

# Corticosteroids Treatment of Patients with Coronavirus Disease 2019: A Propensity Score Matching Study\*

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**Summary:** The role of corticosteroids in the treatment of coronavirus disease 2019 (COVID-19) is controversial. In the present study, we evaluated the effects of adjuvant corticosteroids treatment on the outcome of patients with COVID-19 ( $n=966$ ), using Propensity Score Matching to adjust for potential differences between the corticosteroids group ( $n=289$ ) and the non-corticosteroids group ( $n=677$ ). Analysis of data without adjusting differences in baseline characteristics indicated that the proportion of mechanical ventilation and the mortality was higher in the corticosteroids treatment group in total or severe/critical patients. The duration of viral shedding was longer in the non-corticosteroids treatment group in total or general/mild patients. After adjusting the difference between the corticosteroids and non-corticosteroids treatment group, the analysis revealed that the use of corticosteroids had no effect on the duration of viral shedding, in-hospital mortality or 28-day mortality.

**Key words:** severe acute respiratory syndrome coronavirus 2; coronavirus disease 2019; corticosteroids; mortality; viral shedding

In December, 2019, a series of pneumonia cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, and spread rapidly all over the world<sup>[1, 2]</sup>. Up to December 7, 2020, over 65 million people were infected with SARS-CoV-2 and more than 1 500 000 people died around the world. The abnormal immunologic response caused by the virus leads to the occurrence of cytokine storm and inflammation, which promotes the progression of multiple-organ injury<sup>[3-5]</sup>. Effective suppression of cytokine storm is an important way to improve clinical outcome. However, previous studies on virus infection had shown that using corticosteroids as an effective anti-inflammatory medicine was still highly controversial in the clinical application<sup>[6-12]</sup>. Besides,

the effect of corticosteroids as an adjuvant therapy in coronavirus disease 2019 (COVID-19) is still unclear. In February, 2020, Russal *et al* believed that patients with 2019 novel coronavirus (2019-nCoV) infection will not benefit from corticosteroids, and they might be more likely to be harmed with such treatment<sup>[13]</sup>. A multi-center retrospective study also showed that administration of corticosteroids in severe COVID-19-related acute respiratory distress syndrome (ARDS) is associated with increased 28-day mortality and delayed SARS-CoV-2 RNA clearance<sup>[14]</sup>. Shang raised the opposite view that short courses of corticosteroids were prudently administered at low-to-moderate dose for critically ill patients with COVID-19, based on the experiences of fighting the disease<sup>[15]</sup>. Besides, a recent controlled, open-label trial on the application of corticosteroids showed that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving respiratory support<sup>[16]</sup>. This retrospective single-center study aimed to explore the roles of corticosteroids and their influence on clinical outcomes in confirmed COVID-19 patients.

## 1 MATERIALS AND METHODS

### 1.1 Study Design and Patients Selection

This single-center, retrospective study included

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966 patients who were confirmed with COVID-19 in the Wuhan Union Hospital after January 14, 2020 and were discharged or had died before April 29, 2020. The diagnostic criteria and clinical classification criteria of COVID-19 were defined according to the Diagnosis and Treatment Program of New Coronary Pneumonia (the seventh edition) published by the National Health Commission of China<sup>[17]</sup>. Patients were eligible for enrollment in the study if they were  $\geq 18$  years, but they were excluded if they received corticosteroids as rescue therapy (we defined emergency corticosteroids use as a sudden increase in dose 3 weeks after onset and 3 days before death) or due to chronic obstructive pulmonary disease (COPD)/asthma exacerbation. And those who required long-term use of corticosteroids due to previous illnesses were also excluded. This study was approved by the research ethics commission of Wuhan Union Hospital (0124-1), and the need for informed consent was waived.

### 1.2 Data Collection

The following information was collected from the electronic records for included patients: epidemiology, demographic characteristics, laboratory results (blood routine test, biochemistry indicators, coagulation data, inflammation indicators), medication, other interventions and outcomes. This study used the data of patients on admission, and most blood samples were collected on the first day after admission. Besides, vital signs, laboratory and imaging changes during hospitalization were regularly monitored in all patients.

### 1.3 Corticosteroids Therapy and Other Interventions during Hospitalization

In this study, we recorded the medical treatments and other interventions during hospitalization, and recorded the type, duration and dose of corticosteroids in detail. Systemic corticosteroids treatment was defined as use of corticosteroids (methylprednisolone, prednisolone, dexamethasone and/or hydrocortisone), via oral or intravenous route in hospital.

### 1.4 Endpoints

The primary aim was to determine whether corticosteroids use was associated with mortality including in-hospital mortality and 28-day mortality. We compared the main outcomes in the overall population. In addition, the primary outcome was examined in two subgroups (mild/general subgroup,  $n=734$ ; severe/critical subgroup,  $n=232$ ), respectively.

The secondary outcome included the duration of viral shedding after COVID-19 onset which is defined as the event from the onset to two consecutive tests that turn negative and no more positive tests occur.

### 1.5 Statistical Analysis

Results were analyzed with SPSS 22.0. Discrete variables were expressed as  $n$  (%) and continuous variables as medians and interquartile range (IQR) of 25%–75%. Categorical variables were compared by

Fisher's exact test or Chi-square test, and continuous variables were compared by Mann-Whitney  $U$  test. All tests were two-tailed and  $P < 0.05$  is considered statistically significant.

A propensity score (PS) was estimated by logistic regression to determine the probability of corticosteroids treatment of each patient and the caliper was set to 0.02. Based on the PS, we performed a 1:1 and 1:2 match to match patients who did not receive corticosteroids treatment to who did. After matching all covariates that may had differences, we generated a full-matching PS analysis which allowed us to compare outcomes between two comparable (almost identical) cohorts including the corticosteroids-treated group and the non-corticosteroids-treated group. Confounding factors for matching include variables that were statistically different in the study and had previously been reported related to the outcomes.

Besides, we also analyzed the time from COVID-19 onset to two consecutive tests that turn negative with Kaplan-Meier estimates and compared the duration of viral shedding between corticosteroids treatment group and non-corticosteroids treatment group with log-rank tests.

## 2 RESULTS

A total of 966 patients including 232 severe/critical patients and 734 general/mild patients were included in this study, and the median age was 60 (IQR, 49–68) years. Among them, 289 patients were given corticosteroids (Methylprednisolone succinate is the most common. The maximum dose does not exceed 1–2 mg/kg every day and duration of the corticosteroids was no less than 3 days) during hospitalization and 677 were not. The patients receiving corticosteroids therapy were sicker (higher proportion of severe/critical patients), had more symptoms (sputum, dyspnea and fever on admission), and were more likely to had diabetes than those not receiving corticosteroids treatment. Neutrophil to lymphocyte ratio (NLR), lactate dehydrogenase (LDH), C-reactive protein (CRP), the proportion of D-dimer  $\geq 1$ , mechanical ventilation (MV) use, immunoglobulin therapy, antibiotic therapy, antiflezzing therapy and mortality rate (including in-hospital mortality and 28-day mortality) were increased, and platelet counts (PLT) and the duration of viral shedding were reduced in corticosteroids-treated group (table 1).

We matched the variables including disease severity status, NLR, CRP, D-dimer, LDH, diabetes, antibiotic treatment, immunoglobulin therapy and MV use (1:1 matched and 1:2 matched) between the corticosteroids treatment group and the non-corticosteroids treatment group (The comparison of characteristics after PS match between the two groups was shown in Supplementary materials table S1, and

**Table 1 Characteristics of the total 966 patients with COVID-19 in two groups before propensity score match**

Characteristics	Total (n=966)	Corticosteroids treatment (n=289)	Non-corticosteroids treatment (n=677)	P value
Age, years	60 (49–68)	62 (49–70)	59 (49–67)	0.052
Sex		0.103		
Female	470 (48.7%)	129 (44.6%)	341 (50.4%)	
Male	496 (51.3%)	160 (55.4%)	336 (49.6%)	
Symptoms on admission				
Cough	627 (64.9%)	199 (28.9%)	428 (63.2%)	0.093
Sputum	272 (28.2%)	95 (32.9%)	177 (26.1%)	0.033*
Dyspnea	342 (35.4%)	119 (41.2%)	223 (32.9%)	0.014*
Fatigue	461 (47.7%)	145 (50.2%)	316 (46.7%)	0.319
Fever	755 (78.2%)	243 (84.1%)	512 (75.6%)	0.004*
Laboratory findings				
NLR	3.00 (1.88–5.36)	8.33 (4.66–13.66)	2.83 (1.80–4.91)	0.000*
Platelet ( $\times 10^9/L$ ; normal range: 125–350)	219 (165–276)	199 (142–270)	225 (176–278)	0.000**
LDH (U/L; normal range: 109.0–245.0)	208 (170–296)	281 (204–393)	193 (163–251)	0.000*
ALT (U/L; normal range 5.0–35.0)	32 (20–54)	33 (21–52)	32 (20–55)	0.990
SCr ( $\mu\text{mol/L}$ ; normal range: 41.0–81.0)	66.4 (55.7–79.8)	68.0 (56.3–83.0)	65.7 (55.4–78.2)	0.070
BUN (mmol/L; normal range: 2.9–8.2)	5.32 (3.97–8.68)	5.42 (3.70–9.04)	5.30 (4.05–8.53)	0.268
CRP (mg/L; normal range: 0.0–8.0)	6.34 (2.14–41.02)	32.68 (5.91–70.78)	4.28 (1.29–22.38)	0.000*
D-dimer $\geq 1$ ( $\mu\text{g/L}$ ; normal range: 0.0–0.5)	285 (29.5%)	120 (41.5%)	165 (24.4%)	0.000*
Comorbidity				
Hypertension	305 (31.6%)	100 (34.6%)	205 (30.3%)	0.186
Diabetes	140 (14.5%)	32 (3.3%)	108 (16.0%)	0.049*
CHD	98 (10.1%)	22 (2.3%)	76 (11.2%)	0.089
CPD	57 (5.9%)	22 (2.3%)	35 (5.2%)	0.140
Malignant tumor	47 (4.9%)	12 (1.2%)	35 (5.2%)	0.501
Disease severity status		0.000*		
Mild/General	734 (76.0%)	155 (53.6%)	579 (85.5%)	
Severe/Critical	232 (24.0%)	134 (46.4%)	98 (14.5%)	
Treatment				
MV	62 (6.4%)	50 (17.3%)	12 (1.8%)	0.000*
Immunoglobulin therapy	139 (14.4%)	92 (31.8%)	47 (6.9%)	0.000**
Antiflezzing therapy	248 (25.7%)	119 (41.2%)	129 (18.5%)	0.000**
Antibacterial therapy	640 (66.3%)	260 (90.0%)	380 (54.4%)	0.000*
Outcomes				
In-hospital mortality	29 (3.0%)	24 (8.3%)	5 (0.7%)	0.000*
28-day mortality	15 (1.6%)	10 (3.5%)	5 (0.7%)	0.004*
Duration of viral shedding after COVID-19 onset, days	28 (21–35)	24 (18–33)	30 (21–37)	0.000*

Data are median (IQR) or *n* (%). *P* value were calculated by Mann-Whitney *U* test or Chi-square test, as appropriate. COVID-19: coronavirus disease 2019; NLR: neutrophil to lymphocyte ratio; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; SCr: serum creatinine; BUN: blood urea nitrogen; CRP: C-reactive protein; CHD: chronic heart disease; CPD: chronic pulmonary disease; MV: mechanical ventilation. All the above patients' lung imaging was bilateral infiltration and antiviral treatment was given. \**P*<0.05

the comparison of results after PS match was shown in table 2).

Table S1 shows a total of 400 patients in 200 pairs and 357 patients in 119 pairs were matched and characteristics for patients with or without corticosteroids were well balanced. No significant differences were observed after match in the mortality (in-hospital mortality and 28-day mortality) and duration of viral shedding after COVID-19 onset (table 2; fig. 1A and 1B).

Considering that different types of patients may had different responses to corticosteroids, we divided

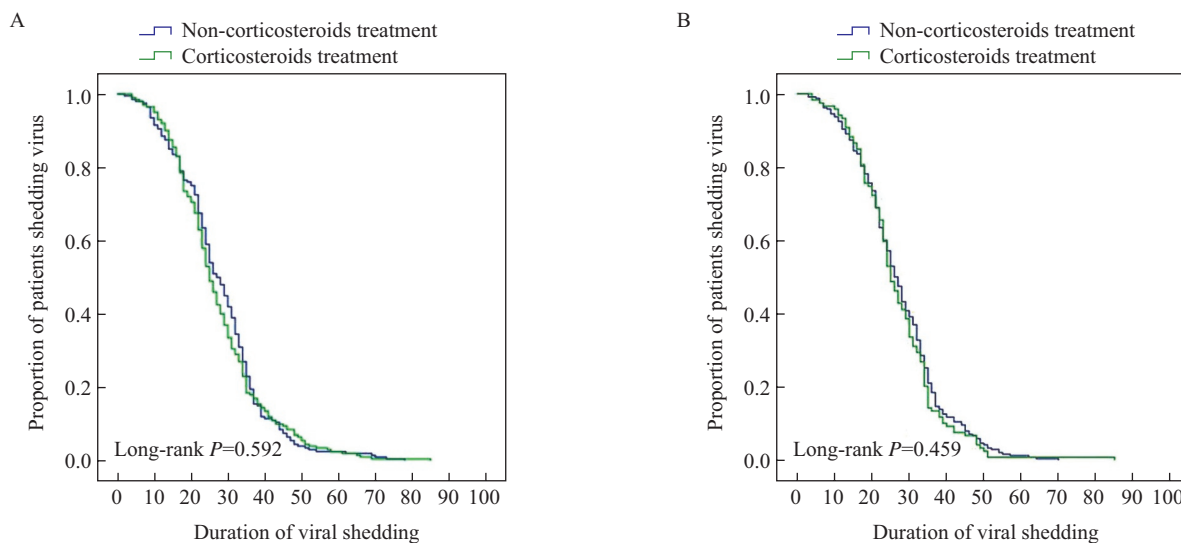
966 patients into two subgroups: severe/critical subgroup (*n*=232) and mild/general subgroup (*n*=734). The characteristics of the two subgroups before matching were shown in the supplementary materials (table S2 and table S3).

Table S2 shows that in the 232 severe/critical patients, there were more males receiving corticosteroids therapy, more symptoms were found (mainly including sputum and dyspnea), there were more patients combined with diabetes, and worse clinical data at admission (higher NLR, LDH, CREA, CRP and lower PLT), more patients received antibacterial therapy,

**Table 2 Outcomes of the patients with COVID-19 after propensity score match (1:1 matched and 1:2 matched) in corticosteroids treatment and non-corticosteroids treatment groups**

Outcomes	1:1 matched				1:2 matched			
	Total (n=400)	Corticosteroids treatment (n=200)	Non-corticosteroids treatment (n=200)	P value	Total (n=357)	Corticosteroids treatment (n=119)	Non-corticosteroids treatment (n=238)	P value
In-hospital mortality	11 (2.8%)	6 (3.0%)	5 (2.5%)	0.760	1 (0.3%)	0 (0%)	1 (0.4%)	1.000
28-day mortality	7 (1.8%)	2 (1.0%)	5 (2.5%)	0.449	1 (0.3%)	0 (0%)	1 (0.4%)	1.000
Duration of viral shedding after COVID-19 onset, days	26 (18–35)	25 (18–34)	28 (20–35)	0.348	26 (20–34)	25 (19–34)	27 (20–35)	0.581

Data are median (IQR) or n (%). P values were calculated by Mann-Whitney U test, Fisher’s exact test or chi-square test, as appropriate. COVID-19: coronavirus disease 2019



**Fig. 1** A: Viral shedding among 400 patients in 200 pairs, adjusted for confounding variables (1:1 matched); B: Viral shedding among 357 patients in 119 pairs, adjusted for confounding variables (1:2 matched)

antiflezzing therapy, immunoglobulin therapy and MV during hospitalization. As compared with the non-corticosteroids treatment group, the in-hospital mortality in the corticosteroids treatment group was higher (17.9% vs. 5.1%,  $P=0.004$ ). However, no statistically significant difference was found in the 28-day mortality and duration of viral shedding after COVID-19 onset between the two groups.

No significant differences were observed in in-hospital mortality, 28-day mortality and duration of viral shedding of severe/critical patients after adjusting for sex, NLR, LDH, CRP, immunoglobulin therapy, antibacterial therapy and MV (table 3 and

fig. 2), and characteristics for patients with or without corticosteroids were well balanced (table S4). Besides, after 1:2 match, there was also no significant differences in in-hospital mortality (0 vs. 1,  $P=1.000$ ), 28-day mortality (0 vs. 1,  $P=1.000$ ) and duration of viral shedding (25 vs. 22,  $P=0.381$ ) between the corticosteroids treatment group and the non-corticosteroids treatment group. Unfortunately, only 3 pairs of 9 patients were matched successfully.

The baseline characteristics of mild/general patients before match were less different. Only differences in fever, NLR, LDH, immunoglobulin therapy, antiflezzing therapy and antibacterial therapy

**Table 3 Outcomes of 96 severe/critical patients with COVID-19 after propensity score match (1:1 matched) in corticosteroids treatment and non-corticosteroids treatment groups**

Outcomes	Total (n=96)	Corticosteroids treatment (n=48)	Non-corticosteroids treatment (n=48)	P value
In-hospital mortality	8 (8.3%)	4 (8.3%)	4 (8.3%)	1.000
28-day mortality	5 (5.2%)	1 (2.1%)	4 (8.3%)	0.362
Duration of viral shedding after COVID-19 onset, days	24 (16–32)	24 (17–30)	24 (15–36)	0.722

Data are median (IQR) or n (%). P values were calculated by Mann-Whitney U test or Fisher’s exact test, as appropriate. COVID-19: coronavirus disease 2019

were found between the corticosteroids treatment group and non-corticosteroids treatment group (table S3).

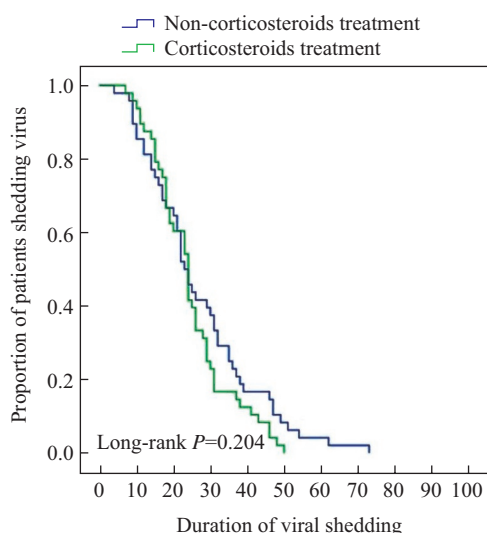
The variables including NLR, LDH, antibacterial therapy, antiflezzing therapy and immunoglobulin therapy were included in the matching model for 1:1 and 1:2 match, matching 262 in 131 pairs and 288 in 96

pairs, respectively (table S5). As there were no death cases in mild/general patients, only the duration of viral shedding between the two groups was compared. The results showed that there was no significant difference in the duration of viral shedding (table 4, and fig. 3A and 3B).

### 3 DISCUSSION

Corticosteroids were widely utilized in the treatment of severe pneumonia, including the Middle East respiratory syndrome (MERS) and SARS. However, this therapy had been controversial so far. This study investigated the impact of corticosteroids on clinical outcomes of patients with COVID-19, and revealed that the use of corticosteroids had no effect on the in-hospital mortality, 28-day mortality or duration of viral shedding of total and severe/critical patients, and had no effect on the duration of viral shedding of mild/general patients.

Severe/critical patients often died from the rapid progress of the disease in a short duration of time. Excessive inflammatory response may be one of the reasons for the increased mortality of patients. Some early studies on SARS and MERS had illustrated that proinflammatory factors in serum increased

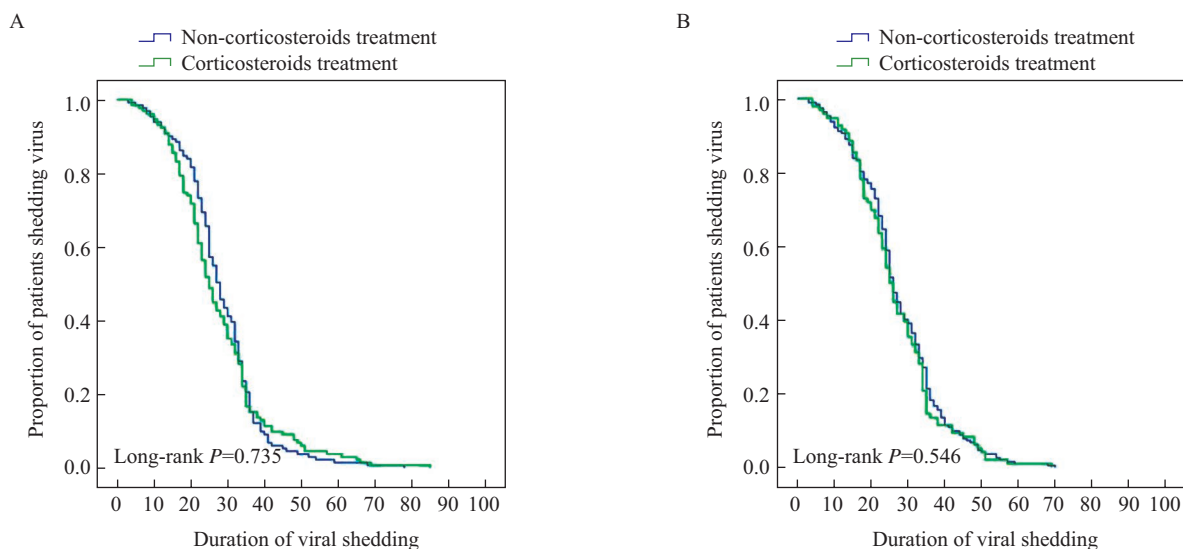


**Fig. 2** Viral shedding among 96 severe/critical patients in 48 pairs, adjusted for confounding variables (1:1 matched)

**Table 4** Outcomes of the mild/general patients with COVID-19 after propensity score match (1:1 matched and 1:2 matched) between corticosteroids treatment and non-corticosteroids treatment groups

Outcomes	1:1 matched				1:2 matched			
	Total (n=262)	Corticosteroids treatment (n=131)	Non- corticosteroids treatment (n=131)	P value	Total (n=288)	Corticosteroids treatment (n=96)	Non- corticosteroids treatment (n=192)	P value
Duration of viral shedding after COVID-19 onset, days	27 (21–34)	25 (18–34)	28 (22–34)	0.165	26 (20–35)	26 (18–34)	26 (21–35)	0.492

Data are median (IQR). P values were calculated by Mann-Whitney U test. COVID-19: coronavirus disease 2019



**Fig. 3** A: Viral shedding among 262 severe/critical patients in 131 pairs, adjusted for confounding variables (1:1 matched); B: Viral shedding among 288 severe/critical patients in 96 pairs, adjusted for confounding variables (1:2 matched)



significantly during viral infection, and after 5–8 days of corticosteroids treatment for SARS the levels of plasma chemokines [IL-8, IFN- $\gamma$  inducible protein 10 (IP-10), monocyte chemotactic protein 1 (MCP-1)] were reduced significantly, thereby relieving chemokine-related lung inflammation of SARS patients<sup>[18, 19]</sup>. Corticosteroids influences the patient's outcome through reducing inflammatory factors and relieving the inflammatory response. At the same time, the article of Craddock about "Hypercortisol" in severe acute diseases demonstrated that the immune response of self-antigens caused by disease or trauma exposure might be suppressed by corticosteroids to offset the possibility of autoimmune attacks<sup>[20]</sup>. A RECOVERY trial verified this view that survival rate was significantly higher in the dexamethasone-treated patients than in the non-dexamethasone treatment group, especially in the subgroup of patients receiving invasive MV<sup>[16]</sup>.

However, our results of this study seem not be in line with above views. The PS-based matching analysis showed that corticosteroids use in COVID-19 patients was not associated with difference in outcomes (mortality and duration of viral shedding after COVID-19 onset) after adjustment for confounders. Two studies had similar results<sup>[21, 22]</sup>: the use of corticosteroids had no correlation with the outcomes (mainly involving in-hospital mortality, virus clearance time, length of hospital stay and duration of symptoms). Considering the limitations of admission, possible selection bias, different timing and dosages, these results deserved further integrated analysis.

Corticosteroids are a double-edged sword, which exert anti-inflammatory and immunosuppressive effects. Prolonged viral shedding, double infection and increased mortality were the most reported adverse events in the literature<sup>[23–26]</sup>. A small prospective, randomized, double-blind, placebo-controlled trial conducted by Lee *et al* also confirmed that patients who received hydrocortisone early had significantly higher concentrations of SARS-Cov RNA in the second and third weeks than the control group. It is considered that the virus removal mainly depends on the body's self-immunity. The early use of corticosteroids may coincide with the period of virus replication, which inhibits the body's self-immunity function, resulting in delay in virus removal<sup>[27]</sup>. Effect of corticosteroids use on duration of viral shedding was not found in this study, which was considered to be related to the late prevalence of corticosteroids treatment in patients (median time from onset to corticosteroids treatment was 14 days) and effective antiviral treatment. Although the use of corticosteroids in confirmed patients did not increase mortality and duration of viral shedding, this study did not further explore the adverse reactions that may be caused by corticosteroids such as superinfection

and gastrointestinal bleeding. The clinical application still needs to be cautious.

Our study also has the following limitations: (1) This experiment is a retrospective study, and due to the limitation of sample size and the partial lack of patient data, it is impossible for us to match all baseline characteristics between groups; (2) The time for the nucleic acid testing of patients is determined by the doctor-in-charge, therefore, the length of virus shedding may be limited by the frequency of specimen collection, and at the same time also limited by the low positive rate of the detection method; (3) Our study only focused on the patients' short-term partial outcomes, superinfections, complications, and long-term side effects of corticosteroids may require further research to ensure the safety of patients receiving corticosteroids therapy.

The current application of corticosteroids in patients with COVID-19 is inconclusive. In conclusion, our analysis of 966 patients with COVID-19 in Wuhan Union Hospital showed that the use of corticosteroids has no effect on the duration of viral shedding, in-hospital mortality or 28-day mortality.

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#### Conflict of Interest Statement

The authors declared no conflict of interest.

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