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The role of methylprednisolone on preventing disease progression for hospitalized patients with severe COVID-19

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Abstract

Background: COVID-19 is a public health emergency that is spreading worldwide and seriously affecting the global economy. Data on the effectiveness and safety of the use of methylprednisolone for patients with severe COVID-19 remain limited.

Methods: In this retrospective study, epidemiological, clinical, laboratory, treatment and outcomes data of hospitalized patients with severe COVID-19 in Zhongnan Hospital of Wuhan University from January 1 to 7 March 2020, were collected. Binary logistic regression model was used to analyse risk factors for disease progression from severe COVID-19 illness to critical illness. The effectiveness and safety of the use of methylprednisolone for patients with severe COVID-19 disease were evaluated.

Results: The results of the multivariate analysis from 175 patients with severe COVID-19 indicate that the use of methylprednisolone was a protective factor against disease progression from severe to critical illness($P < .001$; OR: 0.054 95% CI: 0.017-0.173). Among patients with severe COVID-19 aged < 65 years, both the proportion of patients who progressed to critical illness (42.2% vs 90.0%, $P = .000$) and the mortality(6.7% vs 30.0%, $P = .002$) were lower for patients in methylprednisolone group, compared with those in the non-methylprednisolone group, whereas no statistical differences between the methylprednisolone group and the non-methylprednisolone group were found among patients with COVID-19 older than 65 years. Moreover, both the levels of $CD4^+$ T lymphocyte counts (646 vs 463/μL, $P = .007$) and IL-6 (241.9 vs 82.8 pg/mL, $P = .025$) were higher among patients with severe COVID-19 aged < 65 years, compared with those patients ≥ 65 years old.

Conclusion: Data from the limited sample showed that the early use of low or medium doses of methylprednisolone has a positive effect for patients with severe COVID-19 younger than 65 years old, and excessive immune response and cytokine storm may be some of the reasons for the effectiveness.

KEYWORDS

COVID-19, cytokine storm, methylprednisolone, prognosis, SARS-CoV-2

1 | INTRODUCTION

COVID-19 threatens global health and affects the global economy, making it an international public health event in 2020.[1,2] From the rapid spread of COVID-19 and the large number of confirmed cases in a short period of time, the global economy and health are under enormous pressure. Although there are some drugs in clinical trials, no effective antiviral drugs have been found so far. With few exceptions, the clinical management of COVID-19 still consists of supportive treatment and supplemental oxygen therapy.

Clinical research has proved that some clinical manifestations of severe pneumonia, such as high fever, shortness of breath, decreased oxygen saturation, progressive pneumonitis, various severe complications and even risk of death, are all related to inflammatory factors.[3] Methylprednisolone is typically used to treat severe acute respiratory infections of viral aetiology because of its anti-inflammatory effect. However, the use of methylprednisolone in patients with severe COVID-19 is still controversial.[4-8] In this study, the clinical characteristics, risk factors for disease progression from severe to critical illness, and early outcomes of patients with COVID-19 receiving short courses of methylprednisolone are reported.

2 | METHODS

2.1 | Study population

During the COVID-19 epidemic, the Chinese government adopted a unified policy of isolation and management for confirmed or suspected patients. A number of designated hospitals were assigned to treat patients. Zhongnan Hospital, located in Wuhan, Hubei Province, China, is one of the major tertiary teaching hospitals and was designated by the government for treating patients with COVID-19. All patients with confirmed COVID-19 in this study were admitted to Zhongnan Hospital of Wuhan University from January 1 to 7 March 2020. Ethical approval by the institutional ethics board of Zhongnan Hospital of Wuhan University was obtained for the analysis and summary of clinical data from COVID-19-infected inpatients(No. 2 020 011). Informed written consent was waived by the Ethics Commission of Zhongnan Hospital of Wuhan University in consideration of the retrospective nature of the study and the urgency of reporting on emerging infectious diseases.

Reporting of the study conforms to broad EQUATOR guidelines.[9]

2.2 | Data collection

This is a retrospective study. Epidemiological, clinical, laboratory and radiological characteristics and treatment and outcomes data were obtained with data collection forms from electronic medical records. The data were reviewed by a trained team of physicians. Information recorded included demographic data, medical history, underlying comorbidities, symptoms, signs, laboratory findings, chest computed tomographic (CT) scans, treatment measures (ie antiviral therapy, corticosteroid therapy, respiratory support) and treatment outcome.

2.3 | Diagnostic criteria and definitions of severe and critical COVID-19

All patients with COVID-19 enrolled in this study were diagnosed according to World Health Organization interim guidance.[10]

In severity assessment on admission, severe COVID-19 was defined as satisfying at least one of the following criteria: (a) respiratory rate $\geq$ 30/min; (b) pulse oximeter oxygen saturation (SpO2) $\leq$93% at rest on room air; (c) ratio of partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) $\leq$300 mmHg (1 mmHg = 0.133 kPa).

Critical COVID-19 illness was defined as satisfying at least one of the following criteria: (a) respiratory failure requiring mechanical ventilation; (b) shock; (c) failure of other organ systems requiring care in the intensive care unit (ICU).

2.4 | Definitions on methylprednisolone therapy

Early use of methylprednisolone in this study was defined as the administration of methylprednisolone once patients met the criteria for 'severe' COVID-19.

The dose range of methylprednisolone in this study was 50-80 mg/d. By referring to the previous report in which low to medium doses of methylprednisolone was defined as 25 to 150 mg/d,[11] the dose of methylprednisolone used in this study is considered in the low to medium range.

2.5 | Real-time reverse transcription polymerase chain reaction assay for SARS-CoV-2

COVID-19 was confirmed by detecting SARS-CoV-2 RNA in throat swab samples using a virus nucleic acid detection kit according to the manufacturer's protocol (Shanghai BioGerm Medical Biotechnology Co., Ltd). Briefly, the RT-PCR assay for SARS-CoV-2 amplifies simultaneously two target genes: open reading frame 1ab (ORF1ab) and the ORF for the nucleocapsid protein (N). Target 1 (ORF1ab): forward primerCCCTGTGGGTTTTACACTTAA; reverse

TABLE 1 Characteristics of 175 patients hospitalized with COVID-19 stratified according to the patients' status of disease progression

	All patients (n = 175)	Disease progression group (n = 103)	Disease improved group (n = 72)	*P*-value
Age, median (IQR), y	57 (42, 69)	60 (40, 72)	56 (29, 73)	.019
Male	106 (60.6)	63 (61.2)	43 (59.7)	.848
Age, y				
≥65	65	47 (72.3)	18 (27.7)	.005
<65	110	56 (50.9)	54 (49.1)	
Comorbidities				
Hypertension	52 (29.7)	34 (33.0)	18 (25.0)	.736
Cardiovascular/Cerebrovascular diseases	24 (13.7)	19 (18.4)	5 (6.9)	.030
Diabetes	19 (10.9)	12 (11.7)	7 (9.7)	.687
Malignancy	7 (4.0)	5 (4.9)	2 (2.8)	.490
COPD	4 (2.3)	2 (1.9)	2 (2.8)	.716
Chronic kidney diseases	10 (5.7)	9 (8.7)	1 (1.4)	.039
Chronic liver diseases	9 (5.1)	4 (3.9)	5 (6.9)	.367
Main laboratory findings on admission				
Leukocytosis	10 (5.7)	7 (6.8)	3 (4.1)	.461
Leukocytopenia	56 (32.0)	41 (39.8)	15 (20.8)	.008
Lymphocytopenia	60 (34.3)	38 (36.9)	22 (30.6)	.385
Haemoglobin, g/L	129 (106-153)	129 (109-156)	130 (106-152)	.653
Platelets, 10^9/L	151 (108-233)	152 (107-231)	148 (110-240)	.169
Creatinine, μmol/L	76.5 (55.8-108.8)	84.8 (54.2-112.3)	65.2 (56.2-98.6)	.001
Troponin, pg/mL	14.6 (6.6-16.9)	18.3 (7.8-26.2)	7.8 (4.2-10.2)	.001
Alanine aminotransferase, U/L	76 (24-87)	85 (26-95)	66 (20-83)	.319
Lactate dehydrogenase, U/L	285 (198-332)	306 (204-356)	195 (168-279)	.026
CRP, mg/L	68.0 (42.3-92.1)	82.3 (56.6-102.3)	57.7 (40.9-96.6)	.022
PCT, ng/mL	4.20 (0.63-2.69)	6.08(2.01-7.50)	0.75 (0.44-1.32)	.000
ESR, mm/h	26 (14-30)	32 (18-41)	24 (12-39)	.034
PT, s	28.6 (15.6-22.4)	32.6 (23.1-36.8)	25.2 (12.3-20.6)	.030
D-dimer, ng/mL	1104 (652-1630)	1516 (852-2630)	758 (361-897)	.023
CD4, /μL	581 (436-622)	652 (462-784)	466 (369-605)	.001
IL-6, pg/mL	163 (39-255)	253 (42-302)	78 (33-102)	.000
Use of Oseltamivir	96 (54.8)	54 (52.4)	42 (58.3)	.440
Use of Arbidol Hydrochloride	169 (96.6)	98 (95.1)	71 (98.6)	.215
Use of Lopinavir/Ritonavir or Darunavirand/Cobicistat	90 (51.4)	52 (50.5)	38 (52.8)	.765

primerACGATTGTGCATCAGCTGA;probe5'-VICCCGTC TGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. Target2(N):forward primer GGGGAACTTCTCCTGCT AGAAT; reverse primer CAGACATTTTGCTCTCA AGCTG; probe5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'. Positive (pseudovirus with a fragment of ORF1ab and N) and negative (pseudovirus with a standard fragment) quality control samples were tested simultaneously. A cycle threshold (Ct) value of less than 37 was defined a positive test, while a Ct value of more than 40 was defined as a negative test. For the cases with an intermediate Ct value (37-40), a second sample was tested and weakly positive was defined as a recurrence of Ct value of 37-40.

2.6 | Statistical analysis

All statistical analyses were performed using SPSS Statistics version 23.0 software. Categorical variables were described as frequency rates and percentages, and continuous variables

were described using mean, median and interquartile range (IQR) values. Chi-squaredanalysis was conducted to examine the categorical variables. Means for continuous variables were compared using independent group *t* tests when the data were normally distributed; otherwise, nonparametric comparative test was used. Binary logistic regression model was used to analyse risk factors for disease progression from severe illness to critical illness. The variables with $P < .10$ in univariate analysis were further included in multivariate analysis, and the relative risk and 95% confidence interval of each variable were calculated. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of patients with severe COVID-19

A total of 175 patients with severe COVID-19 were included in this study (Table 1). The median age was 57 years (IQR: 42, 69), and 106 patients (60.6%) were male. They were divided into disease progression group (n = 103) and disease improved group (n = 72). Compared with patients in the disease improved group, those patients in the disease progression group had a higher proportion of aged people(72.3% vs 27.7%, $P = .005$), had more underlying comorbidities including cardiovascular or cerebrovascular disease (18.4% vs 6.9%, $P = .005$) and chronic kidney disease (8.7% vs 1.4%, $P = .005$), were more likely to have leukocytopenia (39.8% vs 20.8%, $P = .008$) and had higher levels of creatinine (84.8 vs 65.2 μmol/L, $P = .001$), troponin (18.3 vs 7.8 pg/mL, $P = .001$), lactate dehydrogenase (306 vs 195 U/L, $P = .026$), CRP (82.3 vs 57.7 mg/L, $P = .022$), PCT (6.08 vs 0.75 ng/mL, $P = .000$), ESR (32 vs 24 mm/h, $P = .034$), PT (32.6 vs 25.2 mm/h, $P = .030$), D-dimer (1516 vs 758 ng/mL, $P = .023$), CD4 + T lymphocyte counts (652 vs 466/μL, $P = .001$) and IL-6 (253 vs 78 pg/mL, $P = .000$).

3.2 | Multivariate analysis of factors associated with COVID-19 progression from severe illness to critical illness

Univariate analysis was conducted on the demographic factors, types of underlying diseases, clinical laboratory test indicators and treatment measures that may affect the progression of patients with severe COVID-19. After excluding confounding factors, the influencing factors $P < .10$ were further included in the multivariate stepwise regression analysis. Nine significant factors in univariate analysis were put into the multivariate analysis to identify reliable predictive factors for the progression of patients with severe COVID-19 (Table 2). The results indicated that age older than 65 years old ($P = .019$; OR: 2.767, 95% CI: 1.180-6.491), underlying chronic diseases ($P = .003$; OR: 3.584, 95% CI: 1.545-8.316), Cr > 104 μmol/L ($P = .001$; OR: 4.206, 95% CI: 2.336-9.872), Troponin > 26.2 pg/mL ($P = .001$; OR: 8.220, 95% CI: 1.360-9.007), PCT > 0.05 ng/mL ($P < .001$; OR: 12.410 95% CI: 4.433-34.744) and IL-6 > 7 pg/mL ($P < .001$; OR: 4.001, 95% CI: 1.630-6.339) were risk factors for the progression from severe to critical illness, while the use of methylprednisolone ($P < .001$; OR: 0.054 95% CI: 0.017-0.173) was protective against the progression from severe to critical illness.

3.3 | Differences in the efficacy of Methylprednisolone by age

To compare the differences in the efficacy of methylprednisolone by age, patients with severe COVID-19 were divided into four groups according to their age and use of methylprednisolone (Table 3). The results indicated that, among patients with severe COVID-19 aged ≥ 65 years, there were no statistically significant differences in the proportion of patients who progressed to critical illness ($P = .156$) or the mortality rate ($P = .106$) between the methylprednisolone group and the non-methylprednisolone group. However, among patients with severe COVID-19 aged < 65 years, both the proportion of patients who progressed to critical illness (42.2% vs 90.0%, $P = .000$) and the mortality rate (6.7% vs 30.0%, $P = .002$) were lower among patients with severe COVID-19 in the methylprednisolone group, compared with those in the non-methylprednisolone group.

3.4 | Comparison of $CD4^+$ T Lymphocyte Counts and IL-6 by age

To determine the reasons for the difference in the efficacy of methylprednisolone by age, the levels of $CD4^+$ T lymphocyte counts and IL-6 were compared between the methylprednisolone group and the non-methylprednisolone group (Table 4). The results indicate that the levels of both $CD4^+$ T lymphocyte counts (646 vs 463/μL, $P = .007$) and IL-6 (241.9 vs 82.8 pg/mL, $P = .025$) were higher among patients with severe COVID-19 aged < 65 years, compared with those patients with severe COVID-19 aged ≥ 65 years.

4 | DISCUSSION

Studies on the use of glucocorticoid in influenza pneumonia and SARS are controversial,[12-17] and there are few studies on the use of glucocorticoid in COVID-19.[18] Until now, WHO,

TABLE 2 Multivariate analysis of factors associated with the progression of patients with severe COVID-19

	Univariate Logistic analysis		Multivariate Logistic analysis	
Variable	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**
Male	1.080 (0.605-1.928)	.795		
Age ≥ 65 y	4.402 (2.201-8.806)	.000	2.767 (1.180-6.491)	.019
Underlying chronic diseases	2.410 (1.274-4.558)	.007	3.584 (1.545-8.316)	.003
Leukocytosis	1.024 (0.420-3.250)	.520		
Leukocytopenia	0.652 (0.320-1.526)	.652		
Lymphocytopenia	2.526 (0.754-6.586)	.426		
Haemoglobin > 175 g/L	0.452 (0.003-1.960)	.446		
Platelets < 300×10^9/L	0.652 (0.320-1.526)	.652		
Cr > 104 μmol/L	3.706 (2.411-5.030)	.035	4.206 (2.336-9.872)	.001
Troponin > 26.2 pg/mL	6.006 (2.611-8.952)	.001	8.220 (1.360-9.007)	.001
Alanine aminotransferase > 100 U/L	2.206 (2.336-6.872)	.023	1.552 (0.760-4.269)	.214
Lactate dehydrogenase > 245 U/L	5.220 (1.324-10.826)	.000	11.032 (0.814-8.466)	.869
CRP > 10 mg/L	21.003 (0.498-36.142)	.856		
PCT > 0.05 ng/mL	23.014 (5.620-46.008)	.000	12.410 (4.433-34.744)	.000
ESR > 20 mm/h	0.652 (0.320-1.526)	.536		
PT > 12.5 s	1.528 (0.960-6.339)	.426		
D-dimer > 500 ng/mL	1.208 (0.526-4.006)	.284		
IL-6 > 7pg/mL	3.263 (1.526-6.002)	.000	4.001 (1.630-6.339)	.000
Use of methylprednisolone	0.059 (0.020-0.171)	.000	0.054 (0.017-0.173)	.000
Use of Oseltamivir	0.851 (0.476-1.520)	.851		
Use of Arbidol Hydrochloride	2.396 (0.521-11.017)	.262		
Use of Lopinavir/Ritonavir or Darunavirand/Cobicistat	0.943 (0.530-1.679)	.843		

US and other guidelines on COVID-19 are based on previous experience with the use of glucocorticoid in other diseases.[19]

According to prior knowledge, the role of glucocorticoid for the treatment of influenza, SARS and sepsis is highly controversial with some published studies showing that glucocorticoid use might reduce mortality and ameliorate acute lung injury induced by virus,[20-22] whereas an increasing number of published studies show the opposite effect.[20,23,24] It is reported that high-dose glucocorticoid may delay viral clearance and increase mortality and the risk of secondary infections.[4,25,26] However, for patients with severe COVID-19, short-course glucocorticoid in some reports is beneficial and safe in critically ill patients with SARS-CoV-2 and was not found to be an independent risk factor of prolonged viral RNA shedding.[27,28] These discordant findings may be explained by the observational nature of the studies, heterogeneity in patient acuity, inconsistent dosing regimens and duration, and timing of initiation of therapy.[6,29]

In this study, it was observed that early use of low or medium doses of methylprednisolone in patients with severe COVID-19 significantly reduced the incidence of critical illness. Other factors, such as age older than 65 years, underlying chronic diseases and elevated levels of Cr, Troponin, PCT and IL-6, were closely related to the progression of severe COVID-19.

This study found that the empirical use of methylprednisolone by clinicians at 50-80 mg/d can decrease the risk of progression from severe to critical illness in patients with COVID-19 and that it may reduce mortality. The results were consistent with that in the Recovery trial, which reported that patients with COVID-19 show a significantly improved outcome with dexamethasone in the treatment of severe COVID-19 requiring oxygen therapy or on mechanical ventilation.[30] However, a relatively low dose of 6 milligrams of dexamethasone was used in the Recovery trial.[30] These data suggested that the use of low doses of glucocorticoid was enough to improve the prognosis of patients with COVID-19 on ventilators or on supplemental oxygen therapy.

Previous reports have found that whether critically ill and septic patients can obtain benefits from glucocorticoid depended on the adrenal function.[31-33] For critically ill and septic patients with adrenal defects, low-dose glucocorticoid can improve their hemodynamic disorder and play an immunomodulatory role, while the use of glucocorticoid in patients

TABLE 3 Differences in the efficacy of methylprednisolone by age

	≥65 y				<65 y			
	Methylprednisolone group (n = 50)	Non-methylprednisolone group (n = 15)	X^2	*P*	Methylprednisolone group (n = 90)	Non-methylprednisolone group (n = 20)	X^2	*P*
Progression to critical illness (n, %)	34 (68.0)	13 (86.7)	2.008	.156	38 (42.2)	18 (90.0)	14.946	<.001
Deaths (n, %)	26 (52.0)	10 (76.9)	1.004	.316	6 (6.7)	6 (30.0)	9.167	.002

with good adrenal function may worsen their condition and even increase their mortality. Based on the above clinical experience, the authors in this study believe that for critically ill COVID-19-infected patients, it is necessary to do an ACTH test to assess adrenal function before glucocorticoid therapy. Although this test was not standardized in this paper due to the sudden outbreak of the epidemic, ACTH testing should be considered in the future prior to glucocorticoid treatment for severe or critically ill COVID-19-infected patients.

As we know, except for respiratory failure, some of the patients with severe COVID-19 have much lower level of lymphocytes, extremely high inflammatory parameters, destroyed immune system, hypercoagulability and multiple organs damage,[34,35] which were risk factors that accelerate disease progression to critical and lead to death. In this study, although only $CD4^+$ T lymphocyte counts and IL-6 were compared between those ≥ 65 and < 65 years old patients with severe COVID-19, previous studies had demonstrated that those ≥ 65 years old COVID-19-infected patients had greater initial comorbidities, more severe symptoms were more prone to bacterial infections and were more likely to experience liver and kidney dysfunction, hyperglycaemia and hypercoagulability,[8,36] compared with younger patients. In this study, it found that early use of low and medium doses of methylprednisolone had a significant effect on patients with severe COVID-19 younger than 65 years old, but the benefit of older patients was limited. The cause could be attributed to the presence of too many other confounding factors affecting the prognosis of those ≥ 65 years old COVID-19-infected patients. We think that if methylprednisolone was used for anti-inflammation therapy to counter excessive and uncontrolled release of pro-inflammatory cytokines, except for the timely anti-inflammation treatment initiated at the right window time, various indicators of different individuals, including the function of the parenchymal organs, metabolism and coagulation functions, also have an impact on therapeutic effects of methylprednisolone. Therefore, methylprednisolone treatment should be tailored in individual patient to achieve the most favourable effects.

As for the use of methylprednisolone, what concerns many scholars is bacterial and fungal infection associated with immunosuppression, thus increasing mortality.[4] However, we found the opposite results. The early use of methylprednisolone not only reduced the risk of progression to critical illness for patients with severe COVID-19, but also reduced the mortality, which indicated the effectiveness and safety of early use of low and medium doses of methylprednisolone. The results are consistent with another report which showed the mortality benefit (HR, 0.38:95% CI, 0.20-0.72) with the use methylprednisolone in COVID-19 patients with ARDS.[37]

Of course, there were some limitations in this study. First, as a single-centre retrospective study, a certain degree selection bias cannot be avoided. Second, due to the lack of standard guidelines on methylprednisolone treatment for patients with severe COVID-19 at the epidemic stage, the duration of methylprednisolone use in different patients is not exactly the same, so the data provided by this paper are insufficient to define the best duration of methylprednisolone use at present. Third, due to the sudden outbreak of COVID-19, patients with severe illness were treated with methylprednisolone at the dose of 50-80 mg/d based on the physicians' previous clinical work experience. In this retrospective study, we were unable to provide data on the use of long-term and high doses of methylprednisolone, which made it difficult to analyse differences in methylprednisolone dose and efficacy. This limitation needs to be remedied by other prospective studies. Fourth, the treatment and management of COVID-19-infected patients are subject to the overall arrangement by the government in Wuhan, China, which objectively increases the difficulty of follow-up observation of patients with COVID-19. The data in this study cannot observe whether patients using methylprednisolone have longer duration of viral shedding. Further exploration should be made on the optimal treatment duration of methylprednisolone and the influence of the methylprednisolone on the duration of SARS-CoV-2 shedding.[25] Last but not least, the number of patients ≥ 65 years old that did not receive methylprednisolone treatment was small, which could therefore affect the power of test, and more clinical data are needed to confirm this conclusion.

In conclusion, data from the limited sample showed that the early use of low and medium doses of methylprednisolone in patients with severe COVID-19 younger than 65 years can significantly reduce the risk of the disease progressing to a critical condition and death. Excessive immune response

TABLE 4 Comparison of $CD4^+$ T lymphocyte counts and IL-6 levels among patients with severe COVID-19 by age

	Normal range	Unit	<65 y	≥65 y	*t*	*P*
$CD4^+$ T lymphocyte counts(Mean ± SD)	345-2350	/μL	646 ± 341	463 ± 303	2.742	.007
IL-6(Mean ± SD)	0-7.0	pg/mL	241.9 ± 69.6	82.8 ± 97.8	2.262	.025

Abbreviation: SD, standard deviation.

and cytokine storm are the hypothesized reasons for the effectiveness of methylprednisolone in patients with severe COVID-19 younger than 65 years.

CONFLICT OF INTEREST

We have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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