Systemic corticosteroids and mortality in severe and critical COVID-19 patients in Wuhan, China

Jianfeng Wu,[1,#] Jianqiang Huang,[2,#] Guochao Zhu,[3,#] Yihao Liu,[4,5#] Han Xiao,[6#] Qian Zhou,[4#] Xiang Si,[1] Hui Yi,[2] Cuiping Wang,[1] Daya Yang,[7] Shuling Chen,[6] Xin Liu,[8] Zelong Liu,[6] Qiongya Wang,[9] Qingquan Lv,[10] Ying Huang,[11] Yang Yu,[12] Xiangdong Guan,[1] Yanbing Li,[5] Krishnarajah Nirantharakumar,[13,14] KarKeung Cheng,[13] Sui Peng,[4*] Haipeng Xiao,[5,15*]

[1] Department of Critical Care Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, People's Republic of China

[2] Division of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, People's Republic of China

[3] Department of Critical Care Medicine, The Affiliated Hospital of Jianghan University (No. Six Hospital of Wuhan), Wuhan, Hubei, 430014, People's Republic of China

[4] Clinical Trials Unit, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, People's Republic of China

[5] Department of Endocrinology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, People's Republic of China

[6] Department of Medical Ultrasonics, Institute of Diagnostic and Interventional Ultrasound, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, People's Republic of China

[7] Department of Cardiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, People's Republic of China

[8] Department of Liver Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, People's Republic of China

[9] Department of Critical Care Medicine, Wuhan Hankou Hospital, Wuhan, Hubei, 430014, People's Republic of China

[10] Department of Gastrointestinal Surgery, Wuhan Hankou Hospital, Wuhan, Hubei, 430014, People's Republic of China

[11] Science and Education Section, Wuhan Hankou Hospital, Wuhan, Hubei, 430014, People's Republic of China

[12] Department of Gastrointestinal Surgery, The Affiliated Hospital of Jianghan University (No. Six Hospital of Wuhan), Wuhan, Hubei, 430014, People's Republic of China

[13] Institute of Applied Health Research, University of Birmingham, United Kingdom

[14] Health Data Research UK, United Kingdom

[15] Precision Medicine Institute, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, People's Republic of China

[#]These authors contributed equally to this work.

*Corresponding authors

Correspondence to:

Haipeng Xiao, MD, Ph.D.

Department of Endocrinology & Precision Medicine Institute, The First Affiliated Hospital, Sun Yat-sen University, No. 58, ZhongShan Road 2, Guangzhou, Guangdong 510080, People's Republic of China

E-mail: xiaohp@mail.sysu.edu.cn

Sui Peng, MD, Ph.D.

Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, No. 58, ZhongShan Road 2, Guangzhou, Guangdong 510080, People's Republic of China

E-mail: pengsui@vip.163.com

Funding information: Not applicable.

Author Disclosure Statement

The authors report nothing to declare. No competing financial interests exist.

Abstract:

Background: Systemic corticosteroids are now recommended in many treatment guidelines, though supporting evidence is limited to one randomised controlled clinical trial (RECOVERY).

Objective: To identify whether corticosteroids were beneficial to COVID-19 patients.

Methods: 1514 severe and 249 critical hospitalized COVID-19 patients from two medical centers in Wuhan, China. Multivariable Cox models, Cox model with time-varying exposure and propensity score analysis (inverse-probability-of-treatment-weighting (IPTW) and propensity score matching (PSM)) were used to estimate the association of corticosteroid use with risk of in-hospital mortality in severe and critical cases.

Results: Corticosteroids were administered in 531 (35.1%) severe and 159 (63.9%) critical patients. Compared to non-corticosteroid group, systemic corticosteroid use was not associated with beneficial effect in reducing in-hospital mortality in both severe cases (HR=1.77, 95% CI: 1.08-2.89, p=0.023), and critical cases (HR=2.07, 95% CI: 1.08-3.98, p=0.028). Findings were similar in time-varying Cox analysis. For severe COVID-19 patients at admission, corticosteroid use was not associated with improved or harmful outcome in either PSM or IPTW analysis. For critical COVID-19 patients at admission, results were consistent with multivariable Cox model analysis.

Conclusion: Corticosteroid use was not associated with beneficial effect in reducing in-hospital mortality for severe or critical cases in Wuhan. Absence of the beneficial effect in our study in contrast to that was observed in the RECOVERY clinical trial may be due to biases in observational data, in particular prescription by indication bias, differences in clinical characteristics of patients, choice of corticosteroid used, timing of initiation of treatment and duration of treatment.

Keywords: Systemic corticosteroids; mortality; severe and critical; COVID-19.

Introduction

The current pandemic of coronavirus disease-19 (COVID-19) has become the most severe global health crisis (1). At present, the cumulative number of confirmed COVID-19 cases worldwide has exceeded 18 million and is still rising rapidly (2). Although most of COVID-19 patients reportedly had mild symptoms and good prognosis, the mortality of hospitalized severe and critical cases was 18.2% and 49%, respectively (3,4). Due to the lack of specific therapies for COVID-19, one of the biggest challenges faced by clinicians in all countries is the clinical management of severe and critical cases with the goal of reducing mortality.

Systemic corticosteroids have been studied extensively with variable and inconsistent results in the treatment of acute respiratory distress syndrome (ARDS) caused by viral pneumonia (5-7). During the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), systemic corticosteroids were used in 79.6% and 48.9% of critical cases, respectively (5,8). Two studies of patients with SARS and influenza A (H1N1) viral pneumonia showed that the use of systemic corticosteroids was associated with reduced mortality in critical patients (6,8). However, several other studies of patients with SARS and one study of patients with MERS all indicated that its use could be harmful (5,9-12). A meta-analysis published in 2019 also showed a significant increase in mortality in influenza pneumonia patients treated with systemic corticosteroids (13). The COVID-19 treatment guidelines released by the China's National Health Commission recommended low-dose and short-term use of systemic corticosteroids for patients with rapidly worsening conditions (14-16). Systemic corticosteroids were used in 44.5% of severe COVID-19 patients in China (17). However, its routine use was not recommended by the World Health Organization (WHO) clinical management guidelines until recently for patients with severe acute respiratory infection when COVID-19 is suspected (18). However a recently concluded controlled open labelled randomised clinical trial (RECOVERY trial) showed 18% reduced mortality in patients requiring oxygen treatment and 36% reduced mortality in patients needing mechanical ventilation (19).

In the current study, we analysed the clinical data of 1514 severe and 249 critical COVID-19 cases from two medical centres in Wuhan city and investigated if the effects of systemic corticosteroids seen in Recovery trial were observed in the Wuhan dataset.

Patients and methods

Study Population

Consecutive inpatients with laboratory confirmed or clinically diagnosed COVID-19 from Wuhan Hankou Hospital and No. Six Hospital of Wuhan between December 26th, 2019 and March 15th 2020 were collected in this study. The final follow up date was March 19th, 2020. Patients who met any of the following conditions were exclude from the study: 1. Non-severe or non-critical cases; 2. Not being diagnosed as severe cases within 24 hours since admission; 3. The time of being diagnosed of severe/critical cases were missing. Severe cases were defined as those who required oxygen therapy during hospital stay. Critical cases were defined based on the 7th trial version of Diagnosis and Treatment Scheme for Pneumonitis caused by COVID-19 Infection (16). Therefore, those who met any of the following conditions during the whole hospital stay were categorised as critical cases: 1. requiring mechanical ventilation; 2. requiring treatment in intensive care unit (ICU); 3. shock occurred in hospital (16).

Ethical considerations

This study was approved by the ethics committees of Wuhan Hankou Hospital, No. Six Hospital of Wuhan and the First Affiliated Hospital of Sun Yat-sen University, and the informed consent was waived. The study followed the tenets of the Declaration of Helsinki and is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Data Collection and Definition

We collected the patients' clinical data, including demographic information, medical history, laboratory indexes, corticosteroid use and prognosis. The admission laboratory indexes were defined as the first records of laboratory indexes since admission. Corticosteroid use was defined as the use of intravenous systemic corticosteroids, including hydrocortisone, methylprednisolone, and dexamethasone. The dose of corticosteroids was converted to methylprednisolone-equivalent doses (1mg methylprednisolone = 0.1875mg dexamethasone = 5mg hydrocortisone) (20). At the time of the study limited guidance existed on when to use corticosteroids and therefore most decision were based on intuitiveness of the clinician following assessment of the clinical state and after excluding any contraindication for corticosteroid use.

Exposure and Outcome

We evaluated whether using corticosteroids could affect the in-hospital mortality of severe/critical cases. The time to death was defined as the time of being diagnosed of severe/critical cases to the date of death from any cause in hospital for the primary analysis.

Statistical Analysis

Data were expressed as mean and standard deviation (SD) if normally distributed, and median and interquartile range (IQR) with non-normal distribution, and frequency and percentages for categorical variables. We compared baseline characteristics and outcomes of patients who received corticosteroids and those who did not receive any corticosteroid using Students' t test, Mann-Whitney test for continuous variables, and chi-square test or Fisher exact test for categorical variables. Survival with or without corticosteroid use was analysed using the Kaplan-Meier method and compared by log-rank test. The 28-day in-hospital mortality and its 95% confidence interval was reported for both corticosteroid use and non-corticosteroid use groups. We evaluated the associations between corticosteroid use and prognosis using two approaches. First, multivariable Cox regression models were applied to evaluate the association between corticosteroid use and mortality. Multivariable analysis was adjusted for age, gender, admission laboratory indexes (including lymphocyte, neutrophil granulocyte, platelet, haemoglobin, glucose, C-reaction protein (CRP), lactate dehydrogenase (LDH), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), pulse oxygen saturation (SpO2), hypertension, diabetes, cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and smoking history. The proportion of missing values of baseline variables was 4.5%, ranging from 0% to 10.6%. The missing data were imputed by multiple imputation for ten times in the multivariable analysis. Second, in Cox regression models, corticosteroid use was accounted as a time-varying exposure to mitigate immortal time bias. In time-varying analysis, data was reconstructed according to the time of corticosteroid use. Therefore, time from a diagnosis of severe/critical case to time of corticosteroid use was categorized as unexposed. The hazards ratios (HRs) and 95% confidence intervals (CIs) of Cox regression models were reported.

We also performed propensity score driven analysis (inverse-probability-of-treatment-weighting (IPTW) and propensity score matching (PSM)) to account for confounding by indication bias in the time-dependant Cox regression analysis (21,22). Multivariable logistic

regression was carried out with corticosteroid use as a binary outcome to obtain the predicted probability of corticosteroid use, which was taken as propensity score (PS). All baseline characteristics were used to construct PS for each three parts of patients. In IPTW, for the group with corticosteroids therapy, the weight was equal to 1/PS, while for the group without corticosteroids therapy, the weight was equal to 1/(1-PS). In PSM, calliper value was set as 20% of the standard deviation of propensity scores. We reported the effect sizes as hazard ratios in all four types of analysis 1) multivariable Cox regression; 2) Cox regression with time-varying exposure; 3) IPTW based analysis; and 4) PSM based analysis. Wilcoxon signed-rank test was used for pairwise comparison of mean blood glucose and lymphocytes before, during and after the use of corticosteroids, and method of Bonferroni was used for correction. We used Stata/MP 14.0 to conduct all data analyses, and statistical significance was set as $p<0.05$ bilaterally.

Results

Baseline characteristics

From Dec 26th, 2019 to Mar 15th, 2020, a total of 2289 consecutive cases of COVID-19 hospitalized patients were collected from two medical centres in Wuhan, China. After excluding non-severe/critical cases (n=126), cases without the exact severe or critical diagnosis timepoint (n=202) and severe or critical cases not being diagnosed on the day of admission (n=198), a total of 1763 COVID-19 hospitalized severe or critical cases were included. Among them, 85.9% (1514/1763) patients were severe cases at admission, and 14.1% (249/1763) patients were critical cases at admission.

Table 1 showed the baseline characteristics of 1514 severe cases at admission. The median age was 61.0 years (IQR: 51.0, 70.0), and 790 (52.2%) were female. The median in-hospital stay was 12.7 days (IQR: 7.5, 19.8). Among them, 531 (35.1%) patients received systemic corticosteroids with a daily average dose equivalent to 40.0 mg (IQR: 37.3, 57.1) methylprednisolone, and 67.6% (359/531) started corticosteroid use within 24 hours after being diagnosed as severe cases. The median initial time of corticosteroid use since being diagnosed as severe cases was 2.2 (0.1, 41.5) hours, and the duration of corticosteroid use lasted 6.0 (3.0, 10.0) days. When comparing the baseline characteristics between corticosteroid use group and non-corticosteroid use group, there were significant differences in age, gender, several admission laboratory values and smoking ($p<0.05$).

Table 2 showed the baseline characteristics of 249 critical cases at admission. The median age was 68.0 years (IQR: 58.0, 78.0), and 102 (41.0%) were female. The median in-hospital stay was 13.9 days (IQR: 5.8, 22.6). Among them, 159 (63.9%) patients received systemic corticosteroids with a daily average dose equivalent to 40.0 mg (IQR: 40.0, 60.0) methylprednisolone, and 79.9% (127/249) started corticosteroid use within 24 hours after being diagnosed as critical cases. The median initial time of corticosteroid use since being diagnosed as critical cases was 0.1 (0, 16.1) hours, and the duration of corticosteroid use lasted 5.0 (3.0, 7.0) days. When comparing the baseline characteristics between corticosteroid use group and non-corticosteroid use group, there were significant differences in several admission laboratory values ($p<0.05$).

Systemic corticosteroid use and association with in-hospital mortality in severe cases

For all 1514 severe cases, we analysed the factors associated with in-hospital mortality. Kaplan-Meier survival curve showed that in-hospital mortality was significantly higher in the corticosteroid use group than in the non-corticosteroid group (log-rank test $p<0.001$). The 28-day in-hospital mortality rates were 20.6% (95% CI: 16.5%-25.6%) in the corticosteroid use group and 3.7% (95% CI: 2.3%-6.0%) in the non-corticosteroid group. The results of univariate regression model were shown in Supplemental Table 1 (23). In the multivariable Cox model, systemic corticosteroid use was independently associated with increased in-hospital mortality (HR=1.77, 95% CI: 1.08-2.89, p=0.023) (Table 3). In the multivariable Cox model with time-varying exposure, systemic corticosteroid use was independently associated with increased in-hospital mortality (HR=2.83, 95% CI: 1.72-4.64, $p<0.001$). After IPTW and PSM (baseline shown in Supplemental Table 2 and 3 (23)), the results showed tendency towards the association between systemic corticosteroid use and increased in-hospital mortality after both propensity score analyses (HR=1.43, 95% CI: 0.82-2.49, p=0.201 in IPTW; HR=1.55, 95% CI: 0.83-2.87, p=0.166 in PSM). Kaplan-Meier survival curves after IPTW and PSM were shown in Figure. 1A and 1B.

Systemic corticosteroid use and association with in-hospital mortality in critical cases

For all 249 critical cases, we analysed the factors associated with in-hospital mortality. Compared with the non-corticosteroid group, the in-hospital mortality was significantly higher in the corticosteroid use group (log-rank test $p<0.001$). The 28-day in-hospital mortality was 51.0% (95% CI: 42.2%-60.5%) in the corticosteroid use group and 17.0%

(95% CI: 10.0%-28.1%) in the non-corticosteroid group, respectively. The results of univariate regression model are shown in Supplemental Table 4 (23). In the multivariable Cox model, systemic corticosteroid use was independently associated with increased in-hospital mortality (HR=2.07, 95% CI: 1.08-3.98, p=0.028) (Table 4). In the multivariable Cox model with time-varying exposure, systemic corticosteroid use was also independently associated with increased in-hospital mortality (HR=3.02, 95% CI: 1.59-5.73, p=0.001). After IPTW and PSM (baseline shown in Supplemental Table 5 and 6 (23)), the results supported that systemic corticosteroid use was independently associated with increased in-hospital mortality in critical cases after both propensity score analysis (HR=3.34, 95% CI: 1.84-6.05, p<0.001 in IPTW; HR=2.90, 95% CI: 1.17-7.16, p=0.021 in PSM). Kaplan-Meier survival curves after IPTW and PSM were shown in Figure. 1C and 1D.

Discussion

In the present study, we investigated the effect of systemic corticosteroids on clinical outcomes in 1514 severe and 249 critical COVID-19 cases from Wuhan. Corticosteroids were used in 35.1% and 63.9% in severe and critical cases, respectively. The use of corticosteroids was mainly low-dose and short-term. Corticosteroid use showed no benefit in reducing in-hospital mortality either in severe or in critical COVID-19 cases. The above results were mostly consistent across multivariable Cox regression and Cox model with time-varying exposure; and after propensity score driven analysis (both IPTW and PSM).

Acute respiratory failure was one of the leading causes of death for severe COVID-19 patients. In the initial phase as there was no specific treatment for coronavirus infection, the treatment mainly relied on supportive care and oxygen therapy, drawing largely on previous experience in treating SARS and MERS. The use of systemic corticosteroids is one of the most controversial interventions (24). It has been reported that corticosteroid use was associated with adverse outcomes in SARS, having higher risk of ICU admission or mortality (25). However, for critically MERS patients, corticosteroid therapy was associated not with

increased mortality, but with delayed coronavirus RNA clearance (5). Two studies on SARS and H1N1 viral pneumonia indicated that use of corticosteroids could reduce mortality in critical patients (6,8). An observational study by Zhou et al. with 15 COVID-19 patients demonstrated that an improvement in oxygen saturation and arterial partial pressure of oxygen (PaO2)/oxygen fraction (FiO2) was observed 3-5 days after the use of systemic corticosteroids (26), therefore advocating for the use of systemic corticosteroids in patients with severe COVID-19 for a short term. The latest COVID-19 treatment guidelines of the China's National Health Commission recommended systemic corticosteroid use in severe COVID-19 patients under certain circumstances. However, strong evidence supporting their recommendations was absent until the recently concluded RECOVERY trial. It is reported that the cortisol levels in seriously-ill COVID-19 patients were only very slightly lower than those in the control ICU group, indicating that such patients show no evidence of cortisol deficiency (27). Furthermore, the level of cortisol was found to be correlated with mortality, as it does in community-acquired pneumonia (28). This large observational study found that the use of systemic corticosteroids was not associated with improved outcomes for severe and critical COVID-19 patients.

The rationale for corticosteroid use includes its potential role in suppressing inflammatory storm, reducing inflammatory exudation, and preventing multiple organs injuries in acute respiratory failure. However, its multifaceted negative impacts on prognosis should not be overlooked. Previous studies suggested that the viral load of the novel coronavirus significantly aggravated the severity of the COVID-19 (29). Systemic corticosteroids may worsen prognosis by promoting virus replication. Immunity may also be suppressed by the use of systemic corticosteroids (30). Our results showed that median lymphocyte count remained low during the use of systemic corticosteroids, which might lead to a higher risk of superinfections. Systemic corticosteroids could also induce hyperglycaemia, which was shown to be an independent risk factor for the prognosis of infection and critically ill patients (31-33). We also found that median blood glucose level was higher during the use of systemic corticosteroids (The change of lymphocyte count and blood glucose level before, during and after corticosteroid use were shown in Supplemental Table 7 (23)). In addition, systemic corticosteroids were more likely to cause complications in the elderly – the median age of severe and critical COVID-19 patients being 61.0 and 68.0 years, respectively in this cohort (34,35).

There are several reasons why our results may be conflicting with RECOVERY trial. Firstly, due to retrospective and non-randomised nature in this study, the baseline conditions of the patients were substantially different between the treated and untreated patients. Although we attempt to get around this problem by using statistical techniques, confounding factors could not be totally eliminated. Secondly, most of the patients under corticosteroid therapy used prednisone in our study. Although dexamethasone and prednisone are both glucocorticoids, there are still many differences between them. Compared with other corticoids, dexamethasone has potential anti-inflammatory and weak mineralocorticoid effects (36). Dexamethasone is 4–5 times more potent than prednisone, and more than 20 times more potent than the naturally occurring hormone cortisol (37). Dexamethasone has long lasting pharmacological effects, which allows for a regimen of one dose per day. Thirdly, the duration and dose of corticosteroid therapy were different between the two studies. In our study, approximately dexamethasone 7.5mg (equivalent steroid dosing) was initiated at the onset of severe illness for a median of 5 days. In the RECOVERY study, dexamethasone 6mg was administered for 7 days.

In our study, the baseline characteristics between the corticosteroid use group and the non-corticosteroid use group were unbalanced. In order to reduce the risk of confounding by indication bias, we performed two different methods of propensity score analysis, namely IPTW and PSM. Baseline characteristics were well balanced after matching, but corticosteroid use was not associated with reduced risk of in-hospital mortality. Since patients in the corticosteroid group were unexposed before the initiation of treatment, the use of corticosteroids was also taken as a time-dependent variable to reduce immortality time bias. The results of time-dependent analysis still showed no benefit of the systemic corticosteroids. Particularly, after matching and using time-dependent analysis, we could observe that the K-M survival curves of corticosteroid use and non-corticosteroid group were close to each other during the first 7 days in both severe and critical cases, suggesting our propensity score matching were robust. Therefore the separation of the curve later on may be either due to harmful effect of corticosteroids or potential indication at time of initiation of corticosteroid, such as rapid worsening of the health condition. The latter will result in confounding by indication bias.

The major limitation of this study is its retrospective nature. Although it was a large scale and the baseline characteristics were balanced between two groups after performing

propensity score analyses and time-dependent analysis, our findings need further evaluation in other observational data, particularly those that have the ability to compare the effect of corticosteroid before and after implementation of the findings from RECOVERY trial into guidelines.

In summary, this large observational study did not identify the beneficial effect observed in the RECOVERY trial for the use of corticosteroids in severe and critical COVID-19 patients. Absence of the beneficial effect in our study in contrast to that was observed in the clinical trial may be due to biases in observational data, in particular confounding by indication bias, differences in clinical characteristics of patients, choice of corticosteroid used, timing of initiation of treatment and duration of treatment.

Acknowledgements

We thank all the hospital staff members for their efforts in working in the front line.

Additional Information

Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References:

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int. Accessed 5 June 2020.
2. World Health Organization. Coronavirus disease (COVID-2019) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 10 August 2020.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
4. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association. [An update on the epidemiological characteristics of novel coronavirus pneumoniaCOVID-19]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41(2):139-144.
5. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767.
6. Li H, Yang SG, Gu L, et al. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses*. 2017;11(4):345-354.
7. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006; 3(9):e343.
8. Chen RC, Tang XP, Tan SY, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. *Chest*. 2006;129(6):1441-1452.
9. Lee DT, Wing YK, Leung HC, et al. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. *Clin Infect Dis*. 2004;39(8):1247-1249.
10. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol*. 2004;31(4):304-309.
11. Li YM, Wang SX, Gao HS, et al. [Factors of avascular necrosis of femoral head and osteoporosis in SARS patients' convalescence]. *Zhonghua Yi Xue Za Zhi*. 2004;84(16):1348-1353.
12. Xiao JZ, Ma L, Gao J, et al. [Glucocorticoid-induced diabetes in severe acute respiratory syndrome: the impact of high dosage and duration of methylprednisolone therapy]. *Zhonghua Nei Ke Za Zhi*. 2004; 43(3):179-182.
13. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. 2019;23(1):99.
14. National Health Commission of the People's Republic of China. The 5th trial version of Diagnosis and Treatment Scheme for Pneumonitis caused by COVID-19 Infection (In Chinese). Available at: http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a.shtml. Accessed 7 May 2020.
15. National Health Commission of the People's Republic of China. The 6th trial version of Diagnosis and Treatment Scheme for Pneumonitis caused by COVID-19 Infection (In Chinese). Available at: http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2.shtml. Accessed 7 May 2020.
16. National Health Commission of the People's Republic of China. The 7th trial version of Diagnosis and Treatment Scheme for Pneumonitis caused by COVID-19 Infection (In Chinese). Available at: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml. Accessed 7 May 2020.
17. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720.
18. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected. Accessed 7 May 2020.
19. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Eng J Med. 2020 (Online ahead of print).
20. Asare K. Diagnosis and treatment of adrenal insufficiency in the critically ill patient. *Pharmacotherapy*. 2007;27(11):1512-1528.
21. Ali MS, Groenwold RH, Belitser SV, et al. Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: a systematic review. *J Clin Epidemiol*. 2015;68(2):112-121.
22. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ*. 2016;352:i189.
23. Wu JF, Huang JQ, Zhu GC, et al. Data from: Systemic corticosteroids and mortality in severe and critical COVID-19 patients in Wuhan, China. *Dryad Digital Repository* 2020. Deposited 29 August 2020. https://doi.org/10.5061/dryad.k0p2ngf6b.

24. Russel CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395(10223):473-475.
25. Auyeung TW, Lee JSW, Lai WK, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. *J Infect*. 2005;51(2):98-102.
26. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. *Signal Transduct Target Ther*. 2020;5(1):18.
27. Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(8):659-660.
28. Christ-Crain M, Stolz D, Julta S, et al. Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. *Am J Respir Crit Care Med*. 2007;176(9):913-920.
29. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63(3):364-374.
30. Brass D, McKay P, Scott F. Investigating an incidental finding of lymphopenia. *BMJ*. 2014;348:g1721.
31. Roberts GW, Quinn SJ, Valentine N, et al. Relative Hyperglycemia, a Marker of Critical Illness: Introducing the Stress Hyperglycemia Ratio. *J Clin Endocrinol Metab*. 2015;100(12):4490-4497.
32. Lee TF, Drake SM, Roberts GW, et al. Relative Hyperglycemia Is an Independent Determinant of In-Hospital Mortality in Patients With Critical Illness. *Crit Care Med*. 2020;48(2):e115-e122.
33. Park BS, Yoon JS, Moon JS, Won KC, Lee HW. Predicting mortality of critically ill patients by blood glucose levels. *Diabetes Metab J*. 2013;37(5):385-390.
34. Masclee GMC, Valkhoff VE, Coloma PM, et al. Risk of Upper Gastrointestinal Bleeding From Different Drug Combinations. *Gastroenterology*. 2014;147(4):784-792.
35. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med*. 2004;141(10):764-770.
36. Meijvis SCA, Hardeman H, Remmelts HHF, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9782):2023-2030.
37. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med*. 2005;20(353):1711-1723.

Table 1. Demographics and baseline characteristics of 1514 severe COVID-19 patients at admission.

Characteristic	Total (n=1514)	No Corticosteroid (n=983)	Corticosteroid (n=531)	*P* value
Age, y	61.0 (51.0, 70.0)	60.0 (50.0, 69.0)	63.0 (53.0, 71.0)	0.001
Female, n (%)	790 (52.2)	550 (56.0)	240 (45.2)	<0.001
Comorbid conditions, n (%)				
Diabetes	181 (12.0)	110 (11.2)	71 (13.4)	0.214
Hypertension	354 (23.4)	232 (23.6)	122 (23.0)	0.799
COPD	42 (2.8)	26 (2.6)	16 (3.0)	0.743
Cancer	22 (1.5)	17 (1.7)	5 (0.9)	0.266
CKD	29 (1.9)	21 (2.1)	8 (1.5)	0.439
Smoking	185 (12.2)	107 (10.9)	78 (14.7)	0.033
Admission laboratory values				
Admission glucose, mmol/L	6.0 (5.2, 7.5)	5.8 (5.0, 6.8)	6.8 (5.7, 8.4)	<0.001
Lymphocyte counts, 10^9/L	1.0 (0.7, 1.4)	1.2 (0.8, 1.5)	0.7 (0.5, 1.0)	<0.001
Neutrophil counts, 10^9/L	3.7 (2.6, 5.2)	3.6 (2.6, 4.7)	4.1 (2.7, 6.5)	<0.001
Platelet counts, 10^9/L	199.0 (151.0, 251.8)	211.0 (163.0, 257.0)	176.0 (138.0, 233.0)	<0.001
Haemoglobin, g/L	127.0 (116.0, 137.0)	126.0 (115.0, 136.0)	129.0 (118.0, 139.0)	0.001
CRP, mg/L	24.8 (4.8, 47.8)	13.8 (2.0, 42.3)	35.7 (20.9, 64.7)	<0.001
SpO_2, %	97.0 (95.0, 99.0)	98.0 (96.0, 99.0)	96.0 (92.0, 98.0)	<0.001
Lactate, mmol/L	1.6 (1.3, 2.1)	1.6 (1.3, 2.1)	1.6 (1.3, 2.2)	0.471
LDH, U/L	224.6 (179.0, 310.0)	202.1 (166.0, 266.1)	285.0 (212.6, 375.6)	<0.001
AST, U/L	26.0 (18.2, 38.2)	23.0 (16.9, 34.0)	31.0 (23.8, 46.0)	<0.001
ALT, U/L	24.2 (15.9, 37.0)	23.0 (15.0, 36.0)	26.0 (18.0, 39.6)	<0.001
D-Dimer, mg/L	0.4 (0.2, 0.8)	0.4 (0.2, 0.7)	0.5 (0.2, 1.1)	<0.001
Creatinine, μmol/L	69.2 (57.3, 83.0)	67.4 (56.1, 80.8)	72.0 (60.0, 89.0)	<0.001
BUN, mmol/L	4.4 (3.5, 5.7)	4.2 (3.4, 5.5)	4.7 (3.8, 6.3)	<0.001
Medications				
The initial time of corticosteroid use since being diagnosed as severe cases, h	-	-	2.2 (0.1, 41.5)	-
≤24 hours	-	-	359 (67.6)	-
24-48 hours	-	-	56 (10.5)	-
48-72 hours	-	-	38 (7.2)	-

Characteristic	Total (n=1514)	No Corticosteroid (n=983)	Corticosteroid (n=531)	*P* value
>72 hours	-	-	78 (14.7)	-
Accumulative corticosteroid dose, mg*	-	-	280.0 (140.0, 480.0)	-
Duration of corticosteroid use, d	-	-	6.0 (3.0, 10.0)	-
Daily average corticosteroid dose, mg	-	-	40.0 (37.3, 57.1)	-
Disease severity				
In-hospital stay, d	12.7 (7.5, 19.8)	11.5 (6.9, 17.8)	15.2 (9.1, 23.8)	<0.001
Progression to critical cases, n (%)	253 (16.7)	104 (10.6)	149 (28.1)	<0.001
Death, n (%)	109 (7.2)	26 (2.6)	83 (15.6)	<0.001

* The dose of corticosteroids was converted to methylprednisolone-equivalent doses.

Abbreviations: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

Table 2. Demographics and baseline characteristics of 249 critical COVID-19 patients at admission.

Characteristic	Total (n=249)	No Corticosteroid (n=90)	Corticosteroid (n=159)	*P* value
Age, y	68.0 (58.0, 78.0)	67.0 (54.0, 82.0)	68.0 (60.0, 75.0)	0.340
Female, n (%)	102 (41.0)	37 (41.1)	65 (40.9)	>0.999
Comorbid conditions, n (%)				
Diabetes	56 (22.5)	21 (23.3)	35 (22.0)	0.875
Hypertension	107 (43.0)	39 (43.3)	68 (42.8)	>0.999
COPD	24 (9.6)	12 (13.3)	12 (7.5)	0.179
Cancer	6 (2.4)	1 (1.1)	5 (3.1)	0.423
CKD	15 (6.0)	9 (10.0)	6 (3.8)	0.056
Smoking	56 (22.5)	18 (20.0)	38 (23.9)	0.530
Admission laboratory values				
Admission glucose, mmol/L	6.9 (5.7, 8.5)	6.1 (5.2, 7.7)	7.3 (6.2, 8.7)	<0.001
Lymphocyte counts, 10^9/L	0.7 (0.5, 1.1)	0.9 (0.6, 1.3)	0.6 (0.4, 1.0)	<0.001
Neutrophil counts, 10^9/L	4.9 (3.5, 8.2)	4.0 (3.0, 5.8)	5.9 (3.8, 9.5)	<0.001
Platelet counts, 10^9/L	187.0 (141.0, 236.0)	198.0 (149.0, 246.0)	182.0 (137.0, 235.0)	0.215
Haemoglobin, g/L	126.0 (114.0, 137.0)	123.7 (109.0, 135.0)	126.0 (115.3, 138.0)	0.054
CRP, mg/L	69.4 (25.7, 140.4)	47.4 (12.0, 109.0)	88.1 (34.6, 151.5)	<0.001
SpO_2, %	95.0 (90.0, 98.0)	97.7 (94.9, 99.0)	94.0 (86.0, 97.2)	<0.001
Lactate, mmol/L	1.6 (1.3, 2.3)	1.5 (1.2, 2.0)	1.7 (1.3, 2.4)	0.062
LDH, U/L	331.0 (208.0, 533.2)	222.8 (162.5, 344.2)	408.0 (265.0, 596.7)	<0.001
AST, U/L	33.8 (21.0, 53.0)	27.1 (19.3, 42.6)	37.5 (22.3, 57.5)	0.001
ALT, U/L	25.7 (16.6, 41.8)	21.2 (15.5, 35.0)	27.2 (17.6, 44.0)	0.045
D-Dimer, mg/L	0.7 (0.4, 2.1)	0.5 (0.4, 1.0)	0.8 (0.4, 3.1)	0.008
Creatinine, μmol/L	75.7 (61.0, 104.0)	75.6 (58.3, 101.8)	75.8 (61.2, 104.0)	0.878
BUN, mmol/L	5.6 (4.2, 8.5)	5.4 (3.9, 7.8)	5.6 (4.4, 9.2)	0.177
Medications				
The initial time of corticosteroid use since being diagnosed as critical cases, h	-	-	0.1 (0.0, 16.1)	-
≤24 hours	-	-	127 (79.9)	-
24-48 hours	-	-	7 (4.4)	-
48-72 hours	-	-	6 (3.8)	-

Characteristic	Total (n=249)	No Corticosteroid (n=90)	Corticosteroid (n=159)	*P* value
>72 hours	-	-	19 (11.9)	-
Accumulative corticosteroid dose, mg*	-	-	240.0 (120.0, 360.0)	-
Duration of corticosteroid use, d	-	-	5.0 (3.0, 7.0)	-
Daily average corticosteroid dose, mg	-	-	40.0 (40.0, 60.0)	-
Disease severity				
In-hospital stay, d	13.9 (5.8, 22.6)	15.6 (7.9, 24.5)	12.9 (5.1, 21.9)	0.203
Death, n (%)	84 (33.7)	14 (15.6)	70 (44.0)	<0.001

* The dose of corticosteroids was converted to methylprednisolone-equivalent doses.

Abbreviations: COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

Table 3. Association of systemic corticosteroid use and in-hospital mortality in severe COVID-19 patients in multivariable Cox regression analysis.

Variables	Before matching				Inverse probability of treatment weighted		Propensity score matching	
	Cox		Time-varying Cox		Time-varying Cox		Time-varying Cox	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Systemic corticosteroid use								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.77 (1.08, 2.89)	0.023	2.83 (1.72, 4.64)	<0.001	1.43 (0.82, 2.49)	0.201	1.55 (0.83, 2.87)	0.166

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval.

Table 4. Association of systemic corticosteroid use and in-hospital mortality in critical COVID-19 patients in multivariable Cox regression analysis.

Variables	Before matching				Inverse probability of treatment weighted		Propensity score matching	
	Cox		Time-varying Cox		Time-varying Cox		Time-varying Cox	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Systemic corticosteroid use								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	2.07 (1.08, 3.98)	0.028	3.02 (1.59, 5.73)	0.001	3.34 (1.84, 6.05)	<0.001	2.90 (1.17, 7.16)	0.021

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; CI, confidence interval.

Figure Legend

Figure. 1. Kaplan-Meier survival curves of the corticosteroid use group and non-corticosteroid group for IPTW and PSM in-hospital mortality in severe cases (A,B), and in critical cases (C,D)， respectively.

Abbreviations: IPTW, inverse-probability-of-treatment-weighting; PSM, propensity score matching.

Figure 1