RESEARCH ARTICLE

Effect of methylprednisolone treatment on COVID-19: An inverse probability of treatment weighting analysis

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Abstract

Objectives

While corticosteroids have been hypothesized to exert protective benefits in patients infected with SARS-CoV-2, data remain mixed. This study sought to investigate the outcomes of methylprednisolone administration in an Italian cohort of hospitalized patients with confirmed SARS-CoV-2 infection.

Methods

Patients with confirmatory testing for SARS-CoV-2 were retrospectively enrolled from a tertiary university hospital in Milan, Italy from March 1st to April 30th, 2020 and divided into two groups by administration of corticosteroids. Methylprednisolone was administered to patients not responding to pharmacological therapy and ventilatory support at 0.5-1mg/kg/day for 4 to 7 days. Inverse probability of treatment weighting (IPTW) was used to adjust for baseline differences between the steroid and non-steroid cohorts via inverse probability of treatment weight. Primary outcomes included acute respiratory failure (ARF), shock, and 30-day mortality among surviving patients.

Results

Among 311 patients enrolled, 71 patients received steroids and 240 did not receive steroids. The mean age was 63.1 years, 35.4% were female, and hypertension, diabetes, heart disease, and chronic pulmonary disease were present in 3.5%, 1.3%, 14.8% and 12.2% respectively. Crude analysis revealed no statistically significant reduction in the incidence of 30-day mortality (36.6% vs 21.7%; OR, 2.09; 95% CI, 1.18–3.70; p = 0.011), shock (2.8% vs 4.6%; OR, 0.60; 95% CI = 0.13–2.79; p = 0.514) or ARF (12.7% vs 15%; OR, 0.82; 95% CI = 0.38–1.80; p = 0.625) between the steroid and non-steroid groups. After IPTW analysis,
the steroid-group had lower incidence of shock (0.9% vs 4.1%; OR, 0.21; 95% CI, 0.06–0.77; p = 0.010), ARF (6.6% vs 16.0%; OR, 0.37; 95% CI, 0.22–0.64; p<0.001) and 30-day mortality (20.3% vs 22.8%; OR 0.86; 95% CI, 0.59–1.26 p = 0.436); even though, for the latter no statistical significance was reached. Steroid use was also associated with increased length of hospital stay both in crude and IPTW analyses. Subgroup analysis revealed that patients with cardiovascular comorbidities or chronic lung diseases were more likely to be steroid responsive. No significant survival benefit was seen after steroid treatment.

Conclusions

Physicians should avoid routine methylprednisolone use in SARS-CoV-2 patients, since it does not reduce 30-day mortality. However, they must consider its use for severe patients with cardiovascular or respiratory comorbidities in order to reduce the incidence of either shock or acute respiratory failure.

Introduction

Since its outbreak in December 2019 in Wuhan, China, the novel coronavirus (SARS-CoV-2) has rapidly become the worst pandemic of the last century [1–3]. To date, SARS-CoV-2 has infected more than 300 million people, causing more than 5 million deaths [4]. Sharing similar genetic constitution and lung pathophysiology with the first SARS-CoV [5], this novel disease has multiple clinical manifestations, ranging from mild symptoms to acute respiratory distress syndrome (ARDS), shock and multiorgan dysfunction [6–9]. At the current time, no treatment has been proven to be effective [6]. Even though remdesivir, hydroxychloroquine and azithromycin have been proposed as possible candidates, strong clinical evidence lacked to support their widespread use [10–13].

Corticosteroids may have a role in the treatment of Covid-19. In particular, due to their anti-inflammatory and anti-fibrotic effects, they may reduce the severity of cytokine release syndrome and prevent progression to pulmonary fibrosis, a severe complication of SARS-CoV-2 disease [14–17]. This hypothesis has been supported by some previous studies [18], and a multicenter randomized controlled trial has reported that early administration may reduce all-cause mortality and duration of mechanical ventilation for ARDS patients [19]. Corticosteroids may not only reduce mortality in sepsis patients [20], but also have beneficial effects in the treatment of Covid-19, especially when administered in the early stages of the disease [21, 22]. Nevertheless, the data is mixed, with some reports supporting their use, especially in severe cases of ARDS [23, 24], and other studies reaching opposite conclusions, arguing that routine administration of corticosteroid can increase mortality [25–28]. To provide further clarity on the potential role of corticosteroids in Covid-19, we used propensity score analysis to study the effect of methylprednisolone on outcomes in a cohort of Italian patients.

Methods

Study design and participants

A retrospective cohort study of SARS-CoV-2 patients was conducted using a cohort of patients hospitalized in a tertiary university hospital in Milan, Italy. SARS-CoV-2 data were retrospectively collected and de-identified from databases of electronic medical records. The study was approved by the Research Committee of Università degli studi di Milano-Bicocca, Milan, Italy.
Medical records of patients admitted to the Emergency ward of Ospedale Maggiore Niguarda, Milan, Italy, from the 1st of March to the 30th of April 2020 were anonymously collected. Due to the retrospective observational nature of our study, the impracticability of obtaining informed consent in debilitated semi-intensive patients and the use of de-identified data, waiver for informed consent was granted. Their data were screened for the following inclusion criteria: 1) Age greater than 18 years old; 2) Confirmation of SARS-CoV-2 pneumonia with a positive swab at admission and typical CT chest pattern of ground-glass opacities and bilateral patchy shadowing. All SARS-CoV-2 patients admitted with a concomitant diagnosis (ie, bowel obstruction, syncope, stroke) were excluded. Glucocorticoids were not prescribed routinely, due to the lack of published data on the issue, but were reserved for severe patients (defined as those with a deteriorating oxygen saturation, not responding to ventilation support), based on the opinion of the physician. Low dose methylprednisolone was used for 4 to 7 days at a dose of 0.5–1 mg/kg/day.

Definitions and outcomes

The following covariates were extracted from the dataset: age, sex, ethnicity, race, smoking status, vital signs including temperature, peripheral oxygen saturation (SpO2), heart rate, respiratory rate (RR), blood pressure (BP), and laboratory results including white blood cell count (WBC), hemoglobin, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), and procalcitonin. We also collected data on the following comorbidities: obesity, immunosuppression, active tumor, pulmonary disease, smoking status, heart disease, vasculopathy, chronic renal failure, arthritis. The outcomes studied included: acute respiratory failure, shock, all-cause mortality and length of hospital stay among surviving patients. We defined acute respiratory failure as the worsening of the general respiratory condition of the patient, necessitating endotracheal intubation and mechanical ventilation.

Statistical analysis

The baseline characteristics of the enrollees were described and compared among steroid-treated and steroid-untreated groups. Categorical variables were presented as a frequency and percentage and were compared between cases and controls using the χ² test. Continuous variables were presented as median and IQR and were compared using the Mann–Whitney U test. To adjust for baseline differences in patient comorbidity and disease severity, inverse probability of treatment weighting (IPTW) was employed. This method was chosen over propensity score (PS) matching because the number of patients between the IHCA and non-IHCA cohorts was highly imbalanced. In IPTW—essentially the inverse of the PS—patients are weighted in inverse proportion to their probability of receiving treatment; thus, those more likely to receive treatment are weighted lower than those less likely. This method creates weighted individual samples, which avoids the loss of unmatched treated patients that might otherwise occur in PS matching. By creating weighted samples of treatment and control individuals with balanced baseline covariates, IPTW mimics a randomized control trial. We created a PS including 23 potential predictors that reflects the conditional probability of receiving steroid treatment versus controls. To visualize the balance of covariates after IPTW, we plotted the standardized mean differences of all covariates before and after IPTW (S1 Fig). In online S1 Table, we report the c-statistics of the PS model, component variables and the respective weights of the component variables. Briefly, the covariates are: age, gender, comorbidities, presenting vital signs, laboratory results and concomitant treatment. To further assess the potential interaction effects, we performed subgroup analyses. For each study outcome, an odd ratio
with associated 95% confidence interval was estimated for the IPTW samples using a weighted binary logistic regression model with a robust variance estimator. In addition, Kaplan–Meier survival plots were generated to track mortality over time for the original and IPTW cohorts. Furthermore, a series of subgroup analyses were performed to test the potential interaction between steroid treatment and the predefined clinically meaningful subgroups, including age, gender, presence of cardiovascular diseases, diabetes or obesity. A p-value of 0.05 or less was considered significant. All analyses were carried out using SAS V.9.3 for Windows (SAS Institute Inc, Cary, North Carolina, USA), and the data are reported in accordance with STROBE guidelines.

Results

A total of 311 patients were eligible for the study. Of these patients, 71 received steroid treatment, while 240 received non-steroid treatment. In the study, the mean age was 63.1 years and there were 35.4% of female patients. A history of hypertension was present in 3.5% of the patients, diabetes mellitus in 1.3%, heart disease in 14.8% and chronic pulmonary disease in 12.2%.

The baseline characteristics for steroid group and non-steroid group are shown in Table 1. Steroid group patients were older (p < 0.001); suffered more from diabetes (p = 0.002), immunosuppression (p = 0.004), active tumor (p = 0.017); had higher respiratory rate in the emergency department (p = 0.029) and lower diastolic blood pressure (p = 0.041). There were no significant differences in sex (p = 0.307), and the following comorbidities: hypertension (p = 0.470), chronic pulmonary disease (p = 1.000), coronary artery disease (1.000), stroke (p = 0.898) and chronic kidney disease (1.000). For the pre-treatment laboratory results of each group, white blood cell count (steroid, 18.359 10^3/mm^3; non-steroid, 6.386 10^3/mm^3; p = 0.038), hemoglobin (steroid, 13.25 g/dL; non-steroid, 13.09 g/dL; p = 0.011), hs-CPR (steroid, 8.61 mg/dL; non-steroid, 6.11 mg/dL; p = 0.008), ALT (steroid, 27.06 U/L; non-steroid, 24.07 U/L; p < 0.001), Creatinine (steroid, 1.65 mg/dL; non-steroid, 1.13 mg/dL; p < 0.001), and Urea (steroid, 13.16 mg/dL; non-steroid, 11.97 mg/dL; p < 0.001) were higher in the steroid treatment group. No significant difference was noted for symptoms; more patients in the steroid group were concomitantly treated with Lopinavir/ritonavir (steroid, 91.5%; non-steroid, 74.6%; p = 0.004).

In the crude analysis, steroid treatment was not significantly associated with reduced incidence of either shock or acute respiratory failure (ARF), however it was associated with an increase in 30-day mortality (steroid, 36.6%; non-steroid, 21.7%; OR, 2.09; 95% CI, 1.18–3.70; p = 0.011) and length of hospital stay among the survived patients (Table 2). After the application of inverse probability of treatment weighting (IPTW), we noted that the steroid-group had lower incidence of shock (steroid, 0.9%; non-steroid, 4.1%; OR, 0.21; 95% CI,0.06–0.77; p = 0.010), ARF (steroid, 6.6%; non-steroid, 16.0%; OR, 0.37; 95% CI, 0.22–0.64; p < 0.001) and 30-day mortality (steroid, 20.3%; non-steroid, 22.8%; OR 0.86; 95% CI, 0.59–1.26 p = 0.436); even though, for the latter no statistical significance was reached (Table 2). Furthermore, steroid use was associated with increased duration of hospitalization both in crude and IPTW analyses.

Additionally, we performed subgroup analysis on post-discharge 30-day mortality after IPTW. We observed that patients with cardiovascular comorbidities or chronic lung diseases were more likely to respond to steroids (Table 3). The 30-day Kaplan–Meier survival curves are shown in Fig 1. There were no mortality differences after IPTW between the steroid and non-steroid groups (Fig 1B). When applying subgroup analyses in acute respiratory distress and acute respiratory failure patients, this persisted (Fig 1C and 1D).
In this study, we investigated the effect of short cycles of low-dose methylprednisolone in patients with SARS-CoV-2 related pneumonia. To do this, we collected data from 311 Italian patients. The results are presented in Table 1.

**Demographics**

|                   | Steroid use (n = 71) | Non steroid use (n = 240) | p-value |
|-------------------|----------------------|---------------------------|---------|
| Age (mean (SD))   | 69.92 (13.72)        | 61.12 (17.07)             | <0.001  |
| Sex male          | 50 (70.4%)           | 151 (62.9%)               | 0.307   |

**Symptoms**

|                  | Steroid use (n = 71) | Non steroid use (n = 240) | p-value |
|------------------|----------------------|---------------------------|---------|
| Fever            | 61 (85.9%)           | 224 (93.3%)               | 0.082   |
| Cough            | 40 (56.3%)           | 144 (60.0%)               | 0.679   |
| Dyspnea          | 25 (35.2%)           | 78 (32.5%)                | 0.777   |
| Headache         | 4 (5.6%)             | 29 (12.1%)                | 0.183   |
| Diarrhea         | 6 (8.5%)             | 33 (13.8%)                | 0.327   |
| Syncope          | 5 (7.0%)             | 9 (3.8%)                  | 0.396   |
| Symptom duration | 5.31 (3.16)          | 5.93 (3.66)               | 0.198   |

**Comorbidity**

|                  | Steroid use (n = 71) | Non steroid use (n = 240) | p-value |
|------------------|----------------------|---------------------------|---------|
| Hypertension     | 4 (5.6%)             | 7 (2.9%)                  | 0.470   |
| Diabetes         | 4 (5.6%)             | 0 (0.0%)                  | 0.002   |
| Active tumor     | 11 (15.5%)           | 14 (5.8%)                 | 0.017   |
| Immunosuppression| 10 (14.1%)           | 9 (3.8%)                  | 0.004   |
| Chronic pulmonary disease | 10 (14.1%) | 36 (15.0%) | 1.000 |
| Coronary artery disease | 9 (12.7%) | 29 (12.1%) | 1.000 |
| Stroke           | 6 (8.5%)             | 17 (7.1%)                 | 0.898   |
| Chronic Kidney disease | 5 (7.0%) | 12 (5.0%) | 0.713 |

**Vital sign on presentation (mean (SD))**

|                  | Steroid use (n = 71) | Non steroid use (n = 240) | p-value |
|------------------|----------------------|---------------------------|---------|
| Temperature      | 37.48 (0.30)         | 37.50 (0.27)              | 0.603   |
| Heart rate       | 97.39 (5.74)         | 98.47 (4.14)              | 0.082   |
| Respiratory rate | 21.40 (2.31)         | 20.96 (1.13)              | 0.029   |
| Systolic blood pressure | 130.88 (11.28) | 130.47 (6.76) | 0.703 |
| Diastolic blood pressure | 75.58 (4.67) | 76.46 (2.59) | 0.041 |

**Laboratory results (mean (SD))**

|                          | Steroid use (n = 71) | Non steroid use (n = 240) | p-value |
|--------------------------|----------------------|---------------------------|---------|
| White blood cell (10^3/mm^3) | 18.36 (8.93)   | 6.39 (3.08)               | 0.038   |
| Hemoglobin concentration (g/dL) | 13.25 (0.68) | 13.09 (0.36) | 0.011   |
| Platelet count (10^3/mm^3)    | 1.84 (7.58)    | 2.00 (7.90)               | 0.145   |
| Absolute neutrophil count (10^3/mm^3) | 4.10 (1.00) | 3.94 (0.72) | 0.135   |
| Absolute lymphocyte count (10^3/mm^3) | 1.33 (2.59) | 1.12 (0.43) | 0.230   |
| hs-CRP (mg/dL)             | 8.61 (7.28)     | 6.11 (6.91)               | 0.008   |
| PCT (ng/mL)                | 1.20 (5.38)     | 1.01 (10.51)              | 0.887   |
| Total bilirubin (mg/dL)    | 0.58 (0.28)     | 0.57 (0.36)               | 0.849   |
| ALT (U/L)                  | 27.06 (5.01)    | 24.07 (3.08)              | <0.001  |
| Creatinine (mg/dL)         | 1.65 (1.74)     | 1.13 (0.76)               | <0.001  |
| Blood sugar (mg/dL)        | 121.81 (23.62)  | 117.68 (13.07)            | 0.058   |
| Urea nitrogen (mg/dL)      | 13.16 (2.87)    | 11.97 (1.37)              | <0.001  |

**Concomitant treatment**

|                          | Steroid use (n = 71) | Non steroid use (n = 240) | p-value |
|--------------------------|----------------------|---------------------------|---------|
| Lopinavir/ritonavir      | 65 (91.5%)           | 179 (74.6%)               | 0.004   |

*Note: hs-CRP, high sensitivity C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase.

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**Discussion**

In this study, we investigated the effect of short cycles of low-dose methylprednisolone in patients with SARS-CoV-2 related pneumonia. To do this, we collected data from 311 Italian patients...
patients at a tertiary referral hospital. After the IPTW analysis, we found that corticosteroid users had a lower incidence of shock and acute respiratory failure, but no reduction in 30-day mortality was evident. Furthermore, we demonstrated that corticosteroid use increased the length of hospital stay; we can hypothesize that this relationship might be due to the possible side effects of its use, such as electrolyte abnormalities, hypertension or hyperglycemia, for example. Patients with cardiovascular comorbidities or chronic lung diseases were more likely to be steroid responsive. The results of our study support the assertion that corticosteroids can

Table 2. Comparison of in-hospital mortality between patients with/without steroid treatment. Survival differences were calculated as odds ratio (OR). We used the IPTW method to adjust for the potential confounding.

|                      | Steroid treatment (n = 71) | Non-steroid treatment (n = 240) | OR (95% CI)   | p-value |
|----------------------|----------------------------|---------------------------------|---------------|---------|
| **Crude analysis**   |                            |                                 |               |         |
| Shock                | 2 (2.8%)                   | 11 (4.6%)                       | 0.60 (0.13–2.79) | 0.5142  |
| Acute respiratory failure | 9 (12.7%)               | 36 (15.0%)                      | 0.82 (0.38–1.80) | 0.6254  |
| 30-day mortality     | 26 (36.6%)                 | 52 (21.7%)                      | 2.09 (1.18–3.70) | 0.0108  |
| Length of hospital stay among the survived patients (median, 25th and 75th quartile) | 10 (8–11) | 7 (6–10) | NA | 0.0016 |
| **IPTW-weighted analysis** (n = 313) (n = 309) |                                 |                                 |               |         |
| Shock                | 3 (0.9%)                   | 13 (4.1%)                       | 0.21 (0.06–0.77) | 0.0096  |
| Acute respiratory failure | 21 (6.6%)               | 49 (16.0%)                      | 0.37 (0.22–0.64) | 0.0002  |
| 30-day mortality     | 63 (20.3%)                 | 71 (22.8%)                      | 0.86 (0.59–1.26) | 0.4364  |
| Length of hospital stay among the survived patients (median, 25th and 75th quartile) | 10 (8–11) | 8 (6–10) | NA | 0.0014 |

Table 3. Subgroup analysis for 30-day in-hospital mortality after IPTW-weighting.

|                  | Hazard ratio (95% CI) | Interaction P |
|------------------|-----------------------|---------------|
| Age > 75 years   | 0.82 (0.59–1.29)      | 0.9299        |
| Age <= 75 years  | 0.75 (0.45–1.27)      |               |
| Male             | 0.90 (0.62–1.31)      | 0.7716        |
| Female           | 0.75 (0.35–1.63)      |               |
| Cardiovascular disease* | 0.53 (0.32–0.88) | 0.0036        |
| Non-cardiovascular disease | 1.26 (0.79–2.03)       |               |
| Acute respiratory failure | 0.92 (0.43–1.95) | 0.8685        |
| Non-acute respiratory failure | 1.02 (0.69–1.51)     |               |
| Shock            | 1.92 (0.24–15.71)     | 0.6340        |
| Non-shock        | 0.88 (0.62–1.64)      |               |
| Chronic lung disease | 0.26 (0.11–0.60)     | 0.0018        |
| No chronic lung disease | 1.15 (0.78–1.67) |               |
| Acute respiratory distress (oxygen dependent) | 0.83 (0.54–1.27) | 0.2012        |
| Non-acute respiratory distress | 1.15 (0.65–2.03) |               |

*Cardiovascular disease includes myocardial infarction, cerebrovascular disease, peripheral vascular disease and congestive heart failure.
be beneficial in severe patients, particularly in those with cardiovascular or respiratory comorbidities, but are not recommended for routine use, considering the risk/benefit ratio and the associated increase in hospitalization duration.

Corticosteroids, due to their anti-inflammatory and anti-fibrotic effects, have been hypothesized to have utility in the management of SARS-CoV-2 related pneumonia and ARDS via reduction of the severity of cytokine release syndrome, preventing progression to pulmonary fibrosis. However, corticosteroid use is accompanied by side effects, including immunosuppression, hyperglycemia, hypokalemia, kidney damage and altered mental state. This

Fig 1. The 30-day Kaplan-Meier cumulative survival analyses between patients with steroid pretreatment versus patients without steroid pretreatment. (A) Before IPTW (B) After IPTW (C) Acute respiratory distress (Oxygen dependent) (D) Acute respiratory failure (requirement of ventilator).

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dichotomy of risk and benefits regarding the use of corticosteroids in SARS-CoV-2 patients could be related to the severity of the disease. In fact, while several studies have stated that the routine administration of corticosteroid can affect survival, increasing mortality [25, 26, 29], a recent multicenter, randomized controlled trial (Randomised Evaluation of COVID-19 therapy trial–RECOVERY) has reported that the early administration of corticosteroid might reduce all-cause mortality and duration of mechanical ventilation for ARDS patients [23].

The RECOVERY trial was a large trial that randomized patients hospitalized with severe Covid-19 infection to receive one (or none) of the trial treatments (including low-dose dexamethasone). The primary outcome was all-cause mortality at 28 days. The RECOVERY trial observed that low-dose dexamethasone could reduce mortality among patients receiving invasive mechanical ventilation or among those receiving oxygen without invasive mechanical ventilation. No beneficial effect was registered among those receiving no respiratory support. However, some limitations were identified. First, the dexamethasone use was found beneficial only for severe patients and could not be applied as a routine therapy. Second, at the end of the 28-day trial period around a third of patients were still hospitalized, thus, their final outcomes were not known.

There are several reasons why our results differ from those in the RECOVERY trial. Firstly, the retrospective and non-randomised nature of our study could have affected our results, due to bias we could not exclude with the analysis. Second, our cohort was composed of a population of patients, coming from the second most hit by SARS-CoV-2 country; in comparison, the British cohort studied in RECOVERY was affected later on. Third, our patients were prescribed methylprednisolone and not dexamethasone. Even though the two drugs are part of the same category; individual effects differ and could have affected the results; in fact, the benefit in mortality might have been more noteworthy over longer follow-up. However, even though some differences between the two studies are present, our results are consistent with the published data. To this end, we demonstrated that methylprednisolone had no beneficial effect in reducing mortality, however similarly to the RECOVERY trial, we observed a potential protective effect of the use of corticosteroid on acute respiratory failure and shock, especially in patients with cardiovascular or respiratory comorbidities. Our study supported a possible beneficial effect of the use of corticosteroid could be applicable to severe patients, while the routine use should be avoided.

Conclusion

Physicians should avoid routine methylprednisolone use in SARS-CoV-2 patients, as its use is not associated with any beneficial effects in reducing 30-day mortality. However, they must consider methylprednisolone use for severe patients in order to reduce the incidence of either shock or acute respiratory failure, especially in patients with cardiovascular or respiratory comorbidities.

Supporting information

S1 Checklist. STROBE statement—Checklist of items that should be included in reports of observational studies.

(PDF)

S1 Fig. Standardized difference graph before and after IPTW. *Note: hs-CRP, high sensitivity C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; wbc, white blood cell count PCT, procalcitonin; HTN, hypertension; CKD, chronic kidney disease; CAD, coronary artery disease.

(TIFF)
S1 Table. Empirical predictors of steroid treatment with associated odds ratios for in the propensity score model. *Note: CKD, chronic kidney disease; hs-CRP, high sensitivity C-reactive protein; PCT, procalcitonin.

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