Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Infectious Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Infectious Medicine

journal homepage: www.elsevier.com/locate/imj

Original article

Effect of methylprednisolone therapy on hospital stay and viral clearance in patients with moderate COVID-19

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ARTICLE INFO

Keywords:
COVID-19
Hospital stay
In-hospital death
Moderate
Viral clearance

ABSTRACT

Background: The benefits and harms of methylprednisolone treatment in patients with moderate coronavirus disease 2019 (COVID-19) remain controversial. In this study, we investigated the effect of methylprednisolone on mortality rate, viral clearance, and hospitalization stay in patients with moderate COVID-19.

Methods: This retrospective study included 4827 patients admitted to Wuhan Huoshenshan and Wuhan Guanggu hospitals from February to March 2020 diagnosed with COVID-19 pneumonia. 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; secondary outcomes were time from admission to viral clearance and hospital stay. Univariate and multivariate logistic or linear regression analysis were used to assess the roles of methylprednisolone in different outcomes. The propensity score matching (PSM) method was used to control for confounding factors.

Results: A total of 1320 patients were included in this study, of whom 100 received methylprednisolone. Overall, in-hospital mortality was 0.91% (12/1320); the 12 patients who died were all in the methylprednisolone group, though multivariate logistic regression analysis showed methylprednisolone treatment was not a risk factor for in-hospital death in moderate patients before or after adjustment for confounders by PSM. Methylprednisolone treatment was correlated with longer length from admission to viral clearance time and hospital stay before and after adjustment for confounders.

Conclusions: Methylprednisolone therapy was not associated with increased in-hospital mortality but with delayed viral clearance and extended hospital stay in moderate COVID-19 patients.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory disease syndrome coronavirus 2 (SARS-CoV-2), has developed into a pandemic since 2019. As of July 11, 2022, there have been 551,226,298 confirmed cases of COVID-19 and 6,345,595 deaths reported globally, with an estimated fatality rate of approximately 1.15% [1]. The severity of COVID-19 can range from asymptomatic infection to life-threatening organ damage. Especially when respiratory failure occurs, the fatality rate of COVID-19 rises sharply [2,3]. Accumulating evidence has suggested that the severity of COVID-19 correlates with a hyper-inflammatory status resembling a cytokine storm [4–6]. Further research has suggested that dysregulation of the immune response, especially T cells, may be significantly involved in the pathological process of COVID-19 [7–9]. Additionally, previous studies have demonstrated that a remarkable reduction in $CD8^+$ T cells could predict mortality in COVID-19 patients [10,11]. However, as one of the essential immunomodulators, corticosteroids have demonstrated efficiency in

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https://doi.org/10.1016/j.imj.2022.09.004
Received 1 August 2022; Received in revised form 11 September 2022; Accepted 29 September 2022
Available online xxx

Please cite this article as: X. Li, X. Yuan, Z. Xu et al., Effect of methylprednisolone therapy on hospital stay and viral clearance in patients with moderate COVID-19, Infectious Medicine, https://doi.org/10.1016/j.imj.2022.09.004

reducing mortality and shorting clinical courses in severe and critically ill patients [12–16], and have been one of the treatments for COVID-19 since the RECOVERY trial confirmed its benefits on 28-day mortality among patients who need respiratory support [17]. Recently, research has suggested that inhaled corticosteroids (ICS) could reduce the probability of needing urgent medical care and enhance clinical recovery in mild patients [18–21]. However, there remains a lack of evidence to determine the effects of corticosteroid treatment on moderate COVID-19 patients.

This study therefore aimed to investigate the effects of methylprednisolone on in-hospital mortality, viral clearance, and length of hospital stay in patients with moderate COVID-19.

2. Materials and methods

2.1. Study design and participants

This retrospective, observational study was conducted on patients diagnosed with COVID-19 pneumonia admitted to Wuhan Huoshenshan Hospital and Wuhan Guanggu Hospital between February 03 and March 30, 2020. All patients were considered for study entry if they were aged ≥18 years and had been diagnosed with moderate SARS-CoV-2 infection. Exclusion criteria were: 1) inability to determine the onset time of the illness; 2) inability to determine the viral clearance time; 3) death or discharge within the first 72h of admission; 4) lacking laboratory test results in the first 72 hours of admission; 5) patients who did not meet either outcome of death or discharge by March 30, 2020. According to the Chinese management guidelines for COVID-19 (version 5.0) [22], SARS-CoV-2 infection is defined as a positive result of real-time reverse transcription-polymerase chain reaction (RT-PCR) tests of nasal and pharyngeal swabs or lower respiratory tract aspirates, or the presence of typical imaging characteristics on chest computed tomography (CT) when laboratory test results are inconclusive. In practical terms, most of the specimens in this study were diagnosed via throat swab.

This study was approved by the Research Ethics Commission of both centers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used for reporting this study [23].

2.2. Data collection

The epidemiological and demographic data as well as comorbidities, laboratory test results, treatments, outcomes, and vital clinical time points were extracted from electronic medical records and recorded using a standardized data collection form. The comorbidities records included hypertension, diabetes, coronary heart disease, cerebrovascular disease, respiratory disease, liver disease, kidney disease, and cancer. Laboratory test results included lymphocyte count, D-dimer, and lactic dehydrogenase (LDH). Treatments included antiviral therapy (including umifenovir, oseltamivir–ribavirin, hydroxychloroquine, chloroquine phosphate, lopinavir, and ritonavir), antibacterial therapy (including moxifloxacin hydrochloride, levofloxacin, meropenem, azithromycin, cefdinir, cefaclor, ceftriaxone, cefoperazone sulbactam, linezolid, fluconazole, voriconazole, caspofungin, and metronidazole), immunoglobulin therapy, anticoagulation therapy, and methylprednisolone therapy (with data including total dosage and duration). The vital clinical time points included illness onset time, admission time, viral clearance time, and time of discharge or death. Viral clearance time was defined as the time of the first of 2 consecutive negative SARS-CoV-2 RNA tests at least 24h apart. The discharge criteria were the clinical symptoms and signs of COVID-19 having improved or alleviated (body temperature within the normal range for 3 consecutive days, respiratory symptoms improved significantly, and CT images showing apparent absorption of bilateral extensive ground-glass opacification and/or consolidation), and no need for additional or alternative treatments.

2.3. Outcomes

The primary outcome was in-hospital death. The secondary outcomes were 2 disease courses: time from admission to viral clearance, and length of hospital stay.

2.4. Statistical analysis

Continuous variables are presented as means ± SD for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed data. Categorical variables are summarized as numbers and frequencies with corresponding percentages (N, %). Comparisons used the chi-square tests for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables. Univariate and multivariate logistic regression were used to explore the risk factors for in-hospital death. Univariate and multivariate linear regression were used to explore the risk factors for different clinical courses. The effect of methylprednisolone on different clinical courses was evaluated using the Kaplan-Meier approach with the log-rank test. The propensity score matching (PSM) method was used to minimize any bias resulting from confounding factors, assuming an imbalance in patient background between the methylprednisolone and non-methylprednisolone groups. Parameters included in the PSM were patient sex, age, number of comorbidities, length from illness onset to admission, lymphocyte count, D-dimer, and LDH because they were considered clinically significant and partly reflected

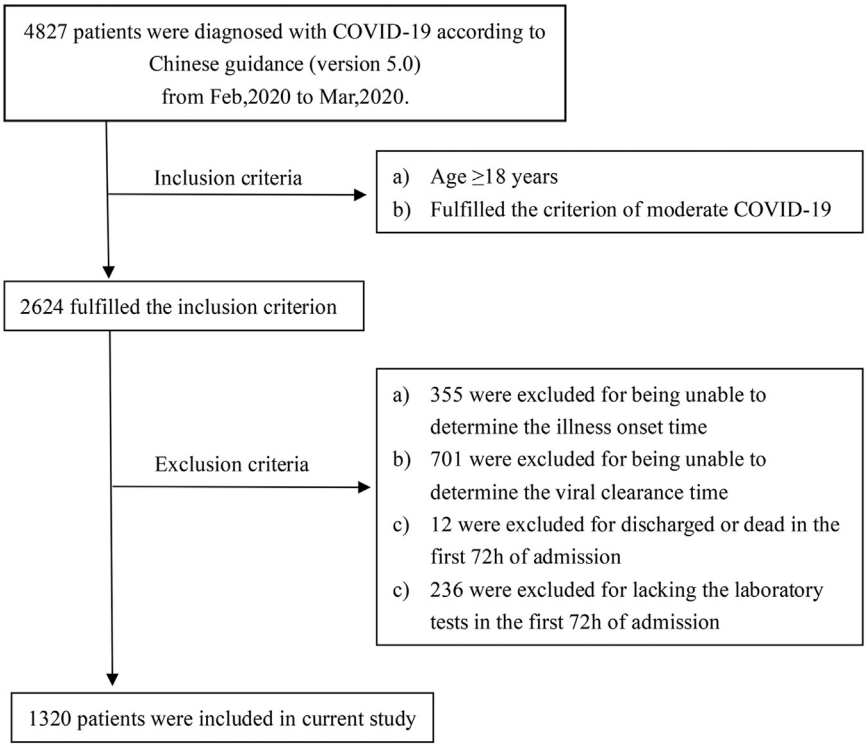

Fig. 1. Flow chart of patient screening and enrollment

the prognosis [3,24,25]. The PSM involved 1:1 matching, using the nearest neighbor method with the caliper width set at 0.2.

A p-value <0.05 was considered statistically significant. Statistical analysis was done using SPSS (version 25.0; IBM, Chicago, IL) and R software (version 4.1.0, R Foundation, Vienna, Austria).

3. Results

3.1. Patient characteristics

Of the 4827 total patients diagnosed with COVID-19 at the 2 study centers, 1320 patients met all inclusion and exclusion criteria and were enrolled. The detailed filtering process is shown in Fig. 1.

As shown in Table 1, the median age of 1320 patients were 58.00 (48.00–66.00) years, 656 patients (49.70%) were males, and the median length from illness onset to admission was 22.44 (13.67–30.69) days. A total of 100 (7.6%) patients received methylprednisolone treatment, and 1220 were in the non-methylprednisolone group. In the methylprednisolone group, the median daily dosage and accumulated dosage of methylprednisolone treatment were 41.82 (40.00–61.43) mg/d and 240.00 (120.00–455.00) mg, with a median duration of 4.50 (3.00–7.00) days. There were significant differences in age, number of comorbidities, the length from illness onset to admission, lymphocyte count, D-dimer, and LDH levels between the 2 groups (all $p < 0.05$).

3.2. Methylprednisolone therapy was not a risk factor for in-hospital death

Overall in-hospital mortality was 0.91% (12/1320), and all 12 patients who finally died were in the methylprednisolone group (Table 1). The median survival time of those 12 patients was 17.72 (11.87–40.61) days. There were significant differences in mortality between the methylprednisolone group and the non-methylprednisolone group before and after PSM ($p = 0.000$ and $p = 0.023$). Table 2 shows the results of the univariate and multivariate logistic analysis of risk factors for in-hospital death between the 2 groups before and after PSM. Among all 1320 patients, methylprednisolone therapy was not associated with in-hospital death before PSM ($p = 0.908$). The LDH (OR = 1.017 [1.003–1.031], $p = 0.017$), anticoagulation therapy (OR = 101.591 [5.290–1950.878], $p = 0.002$), and immunoglobulin therapy (OR = 20.748 [1.307–329.267], $p = 0.032$) were risk factors for in-hospital death (Table 2). After removing the influence of confounding factors by PSM, 90 patients in the methylprednisolone group and 90 patients in the non-methylprednisolone group were analyzed for the primary outcome. Of these 180 patients, all 5 (2.8%) patients who died were in the methylprednisolone group (Table 1). The median survival time of these 5 patients was 19.74 (13.71–40.85) days. In the 90 patients in the methylprednisolone group after PSM, the median daily dosage and accumulated dosage of methylprednisolone treatment were 40.00 (40.00–60.00) mg/d and 200.00 (120.00–380.00) mg, with a median duration of 4.00

Table 1
The characteristics of patients before and after PSM in mortality analysis.

	Before PSM				After PSM			
	All (n=1320)	Methylprednisolone group (n = 100)	Non-methylprednisolone group (n = 1220)	*p*	All (n = 180)	Methylprednisolone group (n = 90)	Non-methylprednisolone group (n = 90)	*p*
Gender (M/F)	656/664	59/41	597/623	0.053	108/72	54/36	54/36	1.000
Age (years)	58.00 (48.00, 66.00)	65.00 (54.00, 71.75)	57.00 (48.00, 66.00)	<0.001	64.00 (53.25, 71.00)	65.00 (53.75, 71.00)	64.00 (53.00, 70.50)	0.821
Number of comorbidities (0/1/2/3/4)	810/333/147/28/2	48/29/21/1/1	762/304/126/27/1	0.006	84/57/32/6/1	43/28/18/0/1	41/29/14/6/0	0.109
Length from illness onset to admission (days)	22.44 (13.67, 30.69)	13.62 (10.12, 19.96)	26.11 (14.53, 30.71)	<0.001	13.52 (8.84, 19.67)	14.80 (10.16, 20.62)	11.75 (7.63, 18.10)	0.232
Laboratory test				<0.001				
Lymphocyte count($\times 10^9$/L)	1.53 (1.17, 1.90)	1.08 (0.79, 1.48)	1.57 (1.21, 1.93)	<0.001	1.13 (0.82, 1.50)	1.12 (0.81, 1.49)	1.14 (0.84, 1.54)	0.524
D-Dimer (mg/L)	0.36 (0.19, 0.66)	0.76 (0.39, 1.68)	0.34 (0.18, 0.62)	<0.001	0.62 (0.34, 1.22)	0.71 (0.38, 1.50)	0.49 (0.32, 1.02)	0.115
LDH (U/mL)	171.55 (149.50, 202.35)	231.10 (182.90, 292.75)	169.45 (147.95, 198.60)	<0.001	220.55 (173.23, 273.28)	224.80 (179.43, 278.60)	217.40 (169.28, 271.93)	0.514
Dead	12 (0.91%)	12 (12.00%)	0	<0.001	5 (3.00%)	5 (6.00%)	0	0.023

LDH: lactic dehydrogenase

(3.00–7.00) days. The multivariate logistic analysis of the 180 matched patients found no risk factor associated with in-hospital death (Table 2).

3.3. Methylprednisolone therapy was associated with longer time from admission to viral clearance and longer hospital stay

We further assessed the effects of methylprednisolone on different clinical courses in 1308 patients who were cured and discharged, of whom 88 were in the methylprednisolone group and 1220 were in the non-methylprednisolone group. The baseline characteristics of these groups are presented in Table 3.

Before being matched by PSM, age, the length from illness onset to admission, the lymphocyte count, D-Dimer, and LDH levels differed significantly between the 2 groups (all $p < 0.05$), and time from admission to viral clearance and duration of hospital stay also had significant differences between the 2 groups (all $p < 0.001$) (Fig. 2A, Fig. 2B). In the 88 patients in the methylprednisolone group before PSM, the median daily dosage and accumulated dosage of methylprednisolone treatment were 40.00 (40.00–60.00) mg/d and 240.00 (120.00–400.00) mg, with a median duration of 4.00 (3.00–7.00) days. Univariate and multivariate linear analysis were used to explore the risk factors for clinical courses between the 2 groups. As shown in Figure 2C, lymphocyte count (OR=−0.084 [−1.372–0.347], p<0.001), LDH (OR=0.116 [1.502–3.913], p<0.001), methylprednisolone therapy (OR 0.116= [1.502–3.913], $p < 0.001$), antiviral therapy (OR = 0.245 [2.270–3.466], $p < 0.001$), and antibacterial therapy (OR = 0.145 [1.215–2.590], $p < 0.001$) were associated with longer time from admission to viral clearance by multivariate linear analysis. Meanwhile, multivariate linear analysis showed sex (OR = 0.051 [0.049–1.486], $p = 0.036$), age (OR = 0.057 [0.004–0.057], $p = 0.026$), lymphocyte count (OR = −0.124 [−2.303 to −0.976], $p < 0.001$), LDH (OR = 0.142 [0.012–0.026], $p < 0.001$), methylprednisolone therapy (OR = 0.126 [2.281–5.318], $p < 0.001$), antiviral therapy (OR = 0.230 [2.740–4.242], $p < 0.001$), antibacterial therapy (OR = 0.157 [1.810–3.543], $p < 0.001$), and immunoglobulin therapy (OR = 0.065 [0.877–6.032], $p = 0.009$) were associated with longer length of hospital stay (Fig. 2D).

After removing the influence of confounding factors by PSM, 83 patients in the methylprednisolone group and 83 in the non-methylprednisolone group were matched (Table 3). In the 83 patients in the methylprednisolone group after PSM, the median daily dosage and accumulated dosage of methylprednisolone treatment were 40.00 (40.00–60.00) mg/d and 240.00 (120.00–400.00) mg, with a median duration of 4.00 (3.00–7.00) days. After matching by PSM, the time from admission to

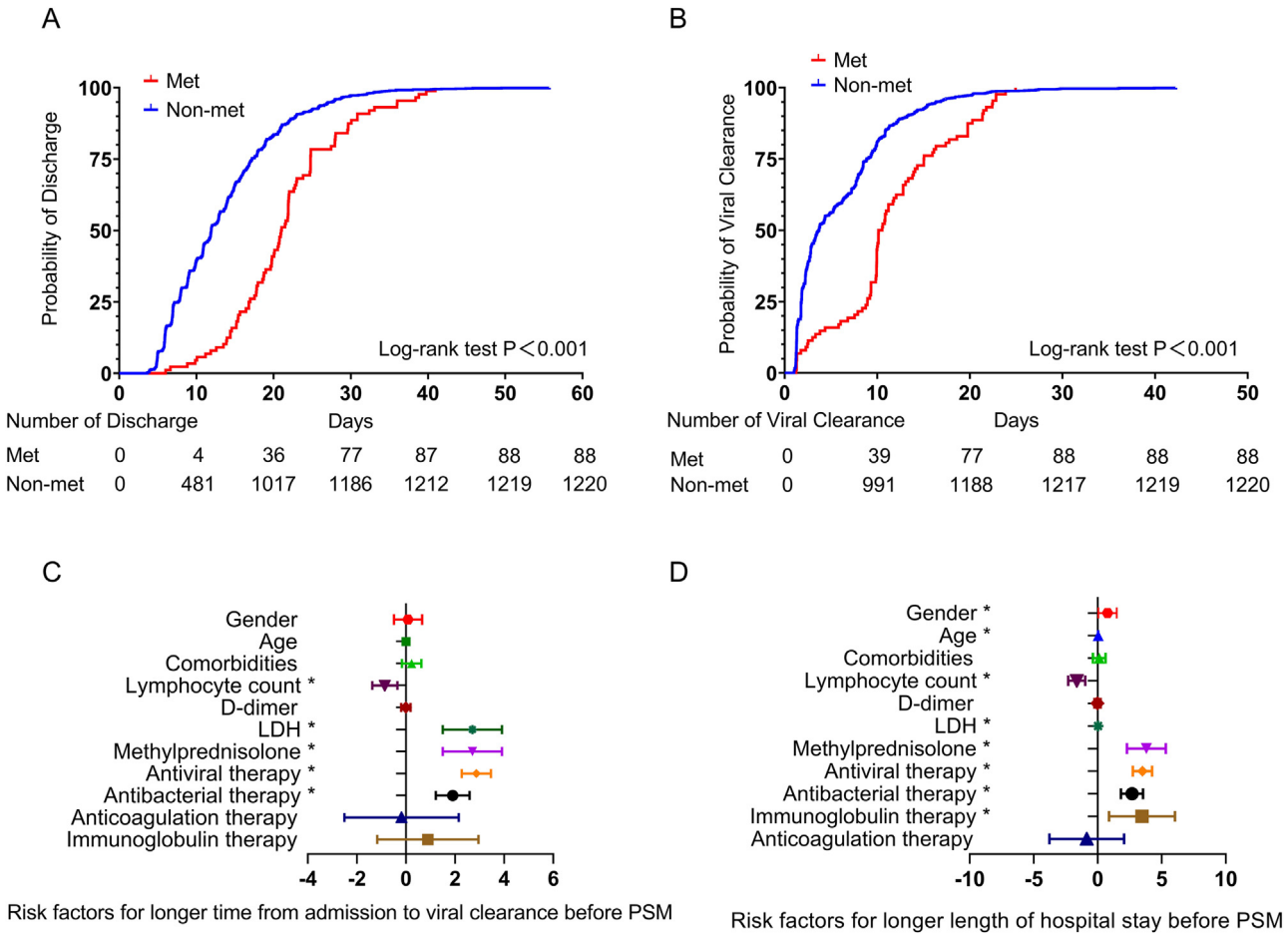

Fig. 2. Kaplan-Meier curves and log-rank test of the probability of discharge (A) and viral clearance (B) between the methylprednisolone group and the non-methylprednisolone group before PSM. Multivariate linear analysis for the time from admission to viral clearance (C) and the hospital stay (D) before PSM. All treatments were compared with YES/NO. Met: the methylprednisolone group. Non-met: the non-methylprednisolone group.

Table 2
Univariate and multivariate logistic analysis for in-hospital death before and after PSM.

	Before PSM				After PSM			
	univariate		multivariate		univariate		multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Gender (Male/Female)	1.42 × 10^19 (0 – +∞)	0.970			0.000 (0 – +∞)	0.999		
Age	8.874 (0 – 1.62 × 10^65)	0.977			0.446 (0 – +∞)	0.999		
Comorbidities	2.80 × 10^12 (0 – 9.10 × 10^265)	0.923			72.023 (0 – +∞)	1.000		
Lymphocyte count	569.84 (0 – 1.66 × 10^131)	0.966			1.82 × 10^12 (0 – +∞)	0.997		
D-dimer	9237.959 (0 – 6.49 × 10^74)	0.913			2310.589 (0 – +∞)	0.995		
LDH	1.289 (0.022 – 76.440)	0.903	1.017 (1.003 – 1.031)	0.017	0.853 (0 – 3.29 × 10^22)	0.995		
Methylprednisolone*	4.61 × 10^99 (0 – +∞)	0.908			0.000 (0 – +∞)	0.998		
Antiviral therapy*	0.034 (0 – +∞)	0.999			0.000 (0 – +∞)	1.000		
Antibacterial therapy*	1.09 × 10^41 (0 – +∞)	0.972			8.79 × 10^31 (0 – +∞)	0.997		
Anticoagulation therapy*	1.79 × 10^22 (0 – +∞)	0.949	101.591 (5.290 – 1950.878)	0.002	1.42 × 10^47 (0 – +∞)	0.990		
Immunoglobulin therapy*	0.007 (0 – +∞)	0.996	20.748 (1.307 – 329.267)	0.032	0.000 (0 – +∞)	0.999		

* All treatments were compared with YES/NO, LDH: lactic dehydrogenase.

viral clearance and hospital stay in the methylprednisolone group were significantly longer than in the non-methylprednisolone group ($p < 0.001$ and $p = 0.006$) (Fig. 3A, Fig. 3B). As shown in Figures 3C and 3D, multivariate linear analysis found that LDH (OR = 0.014 [0.002–0.027], $p = 0.027$), methylprednisolone therapy (OR = 2.172 [0.348–3.995], $p = 0.020$), and antiviral therapy (OR = 3.657 [1.302–5.303], $p = 0.001$) were risk factors for longer time from admission to viral clearance. Meantime, methylprednisolone therapy (OR = 3.904 [1.734–6.073], $p < 0.001$), antiviral therapy (OR = 3.987 [1.653–6.322], $p = 0.001$), and immunoglobulin therapy (OR=6.724 [2.530–10.918], $p = 0.003$) were risk factors for longer length of hospital stay.

Table 3
The characteristics of patients before and after PSM in clinical course analysis.

	Before PSM				After PSM			
	All (n = 1308)	Methylprednisolone Group (n = 88)	Non-methylprednisolone Group (n = 1220)	*p*	All (n = 166)	Methylprednisolone Group (n=83)	Non-methylprednisolone Group (n=83)	*p*
Gender (M/F)	648/660	51/37	597/623	0.103	95/71	48/35	47/36	0.876
Age (years)	58.00 (48.00, 66.00)	64.00 (53.00, 70.75)	57.00 (48.00, 66.00)	0.002	64.00 (53.00, 69.25)	64.00 (53.50, 69.50)	64.00 (53.00, 70.00)	0.805
Number of comorbidities (0/1/2/3/4)	808/329/142/27/2	46/25/16/0/1	762/304/126/27/1	0.051	90/49/21/5/1	43/24/15/0/1	47/25/6/5/0	0.469
Length from illness onset to admission	22.69 (13.84, 30.69)	14.59 (10.28, 20.59)	26.11 (14.53, 30.71)	<0.001	14.17 (9.40, 20.59)	13.52 (7.73, 20.25)	13.52 (7.70, 20.52)	0.401
Laboratory test								
Lymphocyte count($\times 10^9$/L)	1.53 (1.17, 1.90)	1.12 (0.81, 1.50)	1.57 (1.21, 1.93)	<0.001	1.15 (0.81, 1.49)	1.90 (0.81, 1.48)	1.19 (0.80, 1.48)	0.824
D-Dimer (mg/L)	0.36 (0.19, 0.65)	0.70 (0.38, 1.35)	0.34 (0.18, 0.62)	<0.001	0.64 (0.34, 1.19)	0.64 (0.33, 1.11)	0.64 (0.32, 1.17)	0.443
LDH (U/mL)	171.10 (149.32, 201.28)	222.30 (179.28, 278.80)	169.45 (147.95, 198.60)	<0.001	214.75 (169.38, 267.60)	213.30 (167.25, 264.80)	213.30 (165.20, 265.30)	0.374
Clinical courses								
Time from admission to viral clearance	4.03 (1.85, 9.62)	10.33 (8.95, 15.04)	3.67 (1.81, 8.85)	<0.001	9.93 (4.83, 12.80)	10.13 (8.85, 15.03)	7.95 (2.40, 11.71)	0.001
Hospital stay	12.73 (7.89, 18.05)	21.00 (16.84, 24.79)	11.93 (7.59, 17.20)	<0.001	17.94 (12.93, 22.15)	20.91 (16.79, 24.78)	14.71 (10.80, 20.56)	<0.001

LDH: lactic dehydrogenase.

4. Discussion

In multiple studies, corticosteroids have shown clinical benefit in reducing mortality and shortening clinical courses in severe and critically ill COVID-19 patients [12–14,17]. In those studies, researchers also found that corticosteroid therapy might have no benefit in patients with mild or moderate COVID-19. Based on those results, the WHO strongly recommended systemic corticosteroid therapy in patients with severe and critically ill COVID-19, but conditionally recommended against using it in non-severe patients [26]. Other research found that ICS may prevent disease progression, reduce the need for urgent medical care, and shorten clinical recovery time in patients with mild disease [18–21]. Hu et al. found that the short-course and low-dose administration of corticosteroids in non-severe patients may reduce the risk of progression to severe COVID-19. However, there were no differences in viral shedding time or length of hospital stay between the corticosteroid and the non-corticosteroid groups [27]. One meta-analysis focused on non-severe COVID-19 patients and found that the corticosteroid group had significantly higher odds of death than did the non-corticosteroids group, with delayed viral clearance and prolonged hospital stay [28]. However, the effects of methylprednisolone on moderate COVID-19 patients, particularly in terms of virus shedding time and hospital stay, remain ambiguous.

The current study showed that methylprednisolone therapy was not associated with in-hospital death of patients with moderate COVID-19 before or after eliminating the influence of confounding factors. These findings align with those of the RECOVERY study, which demonstrated that among 1534 patients with no oxygen requirement, the 28-day mortality in the dexamethasone group was close to that of the non-dexamethasone group [17]. Conclusions from previous studies also support our finding that corticosteroid therapy did not reduce in-hospital mortality [11]. Meta-analyses have demonstrated that corticosteroid therapy is associated with increased mortality in patients with no need for oxygen support [28,29]; however, confounding factors and potential selection bias may limit the application and promotion of these studies. Persistent inflammation in the upper respiratory mucosa has been reported to be potentially highly associated with the progress to severe COVID-19, and ICS have been observed to exhibit significant inflammatory modulatory effects that reduce epithelial damage and improve T-cell response, preventing clinical deterioration [30]. Considering the remarkable efficacy in treating chronic obstructive pulmonary disease and asthma, which are also known to cause lung damage and are strongly related to the immune response, ICS may be a better choice in the early phase of COVID-19 [31].

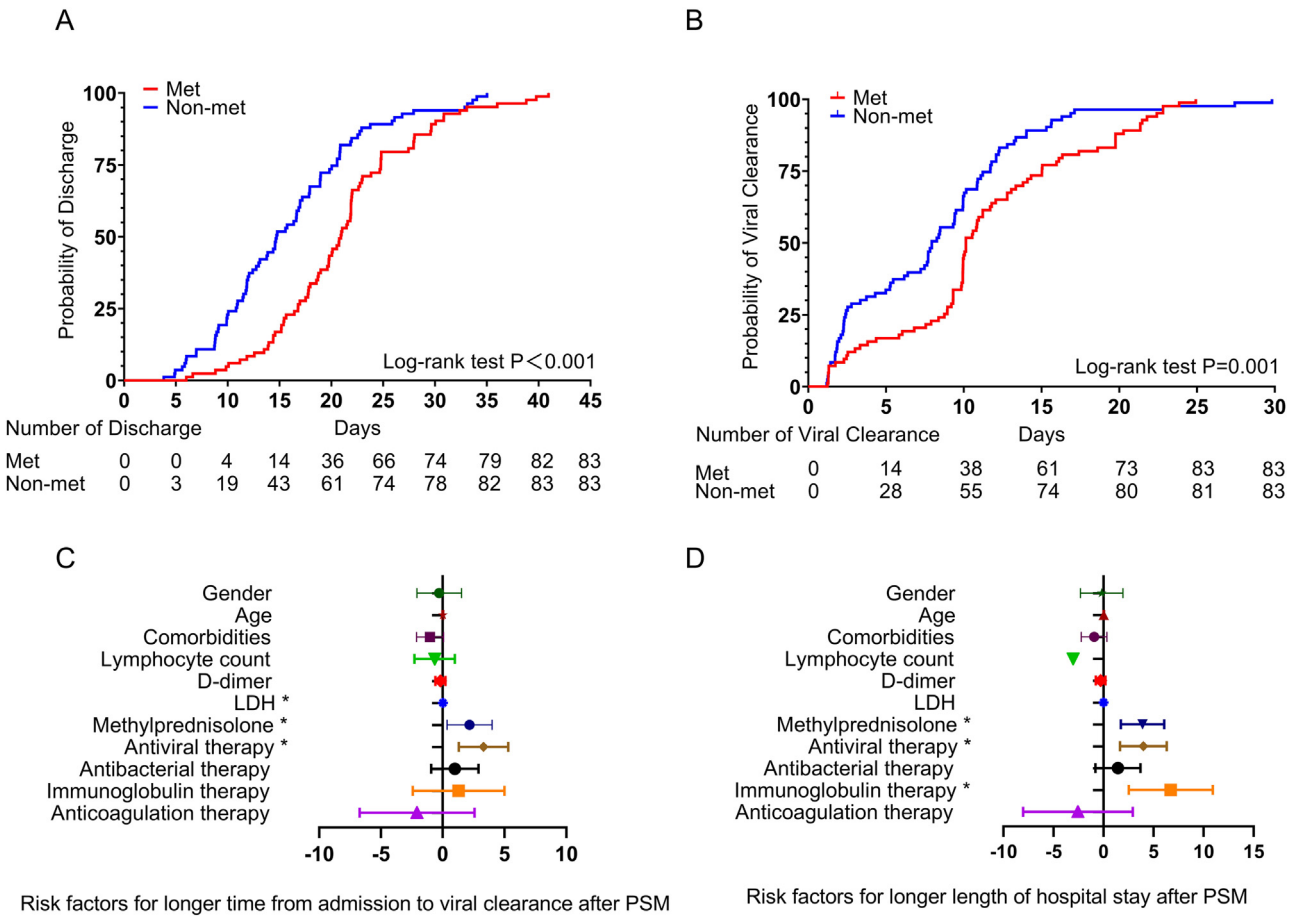

Fig. 3. Kaplan-Meier curves and log-rank test of the probability of discharge (A) and viral clearance (B) between the methylprednisolone group and the non-methylprednisolone group after PSM. Multivariate linear analysis for the time from admission to viral clearance (C) and the hospital stay (D) after PSM. All treatments were compared with YES/NO. Met: the methylprednisolone group. Non-met: the non-methylprednisolone group.

We also found that methylprednisolone treatment significantly prolonged the hospital stay and time from admission to viral clearance. Those changes may be associated with the suppression of immune cells by the application of methylprednisolone, similar to effects observed in the treatment of severe acute respiratory syndrome and the Middle East respiratory syndrome [32,33]. Previous studies and meta-analyses have also demonstrated that those patients who received corticosteroids were inclined to have delayed viral clearance and more extended hospital stays than were patients with no corticosteroids in moderate COVID-19 [11,27,28,34,35]. However, for some of these results no statistical difference was achieved. Yuan et al. found that corticosteroid therapy was associated with delayed viral clearance and hospital stay but without statistical significance, which may have been because of the shorter duration (median 1.9 days) and lower dosage (median 52.2 mg) of corticosteroids therapy in their study than in ours [35]. Hu et al. found that compared with the non-corticosteroid group, the corticosteroid group had longer hospital stays but no significant differences in viral clearance, possibly because their participants were younger and received lower corticosteroid dosage than in our study [27]. Tang et al. reported delayed viral clearance in the methylprednisolone group compared with the findings in a control group, but there was no difference in hospitalization duration between the 2 groups [11]. In addition, it is worth noting that the lengths from illness onset to admission varied considerably in these studies. Considering that COVID-19 is associated with immune response, which changes as the disease progresses, these 2 clinical courses may have been influenced by different lengths of illness onset to admission, as well as by potential treatments we cannot access.

Our study provides new clues to illustrate the effects of methylprednisolone therapy on moderate COVID-19. Although this exploration of the efficacy of methylprednisolone represents a large sample size from 2 centers, and PSM was used to minimize the confounding biases, this study still has limitations. First, this is an observational study based on medical records, and there may have been some undefined biases that cannot be eliminated. Second, this retrospective analysis did not involve imaging or oxygen support therapy data. Third, some patients in this study may have been treated with therapies such as antipyretics before admission, which would not have been

captured in our dataset. Finally, this study lacked a control group who were treated with other kinds of corticosteroids. A recent study found that methylprednisolone significantly reduced the length of hospital stay (7.4 days vs 10.5 days, $p = 0.015$) and the need for mechanical ventilation ($p = 0.04$) compared with dexamethasone [36].

In conclusion, methylprednisolone therapy was not associated with increased in-hospital mortality but with delayed viral clearance and extended hospital stay in moderate COVID-19 patients. In moderate COVID-19, methylprednisolone should be carefully administered considering the disease status and the risk of progression.

Funding

This work was supported by grants from the National Key R&D Program of China (2020YFC0860900) and the Emergency Key Program of Guangzhou Laboratory (EKPG21-30-4).

Author contributions

Xiaoyan Li, Xin Yuan, Zhe Xu, Lei Shi and Lei Huang analyzed and interpreted the patient data and research design; Fu-Sheng Wang and Junliang Fu oversight and leadership responsibility for the research activity planning and execution; Xiaoyan Li and Xin Yuan contributed to writing the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We are grateful to the medical and paramedical staff involved in the care of patients during the study period at Wuhan Huoshenshan Hospital and Wuhan Guanggu Hospital.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

This study was approved by the Research Ethics Commission of both centers. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used for reporting this study.

Informed consent

Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

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