Background: There are controversies regarding corticosteroids using in coronavirus disease-2019 (COVID-19) pneumonia in the current pandemic. Objectives: This study investigates the efficacy and safety profiles of corticosteroids therapy in COVID-19 patients. Methods: Retrospective, multicenter study case series of consecutive patients with confirmed COVID-19 infection at the whole hospital from January 1 to March 1, 2020, were enrolled. Demographic, clinical, radiological, laboratory, and treatment data were collected and analyzed. The effect of corticosteroids therapy on death and organ-failure complications of pneumonia were analyzed by logistic regression. Results: A total of 470 COVID-19 patients at the whole hospital were enrolled. According to the time of corticosteroids initiation and severity of illness, there were 159 patients stratified into critical ill group and 64% (102 of 159) patients received corticosteroids treatments. Ninety-four percent (166 of 176) of corticosteroids were methylprednisolone. The median cumulative corticosteroids dosage was 300 mg equivalent of methylprednisolone over a median duration of 6 days. Multivariate regression analysis showed that corticosteroids use did not affect the mortality. However, corticosteroids therapy at moderate cumulative doses (total exposure 480 mg to 1200 mg) was associated with deceased occurrence of organ-failure complications in critically ill COVID-19. Conclusions: Corticosteroids have no effect to mortality in COVID-19 patients. The moderate cumulative doses of corticosteroids might decrease organ-failure complications in critically ill COVID-19. Further large-scale randomized controlled trials are warranted to confirm our findings, until then use of corticosteroids should be used with caution COVID-19 patients.

Keywords: Acute respiratory distress syndrome, coronavirus disease 2019, corticosteroid, pneumonia

INTRODUCTION

The novel coronavirus disease-2019 (COVID-19) pandemic has presented great challenges in health care.[1] Research has shown that 58% of the patients with COVID-19 received corticosteroids therapy when they were hospitalized.[2] The usefulness and safety of corticosteroids as an adjuvant therapy for COVID-19 pneumonia remain controversial. Corticosteroids may diminish the inflammatory response, a major factor for lung damage and acute respiratory distress syndrome (ARDS) in viral respiratory tract infection.[3] In a randomized controlled trial (RCT), Villar et al. reported that early administration of corticosteroids therapy could reduce mortality in patients with ARDS.[4] However, previous studies on corticosteroids therapy in severe acute pulmonary illness of COVID-19 pneumonia remain controversial. Further large-scale randomized controlled trials are warranted to confirm our findings, until then use of corticosteroids should be used with caution COVID-19 patients.

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respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome coronavirus (MERS-CoV) have shown no benefit to outcomes. In our study, we collected data through a multicenter retrospective study in Wuhan to investigate the effects of corticosteroid treatment on clinical outcomes in COVID-19 patients.

**METHODS**

**Study design and participants**
This multicenter retrospective cohort study was conducted in three medical center Zhongnan Hospital of Wuhan University, Wuhan fourth Hospital, Maternal and Child Health Hospital of Hubei Province) from January 1 to March 1, 2020. The study was approved by the institutional ethics board in each participating hospital. Oral consent for data inclusion was obtained from patients or patients’ relatives. All patients with COVID-19 enrolled in this study were diagnosed according to the World Health Organization interim guidance. Reverse transcription-polymerase chain reaction was used as a gold standard to diagnose COVID-19 in multiple and different clinical specimens when necessary. Corticosteroids were administered according to local recommendation.

**Data collection**
Medical records of the eligible patients were reviewed and data were collected with a standardized case report form in the participating centers. Demographics, laboratory findings, management or treatment strategies, patient outcomes were collected. The cumulative corticosteroids dose was calculated after hospital admission, and the doses were converted to methylprednisolone equivalent doses, and the cumulative corticosteroids dose was then calculated. The type of the corticosteroids was also recorded.

**Outcome**
The primary outcome in this study was hospital mortality. Complications of organ failure during the course of treatment and associated with progression of COVID-19 included ARDS, acute kidney injury (AKI), acute liver injury, acute myocardial injury, and shock. ARDS was defined according to the Berlin definition: Pao2/Fio2 ratio of less than or equal to 200 mmHg and a positive end-expiratory pressure of greater than or equal to 5 cm H2O. AKI was identified according to the Kidney Disease: Improving Global Outcomes criteria clinical practice guidelines: An increase in serum creatinine values greater than or equal to 0.3 mg/dL (26.5 μmol/L) within 48 h, serum creatinine values greater than or equal to 1.5 times the baseline within the previous 7 days, or urine volume less than or equal to 0.5 mL/kg/hr for 6 h. The cardiac injury was defined as one or more of the following: (1) blood levels of cardiac biomarkers (TNI or CK-MB) above the 99th percentile upper reference limit, new abnormalities in electrocardiography, including supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, ventricular fibrillation, bundle branch block, ST-segment elevation/depression, T-wave flattening/inversion, QT interval prolongation, new abnormalities in echocardiography, including decreased EF value (EF <50%) or a worsening of the underlying state (patients with basal state of EF <50%), regional/global ventricular wall motion abnormalities, the presence of pericardial effusion, and pulmonary arterial hypertension (PAH). PAPm was calculated by adding estimated right atrial pressure to mean tricuspid regurgitation pressure, echocardiographic estimation of PAPm with a cutoff value of greater than or equal to 25 mmHg at rest with regard to the diagnosis of PAH.

**Definition**
Critical illness was defined according to the guideline for the diagnosis and treatment of 2019 novel coronavirus infected pneumonia (standard version) of China criterion for critically ill patients, namely: Having a low oxygenation index (OI) (300 mmHg) or pulmonary imaging showing significant progression (>50%) within 24–48 h, or those with respiratory failure requiring mechanical ventilation or other intensive care unit (ICU) care. Patients on admission meeting the criteria of critical illness stratified into “critically ill” group, otherwise into “noncritically ill” group. If patients had a disease progression, the group classification depends on the time of initiating corticosteroids [Figure 1]. The baseline values of corticosteroids group were determined as the median of daily recorded values during the 3 days before the first corticosteroids dose.

**Statistical analysis**
Data are presented in number (%) or median (25th–75th percentiles), as appropriate. Categorical variables and continuous variables were compared using Chi-square test and Mann–Whitney U-test, respectively. Logistic regression analysis was used to adjust for confounding factors. Variables with a P < 0.05 in univariate models were selected into the multivariable model. Analyses were stratified analyses of according to critically ill/noncritically ill status and high (total methylprednisolone equivalent more than 1200 mg), moderate (total methylprednisolone equivalent between 480 mg and 1200 mg), or lower (total methylprednisolone equivalent <480 mg) cumulative doses of corticosteroids exposure. All statistical analyses were performed using Statistical product and service solutions (SPSS 22.0, International Business Machines Corp., USA). The statistical significance level was set at a two-sided P value of <0.05. A odds ratio was reported along with 95% confidence interval.
RESULTS

Characteristics of the patients
A total of 470 patients with COVID-19 infection was included in this study. According to the time of corticosteroids initiation and severity of illness, there were 159 patients stratified into critical ill group and 64% (102 of 159) patients received corticosteroids treatments. There were 311 patients stratified into noncritical ill group and 24% (74 of 311) received corticosteroids treatments. Laboratory data of OI, lymphocyte count, platelet count, creatinine, and urea were significantly different between the critically ill and noncritically ill patients ($P<0.05$). A total of 176 (37.4%) patients received corticosteroids treatments. Among all patients treated with corticosteroids, the median cumulative dosage of corticosteroid was 300 mg and over a median period of 6 days. 37.4% (176 of 420) patients had corticosteroids treatment and 94% (166 of 176) was methylprednisolone, only 1% (2 of 176) was hydrocortisone and 4% (6 of 176) was dexamethasone (dexamethasone 0.75 mg = methylprednisolone 4 mg = hydrocortisone 20 mg). The total mortality was 7% and 18.9% death in critical ill group. The total hospital and ICU stay was 13 and 16 days, respectively. Other details are shown in Table 1.

Multivariate analysis of corticosteroids dosage
Multivariate analysis showed that mortality across different cumulative dosage of corticosteroids did not significantly differ critically ill and noncritical ill group. Multivariable analysis for mortality adjusted for age, sex, comorbidities, laboratory data, and complications of COVID-19 listed in Table 1. The outcome of organ-failure complications in a cumulative dosage of corticosteroids at 480–1200 mg group had a significant difference in critically ill group after adjusting the confounders. The moderate cumulative doses of corticosteroids decreased organ-failure complications in critically ill COVID-19 [Figure 2b]. Multivariable analysis for complications adjusted for age, sex, comorbidities, and laboratory data of COVID-19 is listed in Table 1. There were 10.5% patients of dosage at 480–1200 mg, and the median total durations and daily dosage of patients using corticosteroids at this interval were about 10.4 days and 66 mg, respectively.

DISCUSSION
In our study, we found that the corticosteroids therapy was prescribed in large proportion of COVID-19 patients. Corticosteroids have no effect to mortality in COVID-19 patients. However, in critically ill patients, a moderate cumulative dose of corticosteroids was associated with decrease incidence of organ-failure complications.

Corticosteroids are commonly used for modulation of a variety of inflammatory conditions. It may diminish the inflammatory response, a major factor for lung damage and ARDS in viral respiratory tract infection. The other favor reason to have corticosteroids therapy in COVID-19 patients was that corticosteroids might help accelerate recovery from COVID-19. The current study shown that corticosteroids ciclesonide was capable.
of inhibiting viral replication of the MERS-CoV and other human coronaviruses.\[13\] In a retrospective study of 401 SARS patients administered corticosteroids, reduced mortality and shortened length of hospital stay were demonstrated.\[14\] Our results shown that a moderate cumulative dose of corticosteroids was associated with decrease incidence of organ-failure complications in critically ill patients. The daily dose in our study was low dosage according to our local recommendation. High dose of corticosteroids might deteriorate the low level of lymphocyte, giving rise to severe secondary infections.\[15\]

Our results show that corticosteroids have no effect to mortality. Indeed, the conflicting results of corticosteroids have been reported. In a cohort study in MERS-CoV, the

| Table 1: Characteristics of the patients between noncritically and critically ill coronavirus disease-2019 |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Factors                                         | All (n=470)                                      | Noncritical ill (n=311)                          | Critically ill (n=159)                           |
| Age call n (%)                                  | 143 (30.4)                                      | 76 (24.4)                                       | 67 (42.1)                                       |
| Gender, n (%)                                    | Male                                            | 207 (44.0)                                      | 126 (40.5)                                      | 81 (50.9)                                      |
|                                                  | Female                                          | 263 (56.0)                                      | 185 (59.5)                                      | 78 (49.1)                                      |
| Comorbidities, n (%)                             | Hypertension                                    | 178 (37.9)                                      | 109 (35.0)                                      | 69 (43.4)                                      | 0.078                                          |
|                                                  | Diabetes                                        | 66 (14.0)                                       | 37 (11.9)                                       | 29 (18.2)                                      | 0.061                                          |
|                                                  | Cardiovascular disease                          | 57 (12.1)                                       | 31 (10.0)                                       | 26 (16.4)                                      | 0.045                                          |
|                                                  | Cerebrovascular disease                         | 27 (5.8)                                        | 7 (2.3)                                         | 20 (12.7)                                      | <0.001                                         |
|                                                  | Chronic liver disease                           | 11 (2.3)                                        | 8 (2.6)                                         | 3 (1.9)                                        | 0.642                                          |
|                                                  | Chronic kidney disease                          | 12 (2.6)                                        | 6 (1.9)                                         | 6 (3.8)                                        | 0.226                                          |
|                                                  | Malignancy                                      | 27 (5.8)                                        | 13 (4.2)                                        | 14 (8.9)                                       | 0.040                                          |
| Laboratory data (IQR)                           | Oxygenation index                               | 272.0 (200.5-378.8)                             | 420.0 (342.0-500.0)                             | 233.0 (164.0-272.0)                            | <0.001                                         |
|                                                  | White blood cell count ×10^9/L                  | 4.83 (3.58-6.65)                                | 4.83 (3.80-6.31)                                | 4.80 (3.19-7.16)                               | 0.670                                          |
|                                                  | Neutrophil count ×10^9/L                        | 3.24 (2.26-4.85)                                | 3.17 (2.29-4.56)                                | 3.48 (2.12-5.97)                               | 0.141                                          |
|                                                  | Lymphocyte count ×10^9/L                        | 0.94 (0.65-1.29)                                | 1.05 (0.74-1.40)                                | 0.72 (0.53-1.05)                               | <0.001                                         |
|                                                  | Platelet count ×10^9/L                          | 179.0 (136.0-226.0)                             | 186.0 (145.0-239.5)                             | 156.0 (123.8-205.8)                            | <0.001                                         |
|                                                  | Creatine kinase                                 | 81.0 (47.0-135.0)                               | 86.0 (48.5-131.0)                               | 77.0 (38.0-167.3)                              | 0.894                                          |
|                                                  | Alanine aminotransferase                        | 23.0 (14.0-39.0)                                | 22.0 (13.0-30.0)                                | 29.0 (17.0-47.0)                               | <0.001                                         |
|                                                  | Aspartate aminotransferase                      | 29.0 (21.0-42.0)                                | 26.0 (20.0-35.0)                                | 35.0 (25.0-57.0)                               | <0.001                                         |
|                                                  | Creatinine μmol/L                               | 67.6 (55.4-83.0)                                | 64.0 (53.7-77.6)                                | 75.1 (60.0-92.9)                               | <0.001                                         |
|                                                  | Urea mmol/L                                     | 4.48 (3.46-6.05)                                | 4.23 (3.30-5.35)                                | 5.26 (4.01-7.55)                               | <0.001                                         |
| Treatment, n (%)                                 | Extracorporeal membrane oxygenation             | 4 (0.9)                                         | 0                                               | 4 (2.5)                                        | 0.005                                          |
|                                                  | Noninvasive mechanical ventilation              | 77 (16.4)                                       | 5 (1.6)                                         | 72 (45.3)                                      | <0.001                                         |
|                                                  | Invasive mechanical ventilation                 | 24 (5.1)                                        | 0                                               | 24 (15.1)                                      | <0.001                                         |
|                                                  | Prone position                                  | 7 (1.5)                                         | 0                                               | 7 (4.4)                                        | <0.001                                         |
|                                                  | Steroids use                                    | 176 (37.4)                                      | 74 (23.8)                                       | 102 (64.2)                                     | <0.001                                         |
|                                                  | Cumulative dosage (IQR)                         | 300 (180-480)                                   | 300 (160-420)                                   | 360 (200-540)                                  | 0.016                                          |
|                                                  | <480, n (%)                                     | 137 (77.8)                                      | 62 (83.8)                                       | 75 (73.5)                                      | 0.106                                          |
|                                                  | 480-1200, n (%)                                 | 33 (18.8)                                       | 11 (14.9)                                       | 22 (21.6)                                      | 0.261                                          |
|                                                  | >1200, n (%)                                    | 6 (3.4)                                         | 1 (1.4)                                         | 5 (4.9)                                        | 0.200                                          |
|                                                  | Cumulative days (IQR)                           | 6 (4-9)                                         | 5 (3-8)                                         | 6 (4-9)                                        | 0.155                                          |
|                                                  | Daily dosage mean (minimum-maximum)             | 55.37 (20-160)                                  | 49.96 (20-80)                                   | 58.99 (20-160)                                 | <0.001                                         |
| Complications, n (%)                             | Acid liver injury                               | 144 (30.6)                                      | 46 (14.8)                                       | 98 (61.6)                                      | <0.001                                         |
|                                                  | Acute kidney injury                             | 58 (12.3)                                       | 28 (9.0)                                        | 30 (18.9)                                      | 0.002                                          |
|                                                  | Acute respiratory distress syndrome             | 58 (12.3)                                       | 21 (6.8)                                        | 37 (23.3)                                      | <0.001                                         |
|                                                  | Acute respiratory distress syndrome             | 65 (13.8)                                       | 10 (3.2)                                        | 55 (34.6)                                      | <0.001                                         |
|                                                  | Acute myocardial injury                         | 54 (11.5)                                       | 0                                               | 54 (34.0)                                      | <0.001                                         |
|                                                  | Shock                                           | 18 (4.8)                                        | 0                                               | 18 (13.8)                                      | <0.001                                         |
|                                                  | Acute myocardial injury                         | 26 (6.2)                                        | 6 (2.2)                                         | 20 (13.2)                                      | <0.001                                         |
| Outcome                                          | Death, n (%)                                    | 33 (7.0)                                        | 3 (1.0)                                         | 30 (18.9)                                      | <0.001                                         |
|                                                  | Complications, n (%)                            | 143 (30.4)                                      | 45 (14.5)                                       | 98 (61.6)                                      | <0.001                                         |
|                                                  | Hospital stay (IQR)                             | 13 (9-16)                                       | 11 (9-14)                                       | 15 (12-17)                                     | <0.001                                         |
|                                                  | ICU stay, d                                     | 7 (4-7)                                         | 5 (4-6)                                         | 9 (4-10)                                       | 0.300                                          |

IQR: Interquartile range, ICU: Intensive care unit

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use of corticosteroids was identified as a risk factor for higher mortality.\textsuperscript{[14]} Similarly, in a retrospective study of 78 SARS patients, the use of corticosteroids was associated with adverse outcomes.\textsuperscript{[17]} Our results indicate that the administration of low dose did not improve clinical mortality in critically ill patients, which was consistent with previous studies.\textsuperscript{[18–20]}

In viral pneumonia patients, the host immune products excessive inflammatory cytokines and may cause acute lung injury and ARDS, the corticosteroids may suppress the overwhelming inflammation to reduce the development of organ failure complications.\textsuperscript{[21]} Previous study found that using moderate doses of methylprednisolone (2 mg/kg per day) for 2 weeks was associated with improved outcomes in ARDS.\textsuperscript{[22]} In our study, we found that the corticosteroids administration has no effect to mortality. However, after taking dose into consideration, in patients who received total methylprednisolone equivalent between 480 mg and 1200 mg, experience decreased incidence of organ-failure complications. In this group, the mean total days of corticosteroids administration and daily dosage of corticosteroids was 10.4 days and 66 mg, respectively. This result suggested benefit from a longer duration of corticosteroids use compared to latter expert consensus statement recommending a short period of corticosteroids use in COVID-19 patients in China.\textsuperscript{[23]} According to our results, we suggested that a moderate cumulative dosage of corticosteroids with a longer duration (10.4 days) might decrease the occurrence of organ-failure complications in critical ill COVID-19. The current WHO guidance\textsuperscript{[24]} recommended corticosteroids should not be used in COVID-19 patients, except in the setting of a clinical trial. Based on our results, any such study should explore dose response of corticosteroids therapy in this context. Recently, the RCT from the UK for evaluation corticosteroids therapy in COVID-19 patients showed dexamethasone reduced 28-day mortality.\textsuperscript{[25]} However, evidence is short of corticosteroid doses, disease severity in their study. In our retrospective study, we analyzed different dosage corticosteroids therapy in both critically ill and noncritically ill patients. Moreover, further high-quality RCTs of this kind of study design would confirm our findings.

Our study has several limitations. First, due to retrospective design, some values were missing. Such retrospective design was methodologically flawed in inferring causal association due to confounding factors.\textsuperscript{[26]} Second, longer-term complications such as secondary bacterial or fungal infection and osteonecrosis\textsuperscript{[27,28]} were not evaluated. Third, we only took the cumulative dosage of corticosteroids into consideration. Whether the daily dosage in our study should be further studied. Finally, due to a small sample size, especially in the stratified analyses by corticosteroids dose, the results must be interpreted cautiously and in the future, large-scale RCTs are required to evaluate the true effect of corticosteroids in mortality in hospital in COVID-19 patients.

**Conclusions**

This study showed that corticosteroids use had no obvious effect in mortality in COVID-19 patients. In critically ill patients, administration of corticosteroids at moderate cumulative doses was associated with decreased incidence of complications. Further large-scale RCTs are warranted to confirm our findings, and until then, the use of corticosteroids in COVID-19 patients should be cautious.
Ethics approval and consent to participate
This study was reviewed and approved by the institutional ethics board of Zhongnan Hospital of Wuhan University (No. 20200020). Oral informed consent was obtained from patients or their legal representatives.

Availability of data and material
The data used for this research are available from the corresponding author on reasonable request and subject to Institutional Review Board guidelines.

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Conflicts of interest
Zhiyong Peng is the Executive Editor-in-Chief of the journal. The article was subject to the journal’s standard procedures, with peer review handled independently of these members and their research groups.

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