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Effect of Methylprednisolone on Mortality and Clinical Courses in Patients with Severe COVID-19: A Propensity Score Matching Analysis

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Abstract

Background: Whether methylprednisolone therapy can reduce the mortality rate of patients with severe coronavirus disease 2019 (COVID-19) remains controversial, and its effects on the length of hospital stay and virus shedding time are also unknown. This retrospective study investigates the previous issues to provide more evidence for methylprednisolone treatment in severe COVID-19.

Methods: This retrospective study included 563 of 4827 patients with confirmed COVID-19 admitted to Wuhan Huoshenshan Hospital or Wuhan Guanggu Hospital between February 3, 2020 and March 30, 2020 who met the screening criteria. The participants' epidemiological and demographic data, comorbidities, laboratory test results, treatments, outcomes, and vital clinical time points were extracted from electronic medical records. The primary outcome was in-hospital death, and the secondary outcomes were 2 clinical courses: length from admission to viral clearance and discharge. Univariate and multivariate logistic or linear regression analyses were used to assess the role of methylprednisolone in different outcomes. Propensity score matching was performed to control for confounding factors.

Results: Of the 563 patients who met the screening criteria and were included in the subsequent analysis, 138 were included in the methylprednisolone group and 425 in the nonmethylprednisolone group. The in-hospital death rate between the methylprednisolone and nonmethylprednisolone groups showed a significant difference (23.91% $vs.$ 1.65%, $P < 0.001$), which was maintained after propensity score matching (13.98% $vs.$ 5.38%, $P = 0.048$). However, univariate logistic analysis in the matched groups showed that methylprednisolone treatment (odds ratio [OR], 5.242; 95% confidence interval [CI], 0.802 to 34.246; $P = 0.084$) was not a risk factor for in-hospital death in severe patients. Further multivariate logistic regression analysis found comorbidities (OR, 3.327; 95% CI, 1.702 to 6.501; $P < 0.001$), lower lymphocyte count (OR, 0.076; 95% CI, 0.012 to 0.461; $P = 0.005$), higher lactate dehydrogenase (LDH) levels (OR, 1.008; 95% CI, 1.003 to 1.013; $P = 0.002$), and anticoagulation therapy (OR, 11.187; 95% CI, 2.459 to 50.900; $P = 0.002$) were associated with in-hospital mortality. Multivariate linear regression analysis in the matched groups showed that methylprednisolone treatment was not a risk factor for a prolonged duration from admission to viral clearance (β Value 0.081; 95% CI, –1.012 to 3.657; $P = 0.265$) or discharge (β Value 0.114; 95% CI, –0.723 to 6.408; $P = 0.117$). D-dimer (β Value, 0.144; 95% CI, 0.012 to 0.817; $P = 0.044$), LDH (β Value 0.260; 95% CI, 0.010 to 0.034; $P < 0.001$), and antiviral therapy (β Value 0.220; 95% CI, 1.373 to 6.263; $P = 0.002$) were associated with a longer length from admission to viral clearance. The lymphocyte count (β Value –0.206; 95% CI, –6.248 to –1.197; $P = 0.004$), LDH (β Value 0.231; 95% CI, 0.012 to 0.048; $P = 0.001$), antiviral therapy (β Value 0.143; 95% CI, 0.058 to 7.497; $P = 0.047$), and antibacterial therapy (β Value 0.152; 95% CI, 0.133 to 8.154; $P = 0.043$) were associated with a longer hospitalization duration from admission to discharge. Further stratified analysis revealed that the low daily dose group (≤60 mg/d) and the low total dose group (≤200 mg) had shorter duration from admission to viral clearance (Z=–2.362, $P = 0.018$; Z=–2.010, $P = 0.044$) and a shorter hospital stay (Z=–2.735, $P = 0.006$; Z=–3.858, $P < 0.001$).

Conclusions: In patients with severe COVID-19, methylprednisolone is safe and does not prolong the duration from admission to viral clearance or discharge. Low-dose, short-term methylprednisolone treatment may be more beneficial in shortening the disease course.

Keywords: COVID-19; Clinical courses; In-hospital death; Methylprednisolone; SARS-CoV-2

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in 2019. As of June 9, 2022, 530,869,347 confirmed cases of COVID-19 and 6,301,020 deaths have been reported globally, giving an estimated fatality rate of approximately 1.19%.[1] Patients with severe SARS-CoV-2 show higher proinflammatory cytokine levels than those with nonsevere disease, and early treatment of this hyperinflammation may be necessary to reduce mortality in COVID-19 patients.[2,3] As the leading immunomodulatory agent to regulate systemic inflammation through nongenomic and genomic effects,[4] corticosteroid therapy has been implemented in other coronavirus diseases, which have caused outbreaks worldwide, including

severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome.[5–7] However, known adverse effects and potential slowing of viral clearance prevented the routine use of corticosteroids at the beginning of the outbreak. Since the COVID-19 outbreak, research focusing on corticosteroid treatment has been extensively performed. Initially, researchers explored whether corticosteroids should be used in patients with COVID-19, drawing conflicting conclusions. Some studies and meta-analyses have shown that corticosteroid therapy decreased 28-day mortality and increased the number of ventilator-free days in patients who required oxygen support.[8–12] Based on these results, the World Health Organization (WHO) strongly recommends systemic corticosteroid therapy in patients with severe and critically ill COVID-19.[13] Conversely, other studies have shown that corticosteroid treatment might increase mortality and delay SARS-CoV-2 coronavirus RNA clearance.[14–16] Beyond the initial debate of whether or not corticosteroid therapy should be administered to severe COVID-19 patients, several other factors have become topics of discussion, such as the timing for treatment initiation, type of corticosteroids, dosing, and duration of treatment.

Therefore, in this study, we investigated the effects of methylprednisolone on in-hospital mortality and different clinical courses in patients with severe COVID-19 using propensity score matching (PSM).

2. Subjects and methods

2.1. Ethics approval

This study was approved by the research ethics commission of Wuhan Huoshenshan Hospital (approval number: HSSLL004) and Wuhan Guanggu Hospital (approval number: 2020IEC001). This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist.[17]

2.2. Patients and study design

This retrospective, observational, multicenter study was conducted in 2 cohorts of patients diagnosed with COVID-19 from Wuhan Huoshenshan Hospital and Wuhan Guanggu Hospital between February 3, 2020, and March 30, 2020. Patients were considered for study entry if they were: (1) 18 years or older and (2) confirmed to have severe SARS-CoV-2 infection. The exclusion criteria were as follows: (1) inability to determine the illness onset time; (2) death or discharge in the first 72 hours of admission; (3) lack of laboratory test results in the first 72 hours of admission; and (4) patients who did not meet a definite outcome of death or discharge by March 30, 2020. According to the Chinese management guidelines for COVID-19 (version 5.0),[18] SARS-CoV-2 infection is defined by a positive result on real-time reverse transcription–polymerase chain reaction tests of nasal and pharyngeal swabs or lower respiratory tract aspirates, or the presence of typical imaging characteristics on chest computed tomography when laboratory test results are inconclusive. In consideration of the practical situation in the hospital, most specimens were throat swabs. Patients were classified as having severe SARS-CoV-2 infection if they presented 1 of the following 4 severity criteria: respiratory rate greater than 30 breaths per minute; O_2 saturation less than 93% at rest on room air; a ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) less than 300 (estimated using prespecified charts for patients receiving oxygen through a reservoir mask); and development lung infiltrates involving more than 50% of the lung fields within 48 hours of admission, as shown on chest x-rays.

2.3. Data collection

Epidemiological, demographic, comorbidities, laboratory test results, treatments, outcomes, and vital clinical time points were extracted from the electronic medical records and recorded using a standardized data collection form. The encountered comorbidities included hypertension, diabetes, coronary heart disease, cerebrovascular disease, respiratory disease, liver disease, kidney disease, and cancer. Laboratory test results included lymphocyte count, D-dimer level, and lactate dehydrogenase (LDH). The recorded treatments included antiviral therapy (arbidol, oseltamivir-ribavirin, hydroxychloroquine, chloroquine phosphate, lopinavir, and ritonavir), antibacterial therapy, immunoglobulin therapy, anticoagulation therapy, and methylprednisolone therapy (including total dosage and duration). The vital clinical time points included symptom onset date, admission date, viral clearance date, and discharge or death date. The viral clearance time was determined as the time of the first of 2 consecutive negative SARS-CoV-2 RNA tests at least 24 hours apart. The discharge criteria were as follows: absence of fever for at least 3 days, substantial improvement of respiratory symptoms, and 2 throat swab samples negative for SARS-CoV-2 RNA obtained at least 24 hours apart.

2.4. Outcomes

The primary outcome was in-hospital mortality rate. The secondary outcomes were duration from admission to viral clearance and from admission to discharge.

2.5. Statistical analysis

Continuous variables are presented as the mean ± SD for normally distributed data and as the median (interquartile 1–interquartile 3 [Q1–Q3]) for nonnormally distributed data. Categorical variables are summarized as numbers and frequencies with corresponding percentages (n [%]). Comparisons were performed using the χ^2 or Fisher exact test for categorical variables and Student t test or Mann-Whitney U test for continuous variables. The risk factors for in-hospital death were assessed using univariate and multivariate logistic regression analyses. The effects of methylprednisolone on the 2 disease courses were evaluated using univariate and multivariate linear regressions. The PSM method was used to minimize bias caused by confounding factors, assuming an imbalance in the patient background between the methylprednisolone and nonmethylprednisolone groups. The parameters included in the PSM were age, sex, number of comorbidities, length from symptom onset to admission, lymphocyte count, D-dimer level, and LDH level, because these were considered clinically significant and partly reflected the prognosis.[19–21] The PSM involved 1:1 matching using the nearest neighbor method and caliper at 0.2.

Statistical significance was set at a P value less than 0.05. Statistical analysis was performed using SPSS (version 25.0; IBM, Chicago, IL) and R software version 4.1.0 (R Foundation, Vienna, Austria).

3. Results

3.1. Patients' characteristics

Of the 4,827 patients with confirmed COVID-19 admitted to the 2 centers, 825 fulfilled the inclusion criteria. Of these, 106 were excluded because they were unable to determine the illness onset time, 11 were excluded for being discharged or dead in the first 72 hours of admission, 87 were excluded because of lack of laboratory tests in the first 72 hours of admission, and 58 were excluded for having no definite outcome by March 30, 2020. Finally,
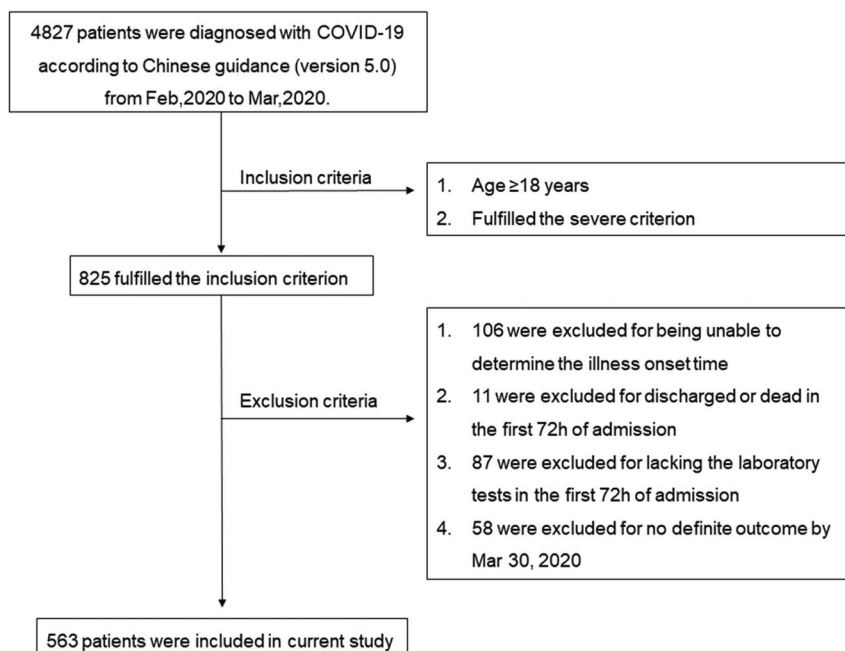
Figure 1: Flow chart showing patient selection.

563 patients were included in this study. The detailed filtering process is illustrated in Figure 1. The median age of all patients was 65 years (56–72 years), 299 (53.11%) were male, and the median length from symptom onset to hospital admission was 21.68 days (13.85–30.67 days). The baseline characteristics of the 563 patients are presented in Table 1. Of the study cohort, 138 (24.51%) and 425 (75.49%) patients were classified into the methylprednisolone and nonmethylprednisolone groups, respectively. In the methylprednisolone group, the median duration of methylprednisolone treatment was 5 days (3–9 days). There were significant differences in sex, duration from symptom onset to admission, lymphocyte count, D-dimer level, and LDH level between the 2 groups (all $P < 0.05$). After balancing the differences in these factors using PSM, 186 patients (93 each in the methylprednisolone and nonmethylprednisolone groups) were included in the primary outcome analysis. Patient characteristics of the unmatched and matched groups are shown in Table 1.

3.2. Methylprednisolone treatment was not a risk factor for in-hospital mortality

The overall in-hospital mortality was 7.10% ($n = 40$). In-hospital mortality in the methylprednisolone group was significantly higher than in the nonmethylprednisolone group (23.91% *vs.* 1.65%; $P < 0.001$; Table 1). After PSM analysis, the statistical difference in mortality between the 2 groups (13.98% *vs.* 5.38%; $P = 0.048$) still remained. Univariate logistic regression analysis demonstrated that methylprednisolone was not a risk factor for in-hospital mortality (odds ratio [OR], 5.242; 95% confidence interval [CI], 0.802 to 34.246; $P = 0.084$; Table 2). Further multivariate analysis found a higher rate of comorbidities (OR, 3.327; 95% CI, 1.702 to 6.501; $P < 0.001$), lower lymphocyte count (OR, 0.076; 95% CI, 0.012 to 0.461; $P = 0.005$), higher LDH level (OR, 1.008; 95% CI, 1.003 to 1.013; $P = 0.002$), and anticoagulation therapy (OR, 11.187; 95% CI, 2.459 to 50.900; $P = 0.002$) associated with in-hospital mortality (Table 2).

3.3. Methylprednisolone treatment was not a risk factor for a prolonged duration from admission to viral clearance and to discharge

We further explored the effects of methylprednisolone on different clinical courses in the 523 patients who survived, of whom 105 were in the methylprednisolone group and 418 in the nonmethylprednisolone group. In the methylprednisolone group, the median duration from admission to viral clearance and discharge was 11.68 days (6.57–17.04 days) and 24.80 days (19.00–39.03 days), respectively. In the nonmethylprednisolone group, the median duration from admission to viral clearance and discharge was 2.78 days (1.76–5.90 days) and 12.82 days (7.69–19.79 days), respectively. The duration from admission to viral clearance and to discharge was significantly different between the 2 groups ($P = 0.001$ and $P < 0.001$, respectively; Table 3). After PSM, 82 patients from each group were included in the secondary outcome analysis. The baseline characteristics of the 2 groups before and after PSM are shown in Table 3. Even after PSM, significant differences in the duration from admission to viral clearance and to discharge between the 2 groups remained ($P = 0.015$ and $P = 0.005$, respectively; Table 3). Multivariate linear regression analysis showed that methylprednisolone was not associated with a longer duration from admission to viral clearance (β Value 0.081; 95% CI, –1.012 to 3.657; $P = 0.265$) or to discharge (β Value 0.114; 95% CI, –0.723 to 6.408; $P = 0.117$; Figures 2A, B). Conversely, a higher D-dimer value (β Value 0.144; 95% CI, 0.012 to 0.817; $P = 0.044$), higher LDH (β Value 0.260; 95% CI, 0.010 to 0.034, $P < 0.001$), and antiviral therapy (β Value 0.220; 95% CI, 1.373 to 6.263; $P = 0.002$) were all associated with a longer duration from admission to viral clearance. The lower lymphocyte count (β Value –0.206; 95% CI, –6.248 to –1.197; $P = 0.004$), higher LDH (β Value 0.231; 95% CI, 0.012 to 0.048; $P = 0.001$), antiviral therapy (β Value 0.143; 95% CI, 0.058 to 7.497; $P = 0.047$), and antibacterial therapy (β Value 0.152; 95% CI, 0.133 to 8.154; $P = 0.043$) were associated with a longer duration from admission to discharge.

Table 1: Baseline characteristics of patients before and after PSM

Variables	Unmatched group				Matched group			
	Total (n = 563)	Methylprednisolone (n = 138)	Nonmethylprednisolone (n = 425)	P	Total (n = 186)	Methylprednisolone (n = 93)	Nonmethylprednisolone (n = 93)	P
Sex				0.012				0.765
Male	299	86	213		114	58	56	
Female	264	52	212		72	35	37	
Age [years, M (Q1–Q3)]	65 (56–72)	66 (58–72)	65 (56–73)	0.435	66 (57–74)	66 (57–74)	65 (57–75)	0.996
Number of comorbidities				0.647				0.647
0	268	64	204		80	44	36	
1	162	40	122		61	26	35	
2	98	23	75		29	16	13	
3	28	10	18		13	6	7	
4	6	1	5		3	1	2	
5	1	0	1		0	0	0	
Duration from onset to admission [days, M (Q1–Q3)]	21.68 (13.85–30.67)	14.68 (10.53–20.71)	30.54 (15.69–30.72)	<0.001	15.96 (10.53–24.70)	17.78 (10.70–22.80)	15.94 (10.53–25.61)	0.984
Laboratory test								
Lymphocyte [×10⁹/L, M (Q1–Q3)]	1.31 (0.85–1.74)	0.83 (0.51–1.23)	1.44 (1.04–1.82)	<0.001	0.98 (0.61–1.45)	1.00 (0.62–1.42)	0.94 (0.61–1.46)	0.992
D-dimer [mg/L, M (Q1–Q3)]	0.68 (0.35–1.56)	1.36 (0.67–4.55)	0.55 (0.31–1.18)	<0.001	1.00 (0.53–2.36)	0.95 (0.53–2.26)	1.23 (0.53–2.59)	0.830
LDH [U/mL, M (Q1–Q3)]	201.90 (166.30–274.40)	332.95 (242.43–439.90)	185.50 (159.30–229.35)	<0.001	263.55 (196.10–331.00)	268.80 (210.70–343.40)	259.70 (188.40–316.60)	0.642
Dead [n (%)]	40 (7.10)	33 (23.91)	7 (1.65)	<0.001	18 (9.68)	13 (13.98)	5 (5.38)	0.048

PSM: propensity score matching; M (Q1 – Q3): median (interquartile 1 - interquartile 3); LDH: lactate dehydrogenase.

Table 2: Multivariate logistic analyses for the in-hospital mortality rate

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex	0.375 (0.065–2,171)	0.274		
Age	0.966 (0.901–1.035)	0.324		
Comorbidities	3.460 (1.602–7.475)	0.002	3.327 (1.702–6.501)	<0.001
Lymphocyte count	0.096 (0.014–0.656)	0.017	0.076 (0.012–0.461)	0.005
D-dimer	1.048 (0.822–1.338)	0.704		
LDH	1.008 (1.002–1.013)	0.004	1.008 (1.003–1.013)	0.002
Methylprednisolone	5,242 (0.802–34.246)	0.084		
Antiviral therapy	0.399 (0.067–2.369)	0.312		
Antibacterial therapy	5.73×10^7 (0- + ∞)	0.997		
Anticoagulation therapy	18.229 (2.875–115.563)	0.002	11.187 (2.459–50.900)	0.002
Immunoglobulin therapy	1.419 (0.285–7.069)	0.669		

LDH: lactate dehydrogenas; OR: odds ratio; CI: confidence interval.

3.4. Low-dose, short-term application of methylprednisolone was related to a shorter clinical course

To investigate the optimal doses, duration, and initial time of methylprednisolone application, we analyzed 2 clinical courses in all patients who received methylprednisolone treatment using the same matched group as the analysis of secondary outcomes. In the low daily dose group (≤60 mg/d), the median duration from admission to viral clearance and to discharge was 9.97 days (3.14–15.17 days) and 20.08 days (16.45–29.30 days), respectively. Meanwhile, in the high daily dose group (>60 mg/d), the median duration from admission to viral clearance and discharge was 14.13 days (9.81–19.84 days) and 29.94 days (20.25–46.76 days), respectively. Mann-Whitney *U* test showed that the low daily dose group had shorter duration from admission to viral clearance (Z=–2.362, *P* = 0.018) and a shorter hospital stay (Z=–2.735, *P* = 0.006; Figure 3A). In the low total dose group (≤200 mg), the median duration from admission to viral clearance and discharge was 9.97 days (2.92–15.19 days) and 19.91 days (14.10–24.74 days), respectively. Conversely, in the high total dose group (>200 mg), the median duration from admission to viral clearance and discharge was 11.82 days (7.22–19.12 days) and 30.99 days (19.89–46.64 days), respectively. The Mann-Whitney *U* test showed that the low total dose group had shorter duration from admission to viral clearance (Z=–2.010, *P* = 0.044) and a shorter hospital stay (Z=–3.858, *P* < 0.001; Figure 3B). After stratifying patients according to the median duration of methylprednisolone use (4 days), 47 patients were classified in the short-term group (≤4 days) and 35 in the long-term group (>4 days). In the short-term group, the median duration from admission to viral clearance and discharge was 9.93 days (2.92–17.04 days) and 20.07 days (14.10–25.77 days), respectively. Meanwhile, in the long-term group, the median duration from admission to viral clearance and discharge was 11.68 days (7.71–15.31 days) and 30.01 days (19.87–43.84 days), respectively. The Mann-Whitney *U* test showed the short-term group had shorter hospital stay (Z= –2.911, P = 0.004) but not duration from admission to viral clearance (Z=–1.561, *P* = 0.119; Figure 3C). However, the shorter hospital stays and admission duration till viral clearance were still longer than those in the nonmethylprednisolone group. We further also grouped the patients according to the median initial time and median duration of corticosteroid use and found no significant difference in the 2 disease courses.

4. Discussion

High-dose dexamethasone has been shown to reduce mortality in COVID-19 patients who need oxygen support and is recommended by the WHO. However, the effects of methylprednisolone on in-hospital mortality and the clinical course in patients with severe COVID-19 are currently unclear. In the present study, multivariate regression analysis using PSM analysis found that methylprednisolone therapy did not increase in-hospital mortality. The RECOVERY study found an age-adjusted rate ratio of 28-day all-cause mortality of 0.83 (95% CI, 0.75 to 0.93), concluding that dexamethasone decreased 28-day mortality in patients who required oxygen supplementation.[8] The CoDEX study showed that intravenous dexamethasone treatment increased the number of ventilator-free days, although there was no evidence that it reduced the 28-day mortality.[9] Fadel et al.[22] found that early short-term methylprednisolone treatment reduced the rate of death and mechanical ventilation in hospitalized patients with COVID-19. Conversely, several studies have conflictingly shown that administration of corticosteroids increases the risk of death in COVID-19 patients with acute respiratory distress syndrome, which also contradicts the results of the present study.[14,16] This inconsistency may be related to differences in the targeted population, stage of the disease, and different practical modalities for corticosteroid treatment. In the WHO REACT study, the fixed-effect summary OR for the association with mortality was 0.64 (95% CI, 0.50 to 0.82; *P* < 0.001) for dexamethasone, and the OR was 0.91 (95% CI, 0.29 to 2.87; *P* = 0.87) for methylprednisolone. Pharmacological differences between methylprednisolone and dexamethasone include mineralocorticoid activity (some *vs.* none) and plasma half-life (3 *vs.* 72 hours). The different studies also showed differences in the dose and duration of corticosteroid treatment. Patients enrolled in the present study tended to be administered a lower dose and shorter duration of methylprednisolone. Consistent with previous studies, in the multivariate analysis, we found that comorbidities, anticoagulation therapy, lymphocyte count, and LDH level were all risk factors for mortality.[16,23–25] A large retrospective cohort study demonstrated that viral RNA positivity persisted until death,[19] and 33 of 40 patients (82.5%) remained RNA positive up to death in the present study, suggesting a possible correlation between viral persistence and poor prognosis. The methylprednisolone group maintained a higher mortality than the nonmethylprednisolone group even after PSM matching in our study, mainly because among the groups matched for epidemiological, demographic, comorbidities, and laboratory test results, the methylprednisolone group still included more rapidly deteriorating patients than in the nonmethylprednisolone group. Another possible explanation is that the adverse effects of corticosteroids may have affected the prognosis. Furthermore, patients receiving

Table 3: Characteristics and secondary outcomes of survived patients before and after PSM

Variables	Unmatched group				Matched group			
	Total (n = 523)	Methylprednisolone (n = 105)	Nonmethylprednisolone (n = 418)	P	Total (n = 164)	Methylprednisolone (n = 82)	Nonmethylprednisolone (n = 82)	P
Sex				0.096				0.428
Male	271	62	209		99	47	52	
Female	252	43	209		65	35	30	
Age [years, M (Q1–Q3)]	65 (56–72)	65 (57–70)	65 (56–72)	0.851	66 (58–74)	66 (60–72)	68 (57–74)	0.959
Number of comorbidities				0.599				0.259
0	258	55	203		71	40	31	
1	150	28	122		53	24	29	
2	90	17	73		29	13	16	
3	20	4	16		9	4	5	
4	4	1	3		2	1	1	
5	1	0	1		0	0	0	
Duration from onset to admission[days, M (Q1–Q3)]	23.70 (14.52–30.67)	14.76 (10.70–20.78)	30.54 (15.69–30.72)	<0.001	15.71 (10.53–23.75)	17.30 (10.70–21.81)	15.59 (10.52–25.61)	0.827
Laboratory test								
Lymphocyte [×10^9/L, M (Q1–Q3)]	1.37 (0.94–1.77)	0.94 (0.63–1.36)	1.44 (1.04–1.82)	<0.001	1.01 (0.70–1.49)	1.01 (0.68–1.47)	0.99 (0.76–1.54)	0.742
D-Dimer [mg/L, M (Q1–Q3)]	0.63 (0.33–1.39)	1.14 (0.56–2.67)	0.55 (0.31–1.14)	<0.001	1.03 (0.51–2.46)	0.99 (0.51–2.35)	1.04 (0.50–2.81)	0.996
LDH [U/mL, M (Q1–Q3)]	197.60 (163.70–258.80)	289.50 (232.40–377.60)	184.35 (158.80–225.00)	<0.001	261.85 (207.05–324.15)	263.85 (210.70–333.00)	260.30 (199.30–315.20)	0.797
Duration from admission to viral clearance [days, M (Q1–Q3)]	2.84 (1.77–10.27)	11.68 (6.57–17.04)	2.78 (1.76–5.90)	0.001	9.73 (2.80–14.98)	11.09 (4.36–16.14)	6.88 (2.11–13.35)	0.015
Duration from admission to discharge [days, M (Q1–Q3)]	15.10 (8.10–23.78)	24.80 (19.00–39.03)	12.82 (7.69–19.79)	<0.001	19.91 (14.89–30.46)	22.02 (17.50–35.88)	18.44 (11.98–27.94)	0.005

The secondary outcomes were duration from admission to viral clearance and from admission to discharge.

PSM: propensity score matching; M (Q1–Q3): median (interquartile 1 - interquartile 3); LDH: lactate dehydrogenase.
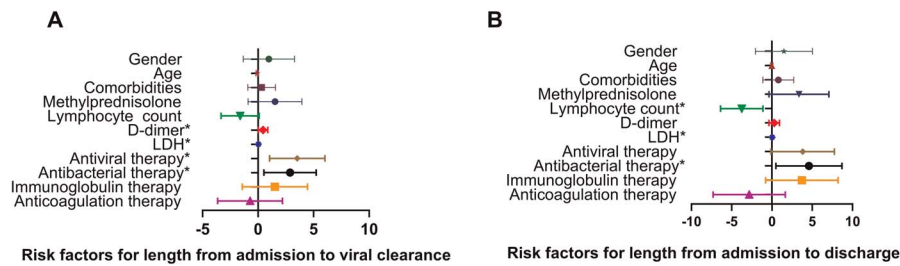
Figure 2: Risk factors for secondary outcomes. (A) Higher D-dimer, higher LDH, antiviral therapy, and antibacterial therapy were found to be linked to a longer duration from admission to viral clearance. (B) Lower lymphocyte count, higher LDH, and antibacterial therapy were related to a longer duration from admission to discharge. LDH: lactate dehydrogenase.

corticosteroid therapy were more likely to develop bacterial infection due to immunosuppression.

Further statistical tests revealed that methylprednisolone therapy was not associated with a longer duration from admission to viral clearance or discharge. Antiviral treatment, antibacterial therapy, and D-dimer and LDH levels were associated with prolonged relevant clinical courses. Previous studies have reported that corticosteroid therapy does not significantly prolong patients' hospital stay.[26–28] The WHO REACT analysis demonstrated that a low dose of methylprednisolone had no significant impact on the duration of viral shedding.[12] Conversely, other studies have shown that corticosteroid treatment has detrimental effects on the remarkably prolonged length of hospital stay in all patients.[14,29] This inconsistency may be because corticosteroid therapy tended to be administered at higher doses and for a longer duration in these studies. In addition, the differences in the initial time of corticosteroid administration may also have an impact because they are related to corticosteroid effects on T-cell responses and interferon pathways.[3] Furthermore, delayed SARS-CoV-2 clearance may occur because of the immunosuppressive effects of corticosteroids. In agreement with the report of Ling et al.,[30] the current study showed that both low-dose and short-term methylprednisolone group clinical courses were longer than those in the nonmethylprednisolone group.

Most prior studies have indicated that patients with severe or critical COVID-19 would benefit from corticosteroid use. However, many questions regarding the optimal use of corticosteroids in the treatment of COVID-19 remain, including the dose, duration, and

appropriate timing of initiation. In this study, we evaluated the efficacy of low-dose, short-term, and early use methylprednisolone in patients with severe COVID-19. Our results showed that low-dose and short-term application of methylprednisolone resulted in shorter clinical courses, consistent with the Chinese guidelines recommending low-dose usage of corticosteroids in severe to critically ill patients (methylprednisolone 40 mg or dexamethasone 5 mg per day, for up to 10 days).[31] The WHO REACT analysis suggested that low-dose methylprednisolone had no significant impact on the duration of viral shedding time, and our study verifies the same. The optimal initial time was substantial as COVID-19 showed a conspicuous inflammatory response. One prospective study found that earlier corticosteroid usage (before or within the first 48 hours of intensive care unit admission) was associated with decreased mortality and shorter intensive care unit stays, but not hospitalization days.[32] Nonetheless, several studies have shown that early use may suppress CD8+ T cells and NK cells and prolong viral shedding time.[33,34] In the present study, changes in disease courses were explored in 2 subgroups with median boundaries (4 days after admission) and did not reveal any meaningful result, which may be due to the long duration from symptoms to hospital admission for our participants (median, 21.68 days). Ideally, corticosteroid therapy should be initiated during the initial phases of the hyperinflammatory state. However, there are concerns regarding whether corticosteroid administration within 7 days of onset may inhibit antibody production.

Our study sheds light on the effects of methylprednisolone on the disease course by providing new and more detailed information. These results remained significant even after adjusting for age, sex,
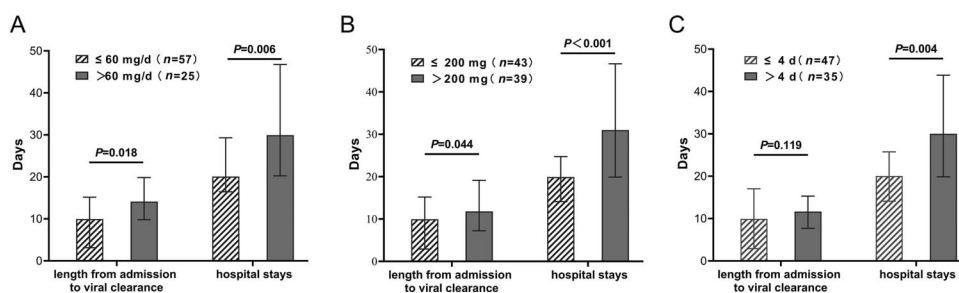
Figure 3: Comparison of the 2 clinical courses in different groups. (A) The low daily dosage group (≤60 mg/d) had a shorter duration from admission to viral clearance and discharge than the higher dosage group (>60 mg/d). (B) The low total dosage group (≤200 mg) had a shorter duration from admission to viral clearance and discharge than higher total dosage group (>200 mg). (C) The short-term group (≤4 d) had a shorter duration from admission to discharge than the long-term group (>4 d).

comorbidities, and duration from symptom onset to admission between the 2 groups. Our results may reinforce the safety assurance of corticosteroid treatment in patients with severe COVID-19. The main strengths of this study include its double-center design, large size, focus on methylprednisolone, and careful minimization of confounding biases through PSM. Nevertheless, our study still had some limitations. First, this retrospective analysis did not include imaging or oxygen-support therapy data. Second, some patients in this study were transferred from other medical institutions, and hence, we could not fully access the patients' prehospital care data.

Overall, our results showed that methylprednisolone is safe and does not prolong the duration from admission to viral clearance or discharge in patients with severe COVID-19. Low-dose, short-term methylprednisolone treatment may be more beneficial in shortening the disease course.

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Author Contributions

Xiaoyan Li, Xin Yuan, Zhe Xu, and Lei Shi analyzed and interpreted the patient data. Lei Huang, Xuechun Lu and Junliang Fu participated in research design. Xiaoyan Li and Xin Yuan contributed to writing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None.

Data Availability Statement

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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