonia.

2. Methods

2.1. Literature retrieval

We followed the preferred reporting items for systematic reviews and meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analysis [9]. We searched PubMed, Google Scholar, MEDLINE for published and preprinted literature from March 2020 to January 2021. Our search was expanded further by manually inspecting the reference sections of the articles for related studies. The keywords used in our searches were "Covid-19" OR "SARS-CoV-2" OR "Covid-19" AND "corticosteroids" OR "glucocorticoids" OR "methylprednisolone" OR "hydrocortisone" OR "prednisone" OR "dexamethasone". According to the local institutional review board, no Ethics Committee approval was required for the study that uses de-identified publicly available data.

2.2. Study selection

We evaluated studies published as journal articles, preprinted literature, meta-analysis, multicenter studies, randomized clinical trials, and retrospective cohort studies. Non-English and non-French studies were excluded from the analysis due to the unavailability of a scientific interpreter that could reliably assess quantitative data. The primary outcome was the frequency of mortality events. Secondary outcomes were the duration of hospitalization, the need for ICU admission, endotracheal intubation, and mechanical ventilation. Reference lists of included studies were screened to identify additional studies. Publications not including outcomes of interests were excluded. Initial screening by reviewers eliminated duplicates and studies without conclusive data. The risk of bias for each study was assessed using the Cochrane Collaboration risk of bias tool.

2.3. Data extraction

Data were extracted for each study included the year of publication, study design, study region/country, number of participants receiving corticosteroids and control group, median or mean age, sex, corticosteroid type, dosage, and duration and outcomes of interest. A second reviewer evaluated all extracted data. Data were directly taken from the text of the study if available or derived from published graphs otherwise.

2.4. Statistical analysis

Data were analyzed and extracted using the RevMan 5.4 software (the Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous outcomes were evaluated using odds ratio (OR) with 95% confidence intervals (CI), and the Mantel-Haenszel (M – H) effects model was applied. Continuous outcome (HLOS) was assessed using mean-difference, with the inverse variance model applied. Heterogeneity was assessed using the I^2 statistic. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance [10]. A p-value of less than 0.05 provided evidence of significant OR and a p-value < 0.10 for assessment of the heterogeneity. Forest plots were generated for data visualization by the same software. A random-effect model was used for variables with high heterogeneity ($I^2 > 50\%$). The symmetry of the funnel plot analysis was used to evaluate a publication bias. In addition, we used the method described by Wan et al. and Hozo et al. to convert median and range into mean and

standard deviation if raw data was not available in the reported study to compute them from [11,12].

3. Results

3.1. Search results

Three hundred forty-five studies were discovered in the initial search. After removing review articles, case reports, duplicate publications, and studies without conclusive data, 101 studies were selected for full-text article reviews. After screening the studies, 29 of them reporting 18,190 patients met the inclusion criteria and were included in the meta-analysis. The Reporting guidelines for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to organize the review and the strategy for selection of eligible studies is provided in Fig. 1.

The details for the included studies (i.e., publication date, study design, study region/country, the number of participants receiving in each group, median or mean age, sex, corticosteroid type, dosage, and outcomes of interest are summarized in Supplemental Table 1.

3.2. Hospital mortality

In 25 studies with 16,349 patients, the overall mortality rate was 23.5%. The mortality rate was 29.3% among the patients treated with some form of corticosteroids during the acute phase of pneumonia, while this rate was 12.2% in those who did not receive steroids. The relative risk of death within the hospital in treated groups over controls was OR = 1.12 with a 95% CI ranging between 0.83 and 1.50 ($P = 0.47$) (Fig. 2).

The mortality rates reported in these studies were heavily heterogeneous, with $I^2 = 90\%$ ($P < 0.0001$). In six of these studies (3 RCTs and 3 observational cohort studies), there was a clear benefit from using steroids in Covid-induced ARDS, as shown by reducing hospital mortality [13–18]. In contrast, five studies demonstrated that the use of corticosteroids was associated with an increased risk of death in hospital settings [19–23]. While, in remaining studies the results on mortality benefits were equivocal for the use of corticosteroids [24–31]. In all remaining studies, there was no significant difference in mortality between the corticosteroid group and controls.

When the studies were limited to include seven prospective RCTs, there were 9,320 patients available for analysis. A meta-analysis of ten RCTs showed a significant reduction of death rate in Covid-19 patients treated with corticosteroids (OR = 0.80 [0.73–0.88] and $P < 0.001$). Meanwhile, the data heterogeneity was reduced to 32% by eliminating 18 observational studies from the analysis (Fig. 2 Lower Panel).

3.3. The need for ICU admission

Among the eligible studies, 11 studies reported the need for ICU admission as an outcome variable. These studies were included for analysis. The rate of ICU admission was 23.4% among 3,730 subjects. The rate of admission to the ICU was 30.1% among the patients who received corticosteroids, while this rate was 18.7% among the controls. Therefore, the relative risk for ICU admission was not significantly affected with corticosteroids treatment OR = 1.43 [0.79–2.58], $P = 0.24$ (Fig. 3). Again, the reported outcome was highly heterogeneous ($I^2 = 90\%$; $P < 0.0001$), and only in one study with 88 subjects, corticosteroid therapy was beneficial in reducing the risk of ICU admission [28]. After limiting the studies to RCTs, there were two studies with 606 patients; still, there was no significant difference in the risk of admission to the ICU due to worsening Covid-19 pneumonia (OR = 0.68 [0.33–1.31]; $P = 0.60$) (Fig. 3). In addition, the corticosteroids use may be the consequence with ICU admission instead of using corticosteroids leading to ICU admission, because it is a common practice to treat the patients with corticosteroids after they are admitted to ICU.

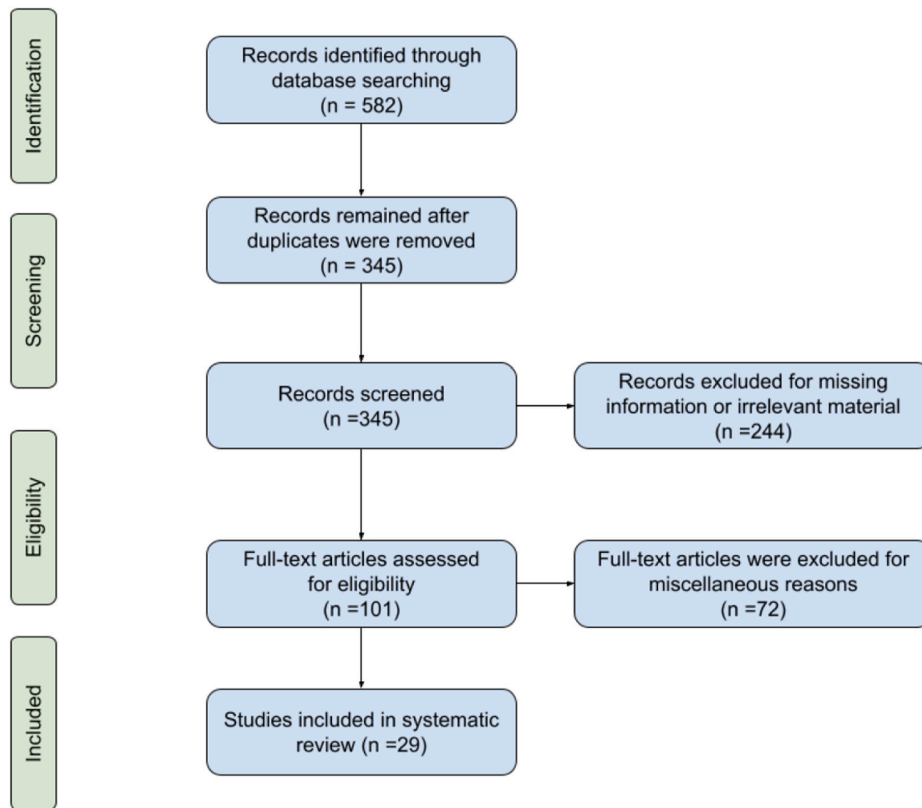


Fig. 1. PRISMA Flow diagram for study selection.

3.4. The need for endotracheal intubation and mechanical ventilation

We identified three studies that addressed the need for endotracheal intubation while the patients were in the ICU. The total number of subjects in these studies was 595, out of which 169 patients (28.4%) required placement of endotracheal tube for mechanical ventilation (OR = 1.19 [0.30, 4.73]; $P = 0.81$) (Fig. 4).

Data were highly heterogenous ($I^2 = 91\%$; $P < 0.00001$). Corticosteroids reduced the risk of intubation in one study [14], while increasing the risk in another [32], and they had no impact on intubation in the third study [33]. Unfortunately, only one study addressed the necessity of endotracheal intubation as an outcome variable that showed a significant reduction of intubation in patients treated with corticosteroids ($P = 0.02$) [14].

Out of the 29 studies meeting the inclusion criteria, 14 studies reported endpoints for needing mechanical ventilation. The meta-analysis is performed for the 14 studies with 9,416 patients, and we found a 15.0% likelihood of needing invasive mechanical ventilation in patients who presented with severe viral pneumonia. However, a course treatment with corticosteroids did not affect the need for mechanical ventilation among these patients compared to controls (OR = 1.21 [0.79, 1.85]; $P = 0.38$) (Fig. 5). Like all other endpoints, the reported effects were heavily heterogeneous, with I^2 values of 88% ($P < 0.0001$). The need for mechanical ventilation was comparable in six RCTs with 8,484 patients ($P = 0.26$).

3.5. Lengths of hospital stay

A total of 4,770 patients from 13 studies that reported HLOS ranged between 5 and 24 days were included in the meta-analysis. The average HLOS was 15.2 ± 7.4 days in patients who received corticosteroids during their admission compared to 13.6 ± 7.0 days in patients who were not treated with any type of corticosteroids. With a mean difference of $+1.47 [-0.11, 3.06]$, HLOS did not differ between the two

groups (Fig. 6). Two RCTs with 606 patients reported the duration of HLOS as an endpoint in their trials. There was no significant difference between the two groups, with a mean difference of -0.33 days and 95% CI of -1.06 – $(+0.39)$ days ($P = 0.97$). However, it seems that patients with corticosteroid treatments tended to have a longer stay and 10 out of 13 studies analyzed supported it. This aligns with the fact that sicker patients were more likely to receive corticosteroid treatment.

4. Discussion

Overall, the use of systemic corticosteroids did not reduce Covid-19 infection-related mortality, the frequencies of hospital admissions, and the need for mechanical ventilation. Moreover, the length of hospital stay was not affected using corticosteroids. When only prospective clinical trials were analyzed, there was a significant reduction in the mortality rate by administering corticosteroids.

The length of hospital stay was 15.2 ± 7.4 days in the corticosteroid-treated group, which was reduced by three days when only the data were included from RCTs. However, the results were skewed with significantly shorter LOS in the study conducted by Fadel et al. [14]. This study carried a weight of 35.5% of the results collected from RCTs. Interestingly, when only retrospective studies were analyzed, the LOS was two days longer in the treated group than in the control cohort. This difference indicates a selection bias in retrospective studies as the corticosteroid therapy was initiated in the sicker group of ICU patients, resulting in a more extended stay in the hospital.

Similarly, among 3,472 patients who were enrolled in RCTs and assigned to receive corticosteroids, the rate of death was 23.8% that was significantly less than 31.0% mortality observed in the treated cohort in all retrospective studies. This observation enhances the risk of selection bias in retrospective studies and may imply that treatment with steroids might have been started late in the disease course, or it was only administered to the patients with more advanced injuries.

The hypothetical benefit of steroid therapy in Covid is mainly based

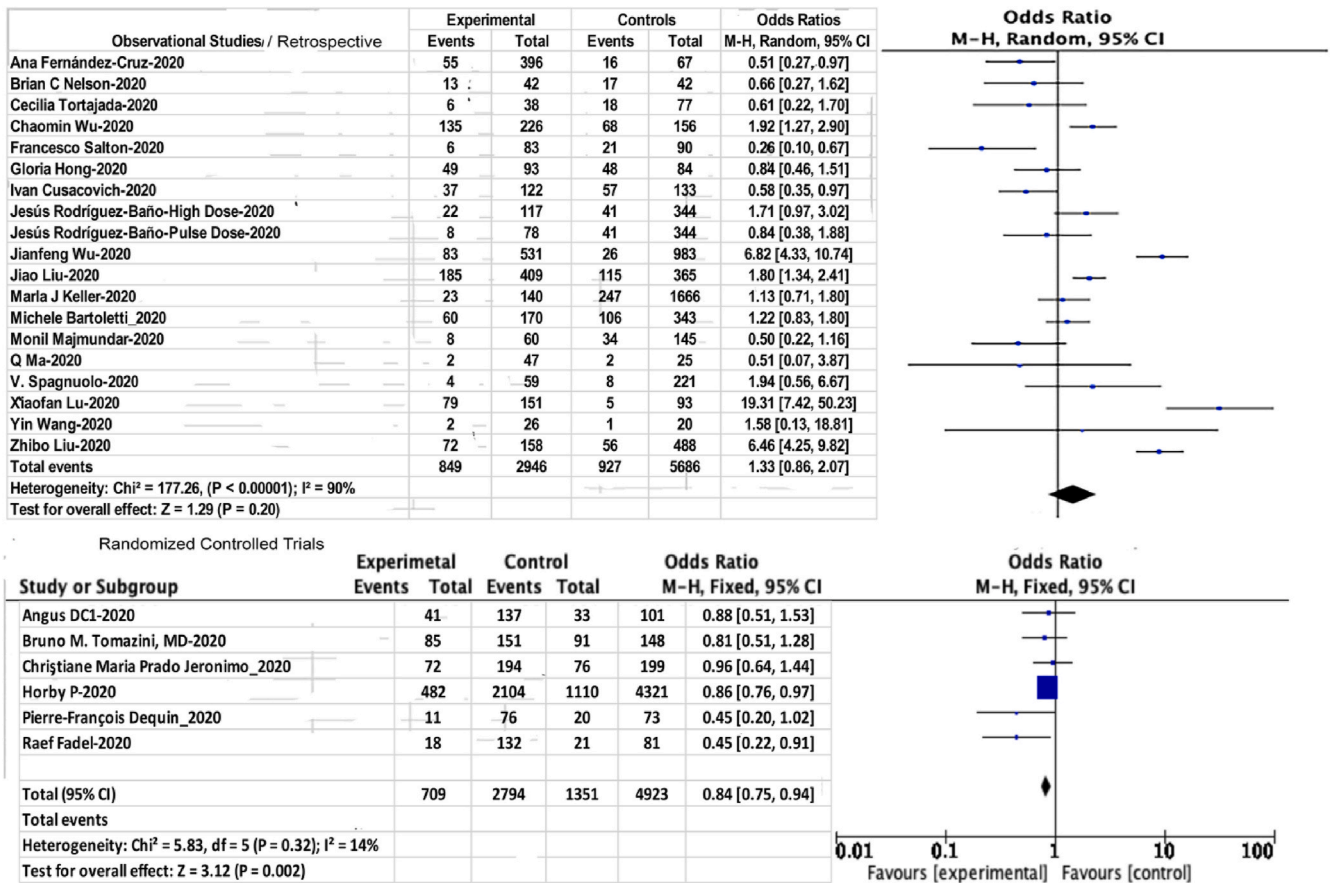


Fig. 2. Forest plot examining the mortality rate of COVID patients comparing the corticosteroid group to control group. The upper panel is only including observational cohort studies while the lower panel includes only randomized controlled trials.

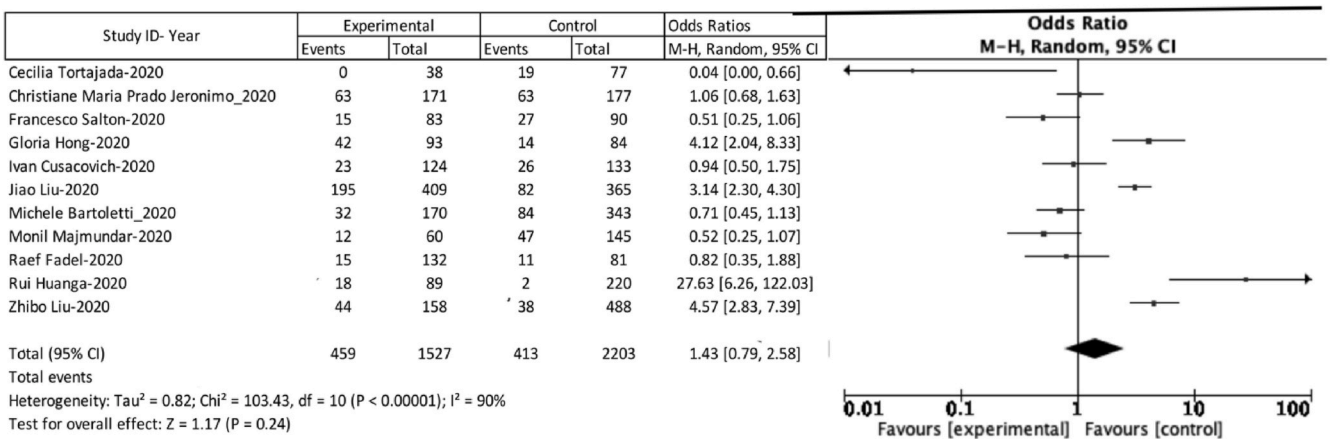


Fig. 3. Forest plot examining the need for ICU admission comparing corticosteroid treatment to controls.

on corticosteroids' ability to inhibit the hyperinflammation or cytokine storm that is well-described among these patients. In this meta-analysis, we have included all studies that compared any steroid use at any dose and compared that to a control cohort who did not receive any steroids whatsoever. In another observational retrospective study, Du Plessis and colleagues examined whether there were differences among patients who received different types of corticosteroids administered in various doses [34]. In this study, patients were treated with high-dose hydrocortisone (N = 88), high-dose methylprednisolone (N = 46), or low-dose dexamethasone (N = 108). During the active phase of Covid-induced respiratory distress. There was no difference in the observed survival

rates among the groups, ranging between 33/3%–38.6%. Additionally, there was no difference in the duration of ICU admission between the groups of patients treated with high-dose hydrocortisone or low-dose dexamethasone. At the same time, there was a slight trend of shorter ICU stay in high-dose methylprednisolone.

We conclude that corticosteroids, when started early in the course of the disease, reduce the mortality rate by 5% in the patients who suffer from pneumonia due to SARS-CoV-2 infection. Other than mortality, the risk of admission to the ICU, placement of the endotracheal tube, and the need for mechanical ventilation are not affected by the administration of corticosteroids. The duration of hospitalization was not affected after

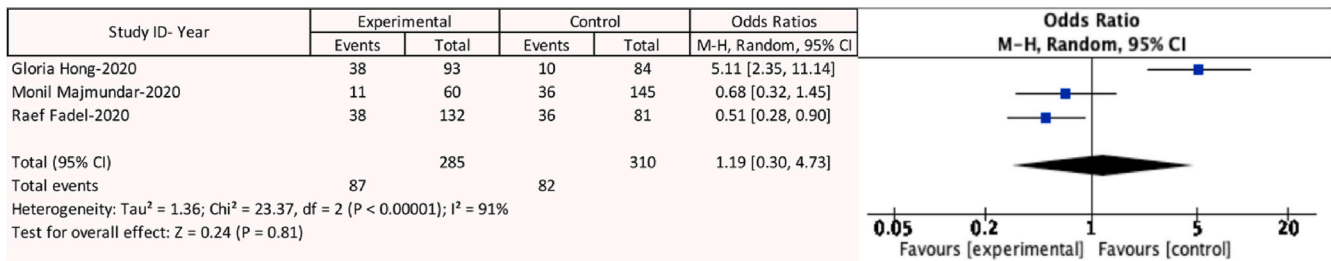


Fig. 4. Forest plot examining the need for placement of an endotracheal tube, comparing the corticosteroid treatment to controls.

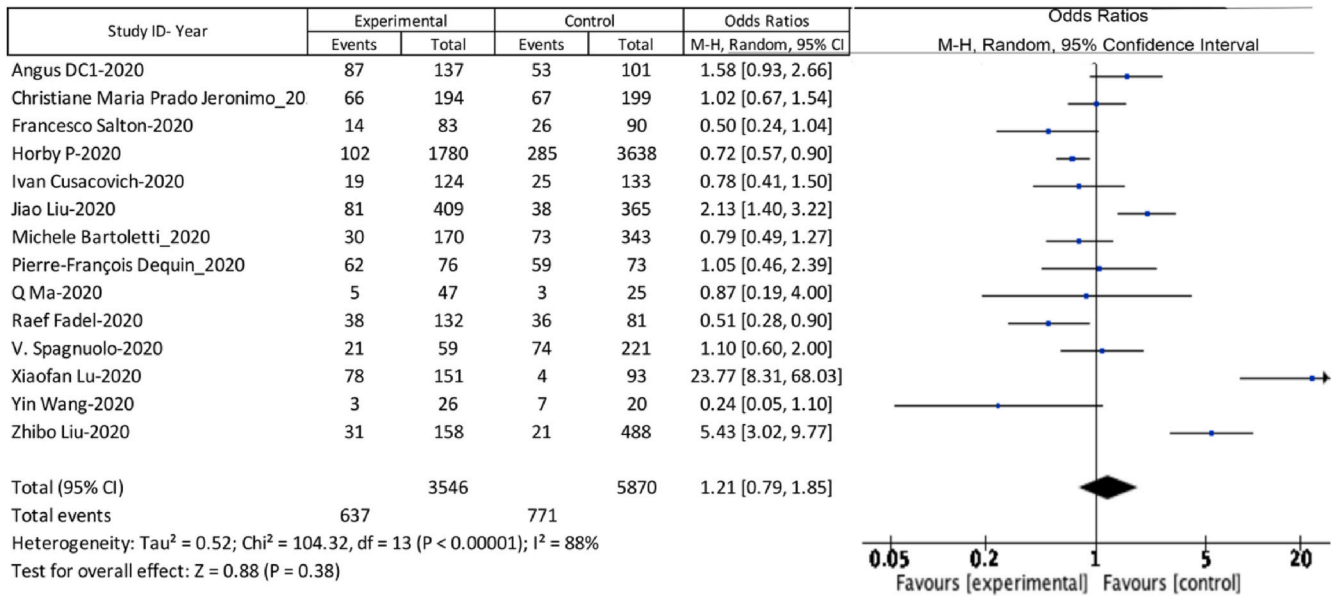


Fig. 5. Forest plot examining the need for mechanical ventilation, comparing corticosteroid treatment to the control group.

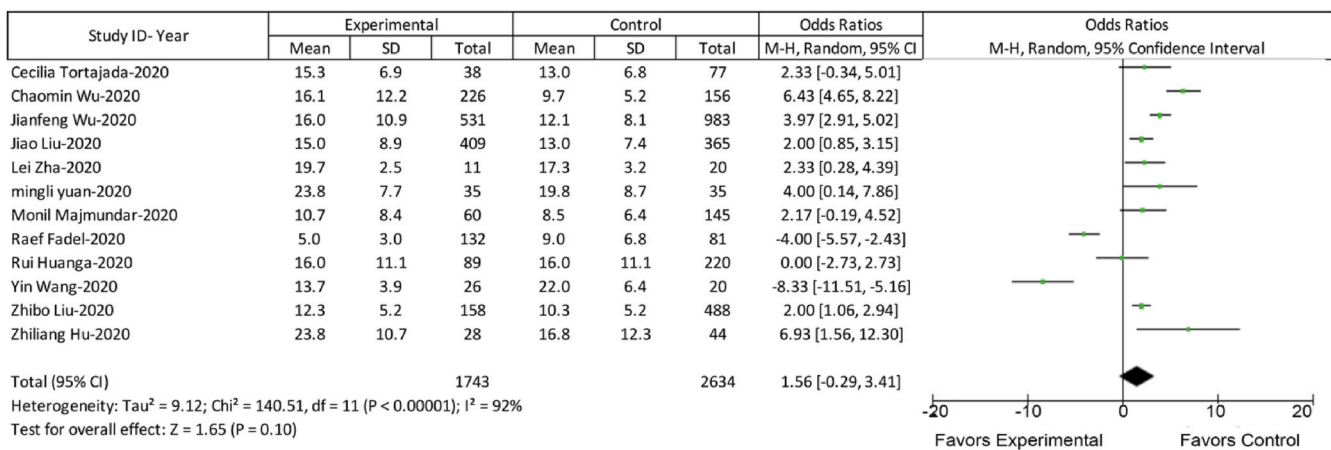


Fig. 6. Forest plot depicting the effect of corticosteroid treatment on the duration of hospital stay when compared to the control group.

this treatment either. We speculate that corticosteroids may benefit only a select group of patients in whom the inflammatory responses are excessive and out of proportion.

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Declaration of competing interest

None was declared by any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pupt.2021.102107>.

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