Methylprednisolone was Associated with Reduced in-Hospital Mortality in COVID-19 Patients with Low Lymphocyte Counts: a Multicenter Retrospective Propensity Analysis

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Abstract

Background: To assess the effect of methylprednisolone on the prognosis of patients with novel coronavirus pneumonia.

Methods: Patients with confirmed novel coronavirus pneumonia discharged from Wuhan Third Hospital Guanggu Campus, Shouyi Campus, and Lei Shen Shan Hospital from January 31, 2020, to March 4, 2020, were included. The patients were divided into treatment and control groups according to whether methylprednisolone was used during hospitalization. Propensity score (PS) matching analysis was used to assess in-hospital mortality as the primary outcome and trends in the changes in lymphocytes and the C-reactive protein, creatinine and transaminase levels 7 days after admission (secondary outcomes).

Results: A total of 2,062 patients with confirmed novel coronavirus pneumonia were included in this study. Univariate Cox regression analysis suggested that methylprednisolone treatment was associated with increased in-hospital mortality (hazard ratio (HR) 3.70, 95% confidence interval (CI) 2.62-5.23, P<0.01). A total of 624 patients were included after PS matching. The patients were further subdivided into a low lymphocyte count group and a normal lymphocyte count group according to a lymphocyte count cutoff value of 0.9×10^9/L. Kaplan-Meier survival curve analysis showed that methylprednisolone treatment reduced the risk of in-hospital death in patients with lymphocyte counts less than 0.9×10^9/L (P=0.022). In contrast, in the normal lymphocyte group, methylprednisolone treatment was not associated with in-hospital mortality (p=0.88).

Conclusion: Treatment with methylprednisolone may be associated with reduced in-hospital mortality in coronavirus disease (COVID) patients with low lymphocyte counts.

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease characterized by pneumonia caused by a novel coronavirus (severe acute respiratory distress coronavirus 2; SARS-CoV-2) infection. With 223 countries worldwide reporting cases of COVID-19, more than 127.34 million cases, and more than 2.78 million deaths have been reported as of March 2021, and COVID-19 has become a public health threat to all humans [1]. The pathogenesis of COVID-19 infection is not yet clear, and there are no effective drugs available thus far.

Previous studies have shown that glucocorticoids significantly improve gas exchange and shorten the duration of mechanical ventilation and intensive care unit (ICU) stay in patients with severe hypoxia in acute respiratory distress syndrome (ARDS) [2]. Glucocorticoids have been widely used in the treatment of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) infections. Retrospective studies have shown that glucocorticoids can reduce morbidity, mortality and hospitalization time in SARS patients [3], however, there are also findings that glucocorticoids may increase mortality and delay viral clearance in SARS patients [4, 5]. The role of glucocorticoids in MERS patients is also controversial [6, 7].
The results of a recent UK randomized controlled trial (RCT) of dexamethasone treatment in hospitalized patients with COVID-19[8] showed that dexamethasone treatment was associated with reduced 28-day mortality in patients (22.9% in the dexamethasone treatment group vs. 25.7% in the control group, age-adjusted RR 0.83, 95% confidence interval (CI) 0.75–0.93). However, a retrospective study by Chen D.C. et al showed that corticosteroid treatment may increase mortality in patients with severe COVID-19 with ARDS (adjusted hazard ratio (HR) 1.46, 95% CI 1.01–2.13, P = 0.045) and delay clearance of SARS-CoV-2 (HR 1.59, 95% CI 1.17–2.15, P = 0.003) [9]. The reason for the contradictory results may be the differences in the disease states of the study subjects. In addition, the RCTs that have yielded positive findings were mainly conducted in patients with more severe disease, such as those on invasive ventilators, and the mechanism is unclear [10]. Previous studies have found that lymphopenia is a common feature of COVID-19 patients [11] and that lower lymphocytes tend to be associated with higher mortality: with lower lymphocytes, the patient may be sicker [12]. The prognosis related to glucocorticoid treatment in patients with different lymphocyte counts is unclear. We hypothesized that methylprednisolone treatment might be associated with reduced in-hospital mortality in patients with low lymphocyte counts. Therefore, we retrospectively analyzed the effect of methylprednisolone on mortality in patients with COVID-19 with different lymphocyte counts by propensity score (PS) matching analysis.

**Methods**

**Study population**

This is a multicenter retrospective study. This study analyzed patients with confirmed novel coronavirus pneumonia who were discharged from Wuhan Third Hospital Guanggu Campus, Shouyi Campus, and Lei Shen Shan Hospital from January 31, 2020, to March 4, 2020. Ethical approval was obtained from Shanghai General Hospital. Patient consent was waived because the study was retrospective and did not disclose any personal information of the patients. All patients were tested for SARS-CoV-2 by real-time RT-PCR using upper respiratory swabs. A retrospective case-control approach was used to divide patients into a group that received methylprednisolone during hospitalization (the MP group) and one that did not (the non-MP group). After PS matching, patients were further subdivided into a low lymphocyte control group, a low lymphocyte methylprednisolone treatment group, a normal lymphocyte control group and a normal lymphocyte methylprednisolone treatment group according to a lymphocyte count cutoff value of 0.90*10^9/L. Epidemiological data, laboratory findings, lung imaging information, and treatment regimen and treatment outcome data were collected from patients. The patients were followed up until April 1, 2020.

**Inclusion and exclusion criteria**

Study inclusion criteria: 1, age ≥ 18 years; and 2, fulfilment of the diagnostic criteria of the Chinese Health and Wellness Commission's "Treatment protocol for novel coronavirus pneumonia (trial 5th edition)"[13] (clinically diagnosed cases or suspected cases with one of the following pathogenic signs: 1. positive novel coronavirus nucleic acid result by real-time fluorescent RT-PCR of respiratory or blood specimens;
and 2. respiratory specimen or blood specimen sequencing for viral genes that are highly homologous to known novel coronaviruses).

The exclusion criteria were as follows: 1, patients with incomplete information; and 2, patients who received glucocorticoid treatment other than methylprednisolone, such as dexamethasone or hydrocortisone treatment, during hospitalization.

**Treatment protocol**

The treatment protocol was as follows. All patients were treated with antiviral therapy with abiraterone, lopinavir/ritonavir or ganciclovir in addition to oxygen therapy. Prophylactic antibiotics (moxifloxacin or cephalexin/sulbactam) were administered according to the patient's admission status. Antibiotic adjustment was employed according to the patient's clinical signs and symptoms and laboratory results. Anticoagulation therapy with low-molecular-weight heparin was administered according to the patient's condition. When the absolute lymphocyte count was below 0.5 × 10⁹/L, intravenous immunoglobulin and/or thymidine α₁ was administered to enhance immune function. Some patients were treated with small doses of intravenous glucocorticoids (methylprednisolone, 1–2 mg/kg) for 5–7 days, depending on their condition. The rest of the treatment was based on the Chinese Health and Wellness Commission's "Treatment protocol for novel coronavirus pneumonia (trial 5th edition)" [13].

**Observation endpoint**

Primary outcome: In-hospital mortality.

Secondary outcome: Trends in the changes in lymphocytes and C-reactive protein, creatinine and transaminase levels 7 days after admission.

**Statistical analysis**

Since the use of methylprednisolone may be preferred for patients with severe disease, to reduce selection bias, we calculated the inverse weighted probability for each patient using propensity analysis in the treatment and control groups. We used the gradient boosting model (GBM) to estimate patients' propensity scores for methylprednisolone to minimize the covariance imbalance between the methylprednisolone and control groups. We chose a matching ratio of 1:2, and the caliper was 0.2. The GBM is a machine learning algorithm that successively constructs new models and forms ensembles of models to provide more accurate estimates of response variables. The main idea is to construct new base learners that maximize the negative gradient correlation with a predefined loss function. In our study, a regression tree was used as the base learner for GBM, and a total of 7 covariates (age, sex, severity, C-reactive protein level, creatinine level, glutamate level, and patient ventilation mode) were used in the model. The primary outcome of in-hospital mortality was analyzed as an indicator of survival using Kaplan-Meier curves, and the Cox proportional risk model was used to calculate the hazard ratios and 95% CIs for the primary outcome. Statistical analyses were performed using R software (R 3.6.1) and Rstudio (1.2.1355, RStudio, Inc.). In the analysis of the two groups, the demographic characteristics, clinical features, laboratory test results at admission and after admission, and treatments were
compared. Categorical variables were expressed as counts (%) using the chi-square test. Continuous normally distributed variables are expressed as the mean (SD) using a t-test for continuous measurements. The Wilcoxon test was used for continuous nonnormally distributed variables, and results are expressed as the median (interquartile range; IQR). Repeated-measures ANOVA was used for multiple-measure continuous variables. P values less than 0.05 were considered to indicate statistical differences.

Results

Basic patient information

A total of 2,062 patients were enrolled in this study, including 1,001 males and 1,061 females, with an average age of 62.00 ± 15.35 years and an average hospital stay of 16.00 ± 8.83 days. According to the grouping criteria, there were 272 patients in the MP group and 1,790 patients in the control group (non-MP group). Confounding factors such as age, sex, disease severity, C-reactive protein level, creatinine level, glutamate transaminase level and oxygen therapy method were controlled by PS matching. After PS matching, a total of 624 patients were included in the study: 208 were in the MP group, and 416 were in the non-MP group. We stratified the patients according to whether their lymphocyte counts were below $0.9 \times 10^9$/L. Of the 624 patients, 19.55% were critical cases, and 29.97% were severe cases. A comparison of the basic characteristics of the patients in both groups is detailed in Table 1.
Table 1
The Demographic data of this Study

|                | Unmatched | Matched |
|----------------|-----------|---------|
|                | Non-MP    | MP      | P-value | SMD1 | Non-MP | MP | SMD2 |
|                | N = 1790  | N = 272 |         |       | N = 416 | N = 208 |       |
| Age (mean (SD))| 59.94 (15.53) | 60.15 (14.17) | 0.836 | 0.014 | 59.63 (14.13) | 59.50 (14.04) | 0.010 |
| Male (%)       | 845 (47.2) | 156 (57.4) | 0.002 | 0.204 | 257 (61.8) | 106 (51.0) | 0.219 |
| Severity of illness (%) | < 0.001 | 0.720 |         |       |         |       | 0.112 |
| Critical       | 132 (7.4) | 75 (27.6) |     |       | 87 (20.9) | 35 (16.8) |       |
| Severe         | 342 (19.1) | 83 (30.5) | 0.150 | 0.096 | 125 (30.0) | 62 (29.8) |       |
| Other          | 1316 (73.5) | 114 (41.9) |     |       | 204 (49.0) | 111 (53.4) |       |
| Campus (%)     | < 0.001 | 0.861 |         |       |         |       | 0.623 |
| Guguang        | 988 (55.2) | 243 (89.3) |     |       | 293 (70.4) | 193 (92.8) |       |
| Lei Shen Shan  | 473 (26.4) | 26 (9.6) |     |       | 66 (15.9) | 12 (5.8) |       |
| Shouyi         | 329 (18.4) | 3 (1.1) |     |       | 57 (13.7) | 3 (1.4) |       |
| Hypertension (%)| 289 (16.2) | 54 (19.9) | 0.150 | 0.096 | 58 (13.9) | 35 (16.8) | 0.080 |
| Heart failure (%)| 25 (1.4) | 8 (2.9) | 0.103 | 0.106 | 6 (1.4) | 4 (1.9) | 0.037 |
| Diabetes (%)   | 137 (7.7) | 55 (20.2) | < 0.001 | 0.369 | 28 (6.7) | 39 (18.8) | 0.366 |
| Coronary artery disease (%) | 99 (5.5) | 20 (7.4) | 0.289 | 0.074 | 20 (4.8) | 14 (6.7) | 0.083 |
| Renal disease (%) | 120 (7.1) | 36 (13.2) | 0.001 | 0.206 | 39 (9.8) | 21 (10.1) | 0.008 |
| Liver disease (%) | 74 (4.4) | 48 (17.6) | < 0.001 | 0.435 | 36 (9.1) | 32 (15.4) | 0.193 |

Abbreviations: WBC: white blood cell; CRP: C reactive protein; Cr: creatinine; AST: aspartate aminotransferase; HFNC: high-flow nasal cannula oxygen therapy; ECMO: extracorporeal membrane oxygenation
|                          | Unmatched          | Matched           |   |
|--------------------------|--------------------|-------------------|---|
| **Lymphocyte (mean (SD))** | 1.37 (0.59)        | 0.83 (0.40)       | < 0.001 |
|                          |                    | 1.062             | 1.02 (0.52) |
|                          |                    | 0.89 (0.41)       | 0.280 |
| **WBC (mean (SD))**      | 5.94 (2.74)        | 5.86 (3.05)       | 0.646 |
|                          |                    | 6.53 (4.07)       | 5.46 (2.86) |
|                          |                    | 0.029             | 0.305 |
| **CRP (mean (SD))**      | 23.42 (46.11)      | 74.98 (75.92)     | < 0.001 |
|                          |                    | 66.72 (71.21)     | 54.73 (61.60) |
|                          |                    | 0.821             | 0.180 |
| **Cr (mean (SD))**       | 102.15 (189.62)    | 107.04 (199.79)   | 0.708 |
|                          |                    | 107.32 (200.22)   | 97.33 (156.06) |
|                          |                    | 0.025             | 0.056 |
| **AST (mean (SD))**      | 34.24 (114.86)     | 46.74 (62.10)     | 0.094 |
|                          |                    | 45.08 (68.63)     | 43.17 (69.75) |
|                          |                    | 0.135             | 0.028 |
| **Oxygen therapy (%)**   |                    | < 0.001           | 0.457 |
| None                     | 889 (49.7)         | 101 (37.1)        | 182 (43.8) |
|                          |                    | 95 (45.7)         |   |
| Oxygen                   | 841 (47.0)         | 129 (47.4)        | 188 (45.2) |
|                          |                    | 99 (47.6)         |   |
| BiPAP                    | 1 (0.1)            | 5 (1.8)           | 1 (0.2) |
| Mechanical Ventilation   | 49 (2.7)           | 31 (11.4)         | 40 (9.6) |
| HFNC                     | 10 (0.6)           | 4 (1.5)           | 5 (1.2) |
| ECMO                     | 0 (0.0)            | 2 (0.7)           | 0 (0.0) |
| Mechanical Ventilation (%)| 49 (2.7)           | 33 (12.1)         | < 0.001 |
|                          |                    | 0.364             | 0.145 |

**Abbreviations:** WBC: white blood cell; CRP: C reactive protein; Cr: creatinine; AST: aspartate aminotransferase; HFNC: high-flow nasal cannula oxygen therapy; ECMO: extracorporeal membrane oxygenation

Patients in the matched MP group had significantly higher rates of dopamine, thymidine and immunoglobulin treatment, with no significant difference in norepinephrine treatment between the two matched groups. The treatment differences between the two groups are detailed in Table 2.
### Table 2
Treatment detail

|                        | Non-MP group in unmatched cohort | MP group in unmatched cohort | P value | Non-MP group in matched cohort | MP group in matched cohort | P value |
|------------------------|----------------------------------|-----------------------------|---------|---------------------------------|----------------------------|---------|
| n                      | 1790                             | 272                         |         | 416                             | 208                        |         |
| Frequency (median [IQR])| 0.00 [0.00, 7.00]                | 8.50 [3.00, 16.00]          | < 0.001 | 0.00 [0.00, 0.00]                | 8.00 [3.00, 15.00]          | < 0.001 |
| Total dose (median [IQR]) | 0.00 [0.00, 280.00]             | 421.00 [120.00, 1040.00]    | < 0.001 | 0.00 [0.00, 0.00]                | 330.00 [120.00, 1040.00]    | < 0.001 |
| LOS (mean (SD))        | 16.17 (8.20)                     | 20.87 (11.40)               | < 0.001 | 16.59 (9.00)                    | 21.71 (11.51)               | < 0.001 |
| DP total dose (mean (SD)) | 0.06 (1.67)                    | 1.40 (12.08)                | < 0.001 | 0.27 (3.47)                     | 1.75 (13.75)                | 0.039   |
| NE total dose (mean (SD)) | 0.04 (0.83)                     | 1.16 (9.89)                 | < 0.001 | 0.17 (1.71)                     | 0.29 (3.24)                 | 0.520   |
| TM total dose (mean (SD)) | 0.13 (1.03)                     | 1.07 (3.44)                 | < 0.001 | 0.21 (1.23)                     | 0.92 (2.97)                 | < 0.001 |
| IG total dose (mean (SD)) | 0.25 (4.06)                     | 7.74 (19.50)                | < 0.001 | 0.15 (1.55)                     | 6.67 (17.61)                | < 0.001 |

Abbreviations: LOS: length of stay; DP: dopamine; NE: norepinephrine; TM: thymidine; IG: immunoglobulin

### Restricted cubic splines of lymphocyte counts and patient in-hospital mortality

In the unmatched group, patient in-hospital mortality increased as lymphocyte counts decreased, especially when the lymphocyte counts decreased below $0.95 \times 10^9/L$ (Fig. 1A). After PS matching, patient in-hospital mortality also increased as lymphocyte counts decreased, and there was a significant difference in the outcome of methylprednisolone treatment in patients with a lymphocyte count higher than and those with a lymphocyte count lower than $0.85 \times 10^9/L$ (Fig. 1B). We therefore chose a cutoff value of $0.9 \times 10^9/L$ to distinguish between the low lymphocyte and normal lymphocyte count groups.

### Methylprednisolone treatment and in-hospital mortality

Univariate Cox regression analysis showed a significantly increased risk of mortality in the unmatched MP group (HR 3.70 95% CI 2.62–5.23, P < 0.01). We performed a PS matching analysis to control for confounding factors. After PS matching, there were 416 patients in the matched non-MP group and 208 patients in the matched MP group. Stratified analysis was performed according to whether the
lymphocyte count was less than \(0.9 \times 10^9/L\). The patients were further subdivided into a low lymphocyte control group, a low lymphocyte treatment group, a normal lymphocyte control group and a normal lymphocyte treatment group according to a lymphocyte count cutoff value of \(0.9 \times 10^9/L\). Kaplan-Meier survival curve analysis showed that methylprednisolone treatment improved in-hospital survival for patients with lymphocyte counts less than \(0.9 \times 10^9/L\) (\(P = 0.022\)), whereas for patients with lymphocyte counts greater than \(0.9 \times 10^9/L\), methylprednisolone treatment had no effect on patient in-hospital survival (\(P = 0.88\)). (Fig. 2). Univariate Cox regression analysis in PS-matched patients with low lymphocyte counts showed that methylprednisolone treatment was associated with reduced in-hospital mortality (HR 0.51, 95% CI 0.28,0.92, \(P = 0.024\)). Multivariate Cox regression analysis of PS-matched patients with lymphocyte counts less than \(0.9 \times 10^9/L\) also showed that methylprednisolone treatment reduced in-hospital mortality (HR 0.48, 95% CI 0.24,0.97, \(P = 0.04\)), while dopamine or norepinephrine treatment, increased age, and heart failure were associated with increased in-hospital mortality (Fig. 3).

Secondary outcomes and laboratory test results

We further analyzed the role of methylprednisolone treatment on lymphocyte count changes, and the results are shown in Fig. 4. The trends in the change in white blood cells, aspartate aminotransferase levels, blood urea nitrogen levels and C reactive protein levels in patients after admission are shown in Fig. 5. Methylprednisolone treatment seemed to be used more often in patients with low lymphocyte counts and appeared to have little effect on changes in lymphocytes, white blood cells, aspartate aminotransferase levels, blood urea nitrogen levels and C reactive protein levels.

Discussion

The widespread use of glucocorticoids may not benefit everyone. Severe COVID-19 may be an indication for glucocorticoid treatment only if an uncontrolled inflammatory response occurs. A decrease in lymphocytes may reflect patient immune system impairment and the possibility of progressing to a severe case. Therefore, glucocorticoids may be able to benefit such patients. Our study suggests that patient in-hospital mortality increases as lymphocyte counts decrease, and methylprednisolone treatment improved in-hospital survival for patients with lymphocyte counts less than \(0.9 \times 10^9/L\).

COVID-19 is an infectious disease that emerged at the end of 2019. The vast majority of patients with novel coronavirus pneumonia present with only mild to moderate symptoms, and a minority of patients progress to severe pneumonia and even develop ARDS and multiorgan failure [14]. Novel coronavirus infection may induce a protective intrinsic and adaptive immune response in the body, but an excessive intrinsic or impaired adaptive immune response will lead to local and systemic tissue damage[15]. In patients with novel coronavirus pneumonia, the serum levels of several proinflammatory cytokines and chemokines are significantly elevated [16, 17], and high levels of proinflammatory cytokines lead to the development of cytokine storms, as evidenced by massive neutrophil and macrophage infiltration, which
lead to diffuse alveolar injury and death from dysfunction of the heart, liver and kidneys. Glucocorticoids can be used to suppress cytokine storms and the intense inflammatory response in lung tissue caused by ARDS, but they may also inhibit host clearance of the virus and thus increase the risk of secondary infection [18]. Therefore, the role of glucocorticoids in novel coronavirus pneumonia is currently controversial.

Chinese experts in respiratory and critical illnesses stated in the "Expert consensus on the use of corticosteroids in patients with 2019-nCoV pneumonia" that glucocorticoids need to be used with caution in patients with novel coronavirus pneumonia [19], and in the WHO guidelines, glucocorticoid therapy is not routinely recommended [20]. However, a recent UK RCT of dexamethasone treatment in hospitalized patients with COVID-19 [8], which included a total of 6,425 patients (2,104 in the dexamethasone treatment group and 4,321 in the control group), yielded positive results. Overall, dexamethasone treatment resulted in a 2.8% reduction in 28-day mortality (22.9% in the dexamethasone treatment group vs. 25.7% in the control group, age-adjusted RR 0.83, 95% CI 0.75–0.93). The greatest benefit was seen for patients receiving invasive mechanical ventilation at randomization, with a mortality rate of 29.3% in the dexamethasone treatment group versus 41.4% in the conventional treatment group (RR 0.64, 95% CI 0.51–0.81). The WHO Rapid Evidence Assessment Working Group also conducted a prospective meta-analysis to determine the prognostic impact of glucocorticoid therapy in critically ill patients with COVID-19 [10], which included data from seven randomized clinical trials with a total of 1,703 critically ill patients; overall, there were 222 deaths in the glucocorticoid treatment group (678 patients) and 425 deaths in the control group (1,025 patients), producing a statistically significant difference in mortality between the two groups (overall OR 0.66, 95% CI 0.53–0.82, p < 0.01 fixed-effects-based meta-analysis). The RCTs [10] in which we found positive findings were mainly conducted in patients with more severe disease, such as those on invasive ventilators, and the mechanism is unclear.

Lymphopenia is a common feature of COVID-19 patients and is the most common prognostic indicator. Reduced peripheral blood lymphocyte counts may be associated with direct viral attack on lymphocytes and lymphoid organs, disorders of inflammatory factors or metabolic disorders such as hyperlactatemia [12]. Lymphocytes express the coronavirus receptor ACE2, which may be a direct target of the virus [21]. Pathological examination of postmortem specimens from COVID-19-infected patients have also showed that SARS-CoV-2 infection can lead to severe tissue damage, including reduced lymphoid follicles, splenic nodule atrophy, histiocytosis and lymphopenia [22, 23]. Our findings also showed that patient in-hospital mortality increased as the lymphocyte count decreased, which is consistent with previous findings. Our Kaplan-Meier survival curve analysis of 624 patients after PS matching showed that methylprednisolone treatment improved in-hospital survival for patients with lymphocyte counts less than 0.9*10^9/L (P = 0.022), whereas for patients with lymphocyte counts greater than 0.9*10^9/L, methylprednisolone treatment had no effect on patient in-hospital survival (P = 0.88). Multivariate Cox regression analysis of PS-matched patients with lymphocyte counts less than 0.9*10^9/L also showed that methylprednisolone treatment reduced patient mortality (P = 0.04). All of these results suggest that glucocorticoid treatment is protective in patients with reduced lymphocyte counts.
The role of glucocorticoids in the treatment of severe viral respiratory infections may depend on the patient, the dose and the timing. Previous studies have shown that dysfunctional monocytes in the peripheral blood of patients with severe novel coronavirus pneumonia lead to sustained activation of the ISG signaling pathway, which may be the main cause of cytokine storm in severe pneumonia [24]. The abnormal immune response is characterized by severe lymphopenia and leukopenia as well as natural killer (NK) cell failure, which lead to a poorer prognosis in some COVID-19 patients [25]. Therefore, in patients with lymphopenia and novel coronavirus pneumonia, glucocorticoid therapy may be protective. Release of SARS-CoV-2 seems to be higher at the beginning of the illness and decreases thereafter [26–29]. High-dose glucocorticoid therapy given specifically when there is minimal inflammation and when viral replication is controlled may cause delayed viral clearance and worse clinical outcomes. The results of a study by D.C. Chen et al. showed a correlation between glucocorticoid treatment at high doses (> 200 mg) and increased early (< 3 days of admission) and 28-day mortality [9]. The results of a clinical trial of dexamethasone [8] have also shown that dexamethasone treatment one week after disease onset reduces mortality in patients with COVID-19, suggesting that immune damage may predominate at this stage of the disease, with active viral replication playing a secondary role.

The present study has some limitations. First, our study was a retrospective analysis, and clarifying the causal relationship between glucocorticoid treatment and mortality was not possible. Second, as this was a retrospective study, the timing, dose and duration of methylprednisolone administration varied, which may lead to biased results. Further prospective large-sample studies are therefore necessary to further confirm the findings.

Declarations

Conflict of interest statement

The authors have declared that no conflict of interest exists.

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Author contributions

ZH contributed to the data collecting work, literature research of this work and writing of the manuscript. MC contributed to the data collecting of this work, statistical analysis and writing of this manuscript. WT contributed to collect the data. XY contributed to the data collecting and analysis of this work. TX contributed to the data collecting work. ZX contributed to the data collecting work. LH contributed to the data collecting. FS contributed to the data collecting and analysis of this work. WR designed this research, revised the manuscript and analyzed the data. Du, Jiang designed this research, write the manuscript, analyzed the data and drew all the figures in this study. Jiang Du takes responsibility for (is
the guarantor of) the content of the manuscript, including the data and analysis (Original Research). All authors reviewed the manuscript.

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**Figures**

![Cubic spline plot](image)

**Figure 1**

The cubic spline plot
Figure 2

The Kaplan-meier survival plot
Figure 3

Multivariate Cox model of MP treatment in low lymphocyte matched cohort
Figure 4

The lymphocyte trends by days in low and high lymphocyte groups
Figure 5

The change of different lab test by days