Original Article

Corticosteroids Utilization in the Management of Critically Ill Coronavirus Disease-2019 Pneumonia

Cheng Yang[1,#], Jiahao Zhang[1,#], Rongzhang Dou[2,3,#], Zhongyi Sun[1], Jie Yang[4], Li He[1], Nanhui Jiang[1], Rong Huang[1], Feng Yuan[1], Guanfa Xiao[1], Quan Gan[5], Qiaofa Lu[4], Zhiyong Peng[1], Lianjiu Su[1]

Departments of [1]Critical Care Medicine, [2]Gastrointestinal Surgery and [3]Gastric and Colorectal Surgical Oncology, Zhongnan Hospital of Wuhan University, [4]Department of Respiratory and Critical Care Medicine, Wuhan Fourth Hospital, [5]Departments of Critical Care Medicine, Maternal and Child Health Hospital, Wuhan, Hubei Province, China

#These authors contributed equally to this work

ABSTRACT

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

Access this article online

Quick Response Code:

Website:
www.tccmjournal.com

DOI:
10.4103/jtccm.JTCCM-D-21-00011

respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome coronavirus (MERS-CoV) have shown no benefit to outcomes.[5] In our study, we collected data through a multiple centers 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.[6] 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:[7] 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.[8,9] 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.[10]

Definition

Critical illness was defined according to the guideline for the diagnosis and treatment of 2019 novel coronavirus infected pneumonia (standard version) of China[11] 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.[12] 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.
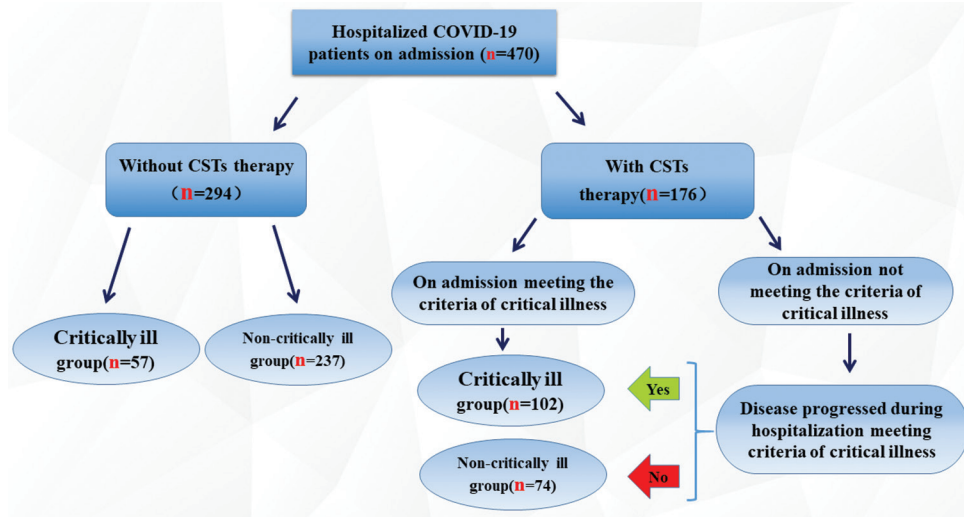
Figure 1: The flow chart of patients indicating the criteria for being stratified into "critically ill" group and noncritically ill group. Note: CSTs: Corticosteroids

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 use

After adjusting the confounders in multivariable analysis, we demonstrated no significant difference in mortality and complications between patients with corticosteroids and without corticosteroids in both critically ill and noncritical ill group [Figure 2a]. Multivariable analysis for mortality adjusted for age, sex, comorbidities, laboratory data, and complications of COVID-19 is listed in Table 1. Multivariable analysis for complications adjusted for age, sex, comorbidities, and laboratory data of COVID-19 is listed 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.[3] The other favor reason to have corticosteroids therapy in COVID-19 patients was that corticosteroids might help accelerate recovery from COVID-19.[13] The current study shown that corticosteroids ciclesonide was capable

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)	*P*
Age call *n* (%)	143 (30.4)	76 (24.4)	67 (42.1)	<0.001
Gender, *n* (%)				
Male	207 (44.0)	126 (40.5)	81 (50.9)	0.031
Female	263 (56.0)	185 (59.5)	78 (49.1)	0.031
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 (13.0-35.0)	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* (%)	144 (30.6)	46 (14.8)	98 (61.6)	<0.001
Acute liver injury	58 (12.3)	28 (9.0)	30 (18.9)	0.002
Acute kidney injury	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 respiratory distress syndrome	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

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 decre**a**se 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
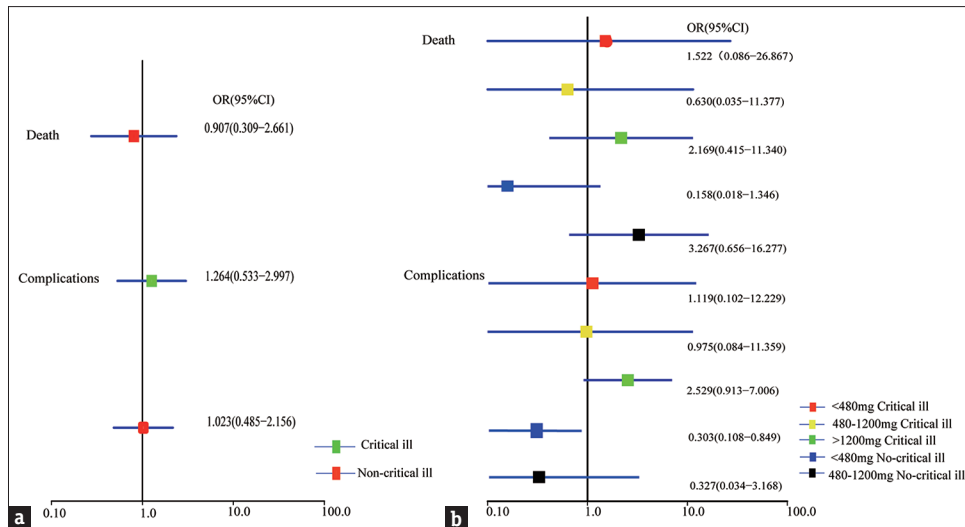
Figure 2: Forest plot of adjusted odds ratio of multivariate analysis. (a) Multivariate analysis of corticosteroids use, (b) multivariable analysis of corticosteroid dose. note: CI: Confidence interval

use of corticosteroids was identified as a risk factor for higher mortality.[16] Similarly, in a retrospective study of 78 SARS patients, the use of corticosteroids was associated with adverse outcomes.[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.[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.[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.[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.[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[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.[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.[26] Second, longer-term complications such as secondary bacterial or fungal infection and osteonecrosis[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.

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.

REFERENCES

1. Su L, Zhang J, Jiang N, Yang J, He L, Xie Q, *et al.* Differential Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on COVID-19. J Transl Crit Care Med 2021;3:10.
2. Liu W, Tao ZW, Lei W, Yuan ML, Liu K, Zhou L, *et al.* Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020;133:1032-8.
3. Sichitiu J, Fakhouri F, Desseauve D. Antenatal corticosteroid therapy and COVID-19: Pathophysiological considerations. Acta Obstet Gynecol Scand 2020;99:952.
4. Villar J, Ferrando C, Martinez D, Ambrós A, Muñoz T, Soler JA, *et al.* Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. Lancet Respir Med 2020;8:267-76.
5. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473-5.
6. World Health Organization. Coronavirus Disease (COVID-19) Technical Guidance: Laboratory Testing for 2019-nCoV in Humans. Geneva: World Health Organization; 2020.
7. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, *et al.* The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1573-82.
8. Edmonston DL, Pun PH. Coronary artery disease in chronic kidney disease: Highlights from a kidney disease: Improving global outcomes (KDIGO) controversies conference. Kidney Int 2020;97:642-4.
9. Zhang J, Rao X, Chen L, Jiang X, Yang C, Wang F, *et al.* Clinical Characteristics and Risk Factors for Acute Kidney Injury in COVID-19. J Transl Crit Care Med 2021;3:12.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
11. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, *et al.* A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020;7:4.
12. Zhang Z. Model building strategy for logistic regression: Purposeful selection. Ann Transl Med 2016;4:111.
13. Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol 2020;84:106560.
14. Chen RC, Tang XP, Tan SY, Liang BL, Wan ZY, Fang JQ, *et al.* Treatment of severe acute respiratory syndrome with glucosteroids: The Guangzhou experience. Chest 2006;129:1441-52.
15. Li XW, Jiang RM, Guo JZ. Glucocorticoid in the treatment of severe acute respiratory syndrome patients: A preliminary report. Zhonghua Nei Ke Za Zhi 2003;42:378-81.
16. Alfaraj SH, Al-Tawfiq JA, Assiri AY, Alzahrani NA, Alanazi AA, Memish ZA. Clinical predictors of mortality of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: A cohort study. Travel Med Infect Dis 2019;29:48-50.
17. Auyeung TW, Lee JS, Lai WK, Choi CH, Lee HK, Lee JS, *et al.* The use of corticosteroid as treatment in SARS was associated with adverse outcomes: A retrospective cohort study. J Infect 2005;51:98-102.
18. Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. PLoS Med 2006;3:e343.
19. Delaney JW, Pinto R, Long J, Lamontagne F, Adhikari NK, Kumar A, *et al.* The influence of corticosteroid treatment on the outcome of influenza A (H1N1pdm09)-related critical illness. Crit Care 2016;20:75.
20. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, *et al.* Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am J Respir Crit Care Med 2018;197:757-67.
21. Shah RD, Wunderink RG. Viral pneumonia and acute respiratory distress syndrome. Clin Chest Med 2017;38:113-25.
22. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, *et al.* Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. JAMA 1998;280:159-65.
23. Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, *et al.* Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E007.
24. Shah R, Reyes-Gordillo K, Cheng Y, Varatharajalu R, Ibrahim J, Lakshman MR. Thymosin beta4 prevents oxidative stress, inflammation, and fibrosis in ethanol and LPS-induced liver injury in mice. Oxid Med Cell Longev 2018;2018:9630175.

25. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al*. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384:693-704.

26. Ma P, Liu J, Shen F, Liao X, Xiu M, Zhao H, *et al*. Individualized resuscitation strategy for septic shock formalized by finite mixture modeling and dynamic treatment regimen. Crit Care 2021;25:243.

27. Ni Y N, 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;23:99.

28. Griffith JF, Antonio GE, Kumta SM, Hui DS, Wong JK, Joynt GM, *et al*. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. Radiology 2005;235:168-75.