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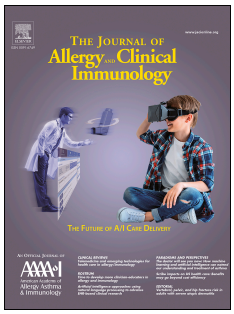

Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan

Xiaochen Li, MD, Shuyun Xu, MD, Muqing Yu, MD, Ke Wang, MD, Yu Tao, MD, Ying Zhou, MD, Jing Shi, MD, Min Zhou, MD, Bo Wu, PhD, Zhenyu Yang, MD, Cong Zhang, MD, Junqing Yue, MD, Zhiguo Zhang, PhD, Harald Renz, MD, Xiansheng Liu, MD, Jungang Xie, MD, Min Xie, MD, Jianping Zhao, MD

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Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan

Xiaochen Li MD[*12]; Shuyun Xu MD[*12]; Muqing Yu MD[*12]; Ke Wang MD[*12]; Yu Tao MD[*12] ; Ying Zhou MD[*12] ; Jing Shi MD[*12] ; Min Zhou MD[*12] ; Bo Wu PhD[*3]; Zhenyu Yang MD[12] ; Cong Zhang MD[12] ; Junqing Yue MD[12] ; Zhiguo Zhang PhD[*4]; Harald Renz MD[5] ; Xiansheng Liu MD[12] ; Jungang Xie MD[12] ; Min Xie MD[†12] ; Jianping Zhao MD[†12]

[1]Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

[2]Key Laboratory of Respiratory Diseases, National Ministry of Health of the People's Republic of China and National Clinical Research Center for Respiratory Disease, Wuhan, China.

[3]United Imaging Healthcare Co., Ltd, Wuhan, China.

[4]School of Medicine and Health Management, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

[5]Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg University Hospital Giessen and Marburg GmbH

[*]Contributed equally

[†]Joint corresponding authors

Corresponding authors: Prof. Jianping Zhao, Tongji Hospital, 1095 Jiefang Avenue, Wuhan 430030, China, E-mail: zhaojp88@126.com; or Prof. Min Xie, Tongji Hospital, 1095 Jiefang Avenue, Wuhan 430030, China; E-mail: xie_m@126.com. Phone +8618602724678

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ABSTRACT

Background: In December 2019, COVID-19 outbreak occurred in Wuhan. Data on the clinical characteristics and outcomes of patients with severe COVID-19 are limited.

Objective: The severity on admission, complications, treatment, and outcomes of COVID-19 patients were evaluated.

Methods: Patients with COVID-19 admitted to Tongji Hospital from January 26, 2020 to February 5, 2020 were retrospectively enrolled and followed-up until March 3, 2020. Potential risk factors for severe COVID-19 were analyzed by a multivariable binary logistic model. Cox proportional hazard regression model was used for survival analysis in severe patients.

Results: We identified 269 (49.1%) of 548 patients as severe cases on admission. Elder age, underlying hypertension, high cytokine levels (IL-2R, IL-6, IL-10, and TNF-a), and high LDH level were significantly associated with severe COVID-19 on admission. The prevalence of asthma in COVID-19 patients was 0.9%, markedly lower than that in the adult population of Wuhan. The estimated mortality was 1.1% in nonsevere patients and 32.5% in severe cases during the average 32 days of follow-up period. Survival analysis revealed that male, elder age, leukocytosis, high LDH level, cardiac injury, hyperglycemia, and high-dose corticosteroid use were associated with death in patients with severe COVID-19.

Conclusions: Patients with elder age, hypertension, and high LDH level need careful observation and early intervention to prevent the potential development of severe COVID-19. Severe male patients with heart injury, hyperglycemia, and high-dose corticosteroid use may have high risk of death.

Clinical Implications

Male, elder age, leukocytosis, high LDH level, cardiac injury, hyperglycemia may be associated with the fatal outcome of patients with severe COVID-19. High-dose corticosteroid use was related to high risk of death.

Capsule summary

The estimated mortality was 32.5% in patients with severe COVID-19 during the average 32 days of follow-up period. Patients with elder age, hypertension, and high LDH level need careful observation and early intervention for the potential development of severe COVID-19.

Key words

COVID-19; SARS-Cov-2; Risk factor; Severity; Mortality

List of abbreviations:

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MERS-CoV	Middle East respiratory syndrome coronavirus
hsCRP	High sensitivity C-reactive protein
ESR	Erythrocyte sedimentation rate
LDH	Lactate dehydrogenase
NT-proBNP	NT-proB-type natriuretic peptide
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
SpO2	Oxygen saturation
ARDS	Acute respiratory distress syndrome

Introduction

In December 2019, an outbreak caused by coronavirus disease 2019 (COVID-19) occurred in Wuhan, Hubei Province, China. As of March 22, 306,506 of COVID-19 cases were reported in over a hundred countries worldwide. More than 12 thousand patients died from infection of this new virus (named severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), urging early identification and intervention for severe cases.

The SARS-CoV-2 virus, as a betacoronavirus, shares 88% of two bat-derived SARS-like coronaviruses and distances from SARS-CoV (around 79%) and Middle East respiratory syndrome coronavirus (MERS-CoV, around 50%).[1] SARS and MERS epidemics posed threats to global health due to high mortality rates of 9.6% for SARS-CoV and 34.4% for MERS-CoV globally.[2, 3] Epidemiological data released by the Chinese Center for Disease Control and Prevention showed that 50,005 confirmed cases have been identified in Wuhan and 31,513 in mainland China except Wuhan as of March 22, 2020. The mortality rate of COVID-19 patients was 5.0% in Wuhan, which was close to that in the world (4.2%) and much higher than that in mainland China except Wuhan (2.4%). This study aims to describe and compare the epidemiological, demographic, clinical, laboratory and radiological characteristics as well as the complications, treatment and outcomes of hospitalized patients with nonsevere and severe COVID-19. Potential risk factors for severe COVID-19 and factors associated with death in severe cases were analyzed to provide scientific data for relieve severe cases and reduce mortality.

Methods

Data source

This study was an ambispective cohort study of consecutive hospitalized patients with COVID-19 enrolled at Sino-French New City Branch of Tongji Hospital, Huazhong University of Science and Technology in Wuhan from January 26, 2020 to February 5, 2020. The final date of follow-up was March 3, 2020. Sino-French New City Branch of Tongji hospital is one of the major nationally designated hospitals only providing medical care for adult COVID-19 patients in Wuhan. All cases with COVID-19 enrolled in this study were diagnosed based on the WHO interim guidance[4] and the diagnostic and treatment guideline for COVID-19 issued by Chinese National Health Committee (version 5). Detection of SARS-CoV-2 nucleic acids was shown in text in the Online Repository.[5] This study was approved by Institutional Review Board of Tongji Hospital, Huazhong University of Science and Technology. Written informed consent was waived in light of the urgent need to collect data.

The epidemiological and demographic data were obtained by face-to-face or telephone interview. Clinical symptoms, laboratory, and radiological findings on admission as well as the complications, treatment and outcomes during hospitalization were extracted from electronic medical records. Serum cytokines (IL-1β, IL-2R, IL-6, IL-8, IL-10 and TNF-α) were measured on admission. Patient data were cross-checked for consistency before final data entry and then entered into a computerized database.

The presence of underlying comorbidities was identified based on the International Classification of Diseases and Injuries-10 diagnostic codes. The complications of COVID-19 after admission were assessed and the definitions were shown in text in the Online Repository. Cardiac injury was one of the complications, which was defined as a serum hypersensitive cardiac troponin I level higher than 15.6 pg/ml without acute coronary symptoms or abnormal electrocardiogram. The clinical outcomes were classified into discharge from hospital, in-hospitalization, and death.

Severe COVID-19 was defined according to 2019 clinical practice guideline from Infectious Diseases Society of America and American Thoracic Society for diagnosis and treatment of adults with community-acquired pneumonia.[6] Based on whether or not requiring ventilatory support on

admission, severe cases upon admission were divided into two cohorts, severely ill and critically ill cases.

Statistical analysis

The descriptive statistics are median and interquartile range (IQR) for continuous data. The statistics for categorical variables are counts and percentages. Mann-Whitney U test were performed for continuous variables and the χ^2 test and Fisher's exact test were employed for categorical variables as appropriate. Kruskal-Wallis test with the Dunn's multiple comparison were used to compare across groups.

Multivariable binary logistic regression analyses were used to assess the association between age, sex, source of infection, underlying comorbidity, number of hospital visit, time from onset to hospitalization, days of fever pre-admission, abnormal laboratory findings and the dependent variable of severity of disease. The odds ratio (OR) along with the 95% confidence interval (95% CI) were reported. Univariable and multivariable analyses to identify factors associated with death from COVID-19 in severe patients were performed by Cox proportional hazards regression model. Considering the total number of deaths (n=87) in our study, nine variables were chosen for multivariate Cox model based on the univariable analysis ($p<0.05$), previous findings and clinical importance, including sex, age, laboratory findings (blood leukocyte count and lactose dehydrogenase) on admission, the complications (cardiac injury and hyperglycemia) and drug therapy (corticosteroid, lopinavir/ritonavir, and umifenovir) during hospitalization. The hazard ratio (HR) along with the 95% CI were reported. A P value less than 0.05 was regarded as statistically significant. All statistical analyses were performed using SPSS 25.0. Detailed statistical analyses were shown in text and Table E6 in the Online Repository.

Results

Epidemiological and demographic characteristics

A total of 549 patients with COVID-19 were enrolled, of whom 548 cases were included in the study. One case not meeting inclusion criteria was excluded due to inclusion criteria. Almost half of the patients (49.1%, 269 of 548) were identified as severe cases and 50.9% (279 of 548) were nonsevere cases on admission. 68.7% (347 of 505) of cases were positive for SARS-CoV-2 nucleic acid test pre-admission. Comparison of findings between nonsevere and severe cases in the patients with positive viral nucleic acid test pre-admission showed essentially the similar differences to that in the total patients (see Table E1 in the Online Repository).

The epidemiological and demographic characteristics are shown in Table 1. 52 (9.5%) of 546 patients got the infection in hospital. 45 (8.2%) of 547 patients were health-care workers and 67 (12.2%) patients were family members of health-care workers. Nonsevere cases had a higher proportion of health-care workers and family members than severe cases (*P<0.001*). The date of onset of the first reported case with COVID-19 was December 1, 2019.[7] The median time from December 1, 2019 to the onset of COVID-19 was 54 days, ranging from 19 days to 63 days.

The median age of study population was 60 years (IQR 48-69), ranging from 18 years to 95 years, of whom 210 (38.3%) were aged 65 years or older. The patients aged 65 years or older in severe cases were almost twice as nonsevere cases of the same age (50.2% vs. 26.9%, *P<0.001*). Slightly more than half (50.9%) of all patients were male and the proportion of males in severe cases is higher than in nonsevere cases (56.9% vs. 45.2%, $P=0.006$).

Clinical characteristics on admission

19.2% of patients with severe COVID-19 were smokers (Table 1). Compared with nonsevere cases, severe cases exhibited more comorbidities, including chronic obstructive pulmonary disease (4.8% vs. 1.4%, $p=0.026$), coronary heart disease (10.4% vs. 2.2%, $p<0.001$), hypertension (38.7% vs. 22.2%, $p<0.001$), and diabetes (19.3% vs. 11.1%, $p=0.009$) respectively. Only five cases of asthma (0.9%) were identified in total population. 42 (7.7%) of 545 patients regularly took angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; no significant difference was found between nonsevere and severe cases.

Most patients reported at least one of the following symptoms: fever (95.2%), fatigue (47.1%), sore throat (5.1%), cough (75.5%), chest pain (7.5%), dyspnea (56.6%), chest tightness (38.1%), dizziness (10.2%), confusion (3.1%), headache (11.3%), myalgia (20.3%), vomiting (8.2%), diarrhea (32.7%), abdominal pain (2.9%). 6 patients were asymptomatic and diagnosed by CT screening. Duration of fever pre-admission was significantly longer among severe cases compared with that in nonsevere cases (P=0.031). Severe cases experienced longer duration from onset to outpatient visit and longer duration from onset to hospitalization compared with nonsevere cases (p=0.018 and p=0.035, respectively). 64 (11.9%) of 540 patients were treated with corticosteroids delivered by oral or intravenous pre-admission. 304 (56.5%) of 538 patients had received at least one of the following antiviral medications: umifenovir (32.9%), oseltamivir (35.1%), lopinavir/ritonavir (2.4%), and ribavirin (1.5%).

Radiographic and laboratory findings on admission

CT scans for 461 patients were evaluated pre-admission, and showed multilobar pulmonary infiltrates in 436 patients (Table 2). The median time from onset to pneumonia diagnosed by CT scan was 4 days. On admission, oxygen saturation (SpO2) less than 93.1% on room air presented in 33.3% of all patients, of whom 163 (89%) were severe cases. 90.2% of all patients experienced lymphopenia (<1500 cells per mm^3) and 29.1% of all patients had thrombocytopenia (<150,000 cells per mm^3). Compared with nonsevere cases, inflammation-related marker levels (hsCRP, ESR, and ferritin) were significantly higher in severe cases The levels of procalcitonin, globulin, lactate dehydrogenase (LDH), NT-proB-type natriuretic peptide (NT-proBNP), d-dimer, alanine aminotransferase, aspartate aminotransferase, total bilirubin, conjugated bilirubin, blood urea nitrogen, and creatinine were elevated in 9.5%, 40.4%, 73.6%, 27.5%, 67.4%, 23.1%, 33.1%, 4.4%, 9.2%, 15.8%, and 27.1% of all patients, respectively. Serum cytokine levels of IL-2R, IL-6, IL-10, and TNF-α were significantly higher in severe patients than those in nonsevere patients (all P<0.01).

Subgroup analysis

Of the 269 severe cases, 46 were classified as critically ill for requiring respiratory support. Compared with severely ill cases, the time from December 1, 2019 to onset was shorter and the time from onset to outpatient visit was longer in critically ill cases (see Table E2 in the Online Repository). There were no significant differences in age and underlying comorbidities between

severely ill and critically ill cases. More abnormal laboratory findings (such as high leukocyte, high procalcitonin, high NT-proBNP, high LDH, high d-dimer, low albumin, and high creatinine) were observed in critically ill cases compared with severely ill cases (all $P<0.05$). 34.1% of critically ill patients received systemic corticosteroids pre-admission, the proportion of whom was significantly higher than that in severely ill cases (12.2%, $P<0.001$).

Compared with nonsevere cases, systemic corticosteroid use pre-admission was more common in severe cases with larger cumulative dose and longer duration ($P=0.007$; $P<0.001$; $P<0.001$; respectively). Stratification of patients by corticosteroid exposure is presented in Table E3 in the Online Repository. Severe patients treated with corticosteroids had higher LDH level compared with severe patients without corticosteroid use pre-admission ($P<0.05$).

Nonsevere cases were more likely to receive antiviral drugs pre-admission, including umifenovir and oseltamivir ($P<0.001$ and $P=0.005$; respectively). In severe case subgroup, the patients receiving umifenovir were younger than those without umifenovir use ($P<0.05$). A comparison of baseline demographic and clinical characteristics between patients with and without antiviral drug use revealed no marked difference in SpO2 or laboratory findings in both nonsevere and severe case subgroups (see Table E4 and E5 in the Online Repository).

Risk factors for severe cases on admission

In the final logistic regression model, variables such as age 65 or older (OR 2.2; 95% CI 1.5-3.5), hypertension (OR 2.0; 95% CI 1.3-3.2), LDH >445 U/L (OR 4.4; 95% CI 2.6-7.6), and d-dimer >1 mg/L (OR 2.2; 95% CI 1.4-3.3) were significantly associated with severe cases with COVID-19 (Figure 1).

Complications, treatment and clinical outcomes during hospitalization and follow-up

In the follow-up period, the complications of COVID-19 were assessed , including acute respiratory distress syndrome (ARDS) (38.3%), cardiac injury (21.7%), liver dysfunction (19.3%), acute kidney injury (17.3%), bacteremia (7.7%), diffuse intravascular coagulation (7.7%), and hyperglycemia (33.2%) (Table 3). All the above-mentioned complications were more common in severe cases, compared with nonsevere cases (all $P<0.05$).

Antiviral drugs were used specifically to treat COVID-19 during hospitalization, including lopinavir/ritonavir (29.9%), umifenovir (73.2%), oseltamivir (40.3%), ribavirin (5.3%), and interferon α nebulization (30.7%). Antiviral drug uses were more common in nonsevere cases than

those in severe cases except for ribavirin. 341 (62.2%) of 548 patients were administered with systemic corticosteroids with a medium duration of 4 days and medium cumulative dose equivalent to 200 mg prednisone. Of the 548 patients, 355 (64.8%) required oxygen support during hospitalization, including nasal cannula or mask (41.6%), high-flow oxygen therapy (4.4%), noninvasive mechanical ventilation (14.2%), and invasive mechanical ventilation (4.6%).

Mortality rates for COVID-19 were estimated to be 1.1% (3 of 277) in nonsevere patients and 32.5% (87 of 268) in severe cases during the average 32 days of follow-up. 72.9% of nonsevere cases and 31.7% of severe cases were discharged from hospital.

Factors associated with death in severe cases

Multivariable Cox proportional hazards regression analysis revealed that male (adjusted HR 1.7; 95% CI 1.0-2.8), age 65 or older (adjusted HR 1.7; 95% CI 1.1-2.7), blood leukocyte count >10 cells per mm^3 (adjusted HR 2.0; 95% CI 1.3-3.3) and LDH >445 U/L (adjusted HR 2.0; 95% CI 1.2-3.3) at admission, cardiac injury (adjusted HR 2.9; 95% CI 1.8-4.8), hyperglycemia (adjusted HR 1.8; 95% CI 1.1-2.8), and administration of high-dose corticosteroids (adjusted HR 3.5; 95% CI 1.8-6.9) during hospitalization were significant risk factors associated with death in severe COVID-19 cases. Lopinavir/ritonavir (adjusted HR 0.4; 95% CI 0.2-0.9) and umifenovir (adjusted HR 0.5; 95% CI 0.3-0.8) were associated with lower death in severe COVID-19 patients. The adjusted Kaplan-Meier estimates of survival for sex, age, sex, leukocyte, LDH, corticosteroid use, lopinavir/ritonavir use, and umifenovir use were shown in Figure E1-7 in the Online Repository.

Discussion

This study provided a comprehensive data on the epidemiological, demographic, clinical, laboratory, and radiological characteristics as well as the complications, treatment, and outcomes of hospitalized patients with nonsevere and severe COVID-19 in Wuhan. Almost half of the patients in this study were identified as severe cases, which may differ from the results of the previous studies.[8] The proportion of patients aged 65 years or older were higher in our study than in Nanshan Zhong's study (38.8% vs. 15.1%, respectively).[9] The time from December 1, 2019 to the onset of most patients was longer than 50 days. During mid-January to early February, Wuhan experienced the highest peak of COVID-19 outbreak, with a family cluster and high prevalence of COVID-19 in older adults. Longer wait for access to medical care was observed in severe cases compared with that in nonsevere cases. More than half of the patients experienced at least two hospital visits, which may increase the risk of nosocomial transmission events. Diagnosis and treatment may be delayed due to the long wait for access to medical care. Severe COVID-19 patients would likely develop ARDS and died of respiratory failure. Although there are currently no effective antiviral drugs for SARS-CoV-2, prompt identification and early respiratory support would relieve severe cases and reduce mortality. The severity of disease in patients with initial positive nucleic acid test was similar to that of all COVID-19 patients. We thus propose that urgent timely diagnosis is crucial, and that early intervention should not be delayed based on nucleic acid test.

There are six coronavirus species currently known to cause human infection. SARS-CoV-2 was most closely related to SARS-CoV through phylogenetic analysis and was revealed to share a similar receptor, ACE-2, to SARS-CoV.[1] This fact hints that COVID-19 may partly mimic SARS infection. The autopsy results of SARS patients showed that high levels of proinflammatory cytokines were expressed in ACE-2-expressing cells infected by SARS-CoV.[10] Plasma cytokine profiles of SARS patients showed Th1-dominated responses with markedly elevated proinflammatory cytokine levels (INF-γ, IL-1β, IL-6, IL-8, IL-12, and TNF-α) and were associated with the development of ARDS.[11-13] In our study, severe COVID-19 patients had significantly higher levels of Th1 cytokines (IL-6 and TNF-α) and higher incidence rate of ARDS,

compared with nonsevere cases. Interestingly, the prevalence of asthma in COVID-19 patients (0.9%) in our study was markedly lower than that reported in the adult population of Wuhan (6.4%).[14-16] We thus speculate that Th2 immune response in asthmatic patients may counter the inflammation process induced by SARS-CoV-2 infection. Further studies are required to characterize the immune response and inflammation features of COVID-19.

The majority of severe patients showed rapid progression and multiple organ dysfunction. The median time from onset to pneumonia diagnosed by CT scan was only 4 days. Approximately one third of the patients experienced gastrointestinal symptoms. During hospitalization, a substantial proportion of patients presented cardiac injury, liver and kidney dysfunction, and hyperglycemia. It was proved that the fecal and urine samples and rectal swabs of COVID-19 patients were positive for SARS-CoV-2 nucleic acids.[9] ACE-2 was reported to be expressed in small intestinal epithelial cells, cholangiocytes, and the pancreas,[17-19] indicating that SARS-CoV-2 infection may induce the multi-organ injury in COVID-19 patients. The shorter duration from December 1, 2019 to onset in critically ill cases than that in severely ill cases may reflect a higher virulence of SARS-Cov-2, or earlier onset of COVID-19.

The risk factors for severity identified in this study included age, high LDH level, and high d-dimer level, consistent with those in previous reports.[15, 20] However, different from the findings of previous studies[21], hypertension was the only comorbidity associated with the severity of COVID-19 after adjustment for age, sex and smoking status. The distinct features of pneumonia and high severity in patients with COVID-19 in this study may lead to this difference from previous reports. ACE2, a gateway to SARS, was reported to be a protective factor against SARS-CoV-induced lung injury.[22, 23] The association between ACE2 expression and hypertension was confirmed in a previous study.[24] This fact may partly explain the high prevalence of severe COVID-19 in patients with hypertension. LDH has been recognized as a marker for severe prognosis in various diseases, including cancer and infection.[25] The high LDH level in COVID-19 in severe cases suggested that LDH may be associated with lung injury and tissue damage, warranting an investigation for the potential mechanism.

This study evaluated pre-admission medications for patients with severe COVID-19. Although the proportion of nonsevere cases in patients receiving oseltamivir was higher than that in patients without oseltamivir use, stratification analysis showed that there was no significant difference in

hypoxia between patients with and without oseltamivir use either in the severe case or nonsevere case subgroup. Therefore, oseltamivir use may just be an indicator of disease severity. The patients receiving umifenovir were younger than those without umifenovir use, indicating that younger patients may have easier access to drugs or prefer umifenovir.

Older age, leukocytosis and high LDH level were reported to be risk factors associated with in-hospital death in previous studies.[20, 26, 27] The present study also revealed that hyperglycemia was related with increased mortality in COVID-19 patients. The prevalence of hyperglycemia may be associated with underlying diabetes and corticosteroid therapy. However, the localization of ACE2 expression in the pancreas in SARS was reported to damage islets, resulting in hyperglycemia[19]; this finding suggested that hyperglycemia may also be an indicator of severe COVID-19.

This study indicated that corticosteroid use was more common in severe cases than in nonsevere cases and that high-dose corticosteroid use was related to high risk of death in severe COVID-19 patients. High-dose steroid use may be an indicator of disease severity rather than a predisposing factor. In a previous study, treatment with methylprednisolone was shown to be beneficial for COVID-19 patients who developed ARDS.[20] However, critically ill cases had more signs of infection and abnormal laboratory findings, including high leukocyte, high procalcitonin, high d-dimer, low albumin, and high creatinine levels. High-dose corticosteroid use should be used with cautious in critically ill patients to avoid aggravating complications.

A recent study by Bin Cao et al showed that lopinavir/ritonavir treatment offered no significant benefit over the standard care for hospitalized adult COVID-19 patients.[28] Cao's study also reported that lopinavir/ritonavir led to a shorter median time to clinical improvement than the standard care (HR 1.39; 95% CI 1.00 to 1.91) in a modified intention-to-treat analysis. Compared with Cao's study, the severity of patients was more serious and lopinavir/ritonavir treatment was associated with a lower risk of death in severe COVID-19 patients in this study. However, our study was an observational study; thus, the benefit of lopinavir/ritonavir for severe COVID-19 patients needs to be further confirmed.

There were limitations to the current study. Firstly, epidemiological data were collected respectively and recall bias might have occurred. Secondly, missing data on some variables, such as detailed information of CT scan, may cause bias in the estimation and reduce the

representativeness of the samples. Thirdly, laboratory findings were measured upon admission and may indicate the severity of COVID-19. The causal relationship between abnormal laboratory findings and severity could not be determined. Fourthly, this study was an observational study with limitations in terms of evaluating the efficacy of corticosteroids and antiviral drugs. Finally, the absence of comparative data from COVID-19 patients not admitted or from other critically ill patients were limitations of this study.

In conclusion, COVID-19 outbreak caused widespread concern and has threatened the global public health security. Recent evidence of possible fecal-oral transmission in SARS-Cov-2 infection, asymptomatic infection,[8, 29, 30] and positive result for SARS-Cov-2 test in recovered patients,[31] warrant aggressive measures to suppress and prevent epidemic spreading, such as hygiene maintenance, early screening and intervention, and self-isolation after recovery. As a major transportation hub of China, Wuhan faced increased difficulties in outbreak control. Efforts to control COVID-19 need to take into account globalization processes.[32] Severe male patients with heart injury, hyperglycemia, and high-dose corticosteroid use may have high risk of death.

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Reference

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020.

2. World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003.] Available from https://www.who.int/csr/sars/country/table2004_04_21/en/.

3. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV).] Available from http://www.who.int/emergencies/mers-cov/en/.

4. World Health Organization. Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance.] Available from https://www.who.int/internal-publications-detail/clinical-managementof-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

5. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases.] Available from https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117.

6. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical

Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019; 200:e45-e67.

7. 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.

8. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.

10. He L, Ding Y, Zhang Q, Che X, He Y, Shen H, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. J Pathol 2006; 210:288-97.

11. Lam CW, Chan MH, Wong CK. Severe acute respiratory syndrome: clinical and laboratory manifestations. Clin Biochem Rev 2004; 25:121-32.

12. Sheng WH, Chiang BL, Chang SC, Ho HN, Wang JT, Chen YC, et al. Clinical manifestations and inflammatory cytokine responses in patients with severe acute respiratory syndrome. J Formos Med Assoc 2005; 104:715-23.

13. Zhu M. SARS Immunity and Vaccination. Cell Mol Immunol 2004; 1:193-8.

14. Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet 2019; 394:407-18.

15. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020.

16. Wang XD, Zheng M, Lou HF, Wang CS, Zhang Y, Bo MY, et al. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. Allergy 2016; 71:1170-80.

17. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 2012; 487:477-81.

18. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv 2020:2020.02.03.931766.

19. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010; 47:193-9.

20. Wu C, Chen X, Cai Y, Xia Ja, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Internal Medicine 2020.

21. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J 2020.

22. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005; 436:112-6.

23. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin

converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11:875-9.

24. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002; 417:822-8.

25. Erez A, Shental O, Tchebiner JZ, Laufer-Perl M, Wasserman A, Sella T, et al. Diagnostic and prognostic value of very high serum lactate dehydrogenase in admitted medical patients. Isr Med Assoc J 2014; 16:439-43.

26. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054-62.

27. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020.

28. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020.

29. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395:514-23.

30. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med 2020; 382:970-1.

31. Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, et al. Positive RT-PCR Test Results in Patients Recovered From COVID-19. JAMA 2020.

32. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol 2020.

Figure legend

Figure 1. The effect of various potential risk factors on patients with severe COVID-19 at admission.

OR=odds ratio. CI=confidence interval.

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620 **Table 1. Epidemiological, demographic and clinical characteristics of hospitalized patients with**
621 **COVID-19**

	All patients (n=548)	Nonsevere (n=279)	Severe (n=269)	p value
Age, years	60 (48-69)	56 (44-66)	65 (54-72)	0.000
0-44	107/548 (19.5%)	75/279 (26.9%)	32/269 (11.9%)	0.000
45-64	231/548 (42.2%)	129/279 (46.2%)	102/269 (37.9%)	
≥65	210/548 (38.3%)	75/279 (26.9%)	135/269 (50.2%)	
Male	279/548 (50.9%)	126/279 (45.2%)	153/269 (56.9%)	0.006
Body mass index, kg/m^2	24.7 (22.4-26.7)	24.5 (22.4-26.0)	25.3 (22.4-27.6)	0.257
Source of infections				
Household contact	494/546 (90.5%)	245/278 (88.1%)	249/268 (92.9%)	0.060
Hospital-acquired infections	52/546 (9.5%)	33/278 (11.9%)	19/268 (7.1%)	
Disease risk				
Health-care workers	45/547 (8.2%)	36/279 (12.9%)	9/268 (3.4%)	0.000
Family member of health-care workers	67/547 (12.2%)	42/279 (15.1%)	25/268 (9.3%)	
Not health-care workers or their family members	435/547 (79.5%)	201/279 (72.0%)	234/268 (87.3%)	
Time of onset[a], days	54 (51-56)	54 (52-56)	54 (51-56)	0.394
Time from onset to outpatient visit, days	3 (1-6)	3 (1-5)	4 (1-7)	0.018
0-3	283/522 (54.2%)	158/270 (58.5%)	125/252 (49.6%)	0.044
>3	239/522 (45.8%)	112/270 (41.5%)	127/252 (50.4%)	
Time from onset to hospitalization, days	10 (7-12)	9 (7-12)	10 (7-12)	0.035
Number of hospital visit ≥2	307/548 (56.0%)	144/279 (51.6%)	163/269 (60.6%)	0.039
Smoking history				
Never smokers	452/544 (83.1%)	238/279 (85.3%)	214/265 (80.8%)	0.051
Former smokers	51/544 (9.4%)	18/279 (14.7%)	33/265 (12.5%)	
Current smokers	41/544 (7.5%)	23/279 (8.2%)	18/265 (6.8%)	
Underlying comorbidity				
Chronic obstructive pulmonary disease	17/548 (3.1%)	4/279 (1.4%)	13/269 (4.8%)	0.026

Asthma	5/548 (0.9%)	2/279 (0.7%)	3/269 (1.1%)	0.681
Tuberculosis	9/548 (1.6%)	5/279 (1.8%)	4/269 (1.5%)	1.000
Diabetes	83/548 (15.1%)	31/279 (11.1%)	52/269 (19.3%)	0.009
Hypertension	166/548 (30.3%)	62/279 (22.2%)	104/269 (38.7%)	0.000
Coronary heart disease	34/548 (6.2%)	6/279 (2.2%)	28/269 (10.4%)	0.000
Hepatitis B	5/548 (0.9%)	3/279 (1.1%)	2/269 (0.7%)	1.000
Chronic kidney disease	10/547 (1.8%)	4/278 (1.4%)	6/269 (2.2%)	0.539
Tumor	24/513 (4.7%)	10/256 (3.9%)	14/257 (5.5%)	0.531
Previous drugs use				
ACEI/ARB	42/545 (7.7%)	23/279 (8.2%)	19/266 (7.1%)	0.748
Systemic corticosteroids	6/548 (1.1%)	4/279 (1.4%)	2/269 (0.7%)	0.686
Inhaled corticosteroids	5/548 (0.9%)	3/279 (1.1%)	2/269 (0.7%)	1.000
Antibiotics	7/548 (1.3%)	3/279 (1.1%)	4/269 (1.5%)	0.720
Anticoagulants	16/547 (2.9%)	5/278 (1.8%)	11/269 (4.1%)	0.132
Immunosuppressant drugs	5/548 (0.9%)	3/279 (1.1%)	2/269 (0.7%)	1.000
Antiviral drugs	2/548 (0.4%)	1/279 (0.4%)	1/269 (0.4%)	1.000
Symptoms				
Fever of pre-admission	476/500 (95.2%)	248/260 (95.4%)	228/240 (95.0%)	1.000
Highest temperature, □	38.8 (38.2-39)	38.8 (38-39)	38.8 (38.4-39)	0.416
Duration, days	9 (6-11)	8.5 (6-11)	10 (7-12)	0.031
Fatigue	258/548 (47.1%)	128/279 (45.9%)	130/269 (48.3%)	0.608
Sore throat	28/548 (5.1%)	17/279 (6.1%)	11/269 (4.1%)	0.335
Cough	415/548 (75.7%)	212/279 (76.0%)	203/269 (75.5%)	0.921
Chest pain	41/548 (7.5%)	25/279 (9.0%)	16/269 (6.0%)	0.197
Dyspnea	310/548 (56.6%)	112/279 (40.1%)	198/269 (73.6%)	0.000
Chest tightness	162/425 (38.1%)	86/245 (42.2%)	76/180 (38.1%)	0.157
Dizziness	56/548 (10.2%)	29/279 (10.4%)	27/269 (10.0%)	1.000
Confusion	17/548 (3.1%)	1/279 (0.4%)	16/269 (6.0%)	0.000
Headache	62/548 (11.3%)	37/279 (13.3%)	25/269 (9.3%)	0.177
Myalgia	111/548 (20.3%)	62/279 (22.2%)	49/269 (18.2%)	0.288
Vomiting	45/548 (8.2%)	25/279 (9.0%)	20/269 (7.4%)	0.537
Diarrhea	179/548 (32.7%)	94/279 (33.7%)	85/269 (31.6%)	0.649
Abdominal pain	16/548 (2.9%)	4/279 (1.4%)	12/269 (4.5%)	0.043
Administration of systemic corticosteroids pre-admission	64/540 (11.9%)	22/274 (8.0%)	42/266 (15.8%)	0.007
Duration, days	1 (0-3)	0 (0-1)	2.5 (1-4)	0.000
Cumulative dose[b], mg	50 (0-150)	0 (0-66.7)	100 (50-187.5)	0.000
Administration of antiviral drugs pre-admission				
Lopinavir/ritonavir	13/541 (2.4%)	10/276 (3.6%)	3/265 (1.1%)	0.089
Umifenovir	177/538 (32.9%)	113/274 (41.2%)	64/264 (24.2%)	0.000
Oseltamivir	189/538 (35.1%)	112/274 (40.9%)	77/264 (29.2%)	0.005
Ribavirin	8/538 (1.5%)	2/274 (0.7%)	6/264 (2.3%)	0.169

622 Data are expressed as median (IQR), n (%), or n/N (%), where N is the total number of patients with

623 available data. P values comparing nonsevere cases and severe cases are from χ^2 test, Fisher's exact test,
624 or Mann-Whitney U test.
625 [a] Days from December 1, 2019 to the date of onset.
626 [b] Equivalent doses of prednisone.
627 ACEI/ARB=angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.
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637 **Table 2. Radiographic and laboratory findings of patients with COVID-19**

	All patients (n=548)	Nonsevere (n=279)	Severe (n=269)	p value
CT findings pre-admission				
Negative	4/461 (0.9%)	4/228 (1.8%)	0	0.032
Unilobar lesion	21/461 (4.6%)	14/228 (6.1%)	7/233 (3.0%)	
Multilobar lesion	436/461 (94.6%)	210/228 (92.1%)	226/233 (97.0%)	
Time from onset to pneumonia diagnosed by CT scan, days	4 (2-7)	4 (2-6)	4 (2-7)	0.258
SARS-CoV-2 nucleic acid test*				
Positive	347/505 (68.7%)	180/270 (66.7%)	167/235 (71.1%)	0.503
Suspected positive	41/505 (8.1%)	22/270 (8.1%)	19/235 (8.1%)	
Negative	117/505 (23.2%)	68/270 (25.2%)	49/235 (20.9%)	
SpO2, %				
≤93	182/546 (33.3%)	19/278 (6.8%)	163/268 (60.8%)	0.000
>93	364/546 (66.7%)	259/278 (93.2%)	105/268 (39.2%)	
Blood leukocyte count, × 10 ·/L				
>10	63/542 (11.6%)	8/275 (2.9%)	55/267 (20.6%)	0.000
<4	130/542 (24.0%)	84/275 (30.5%)	46/267 (17.23%)	0.000
Neutrophil count, × 10 ·/L				
>6.5	118/542 (21.8%)	22/275 (8.0%)	96/267 (36.0%)	0.000
≤2.0	67/542 (12.4%)	50/275 (18.2%)	17/267 (6.4%)	0.000
Lymphocyte count, × 10 ·/L				
<1.5	489/542 (90.2%)	234/275 (85.1%)	255/267 (95.5%)	0.000
≤0.5	85/542 (15.7%)	21/275 (7.6%)	64/267 (24.0%)	0.000
Platelet count <150 × 10 ·/L	157/539 (29.1%)	68/274 (24.8%)	89/265 (33.6%)	0.029
High sensitive c-reactive protein, mg/L				
> 10	460/540 (85.2%)	205/272 (75.4%)	255/268 (95.2%)	0.000
> 100	138/540 (25.6%)	40/272 (14.7%)	98/268 (36.6%)	0.000
Procalcitonin > 0.5 ng/ml	46/486 (9.5%)	3/249 (1.43%)	43/237 (18.9%)	0.000

Erythrocyte sedimentation rate > 20 mm/h		377/518 (72.8%)	179/264 (67.8%)	198/254 (78.0%)	0.010
Ferritin >500 μg/L		211/313 (67.4%)	95/171 (55.9%)	116/142 (81.7%)	0.000
D-dimer >1 mg/L		227/501 (45.3%)	78/254 (31.1%)	149/247 (56.4%)	0.000
NT-proB-type natriuretic peptide >500 pg/L		92/335 (27.5%)	17/136 (13.3%)	75/199 (37.9%)	0.000
Lactate dehydrogenase, U/L					
	>250	393/534 (73.6%)	162/272 (59.6%)	231/262 (88.2%)	0.000
	>445	133/534 (24.9%)	25/272 (9.2%)	108/262 (41.2%)	0.000
Globulin >35 g/L		218/540 (40.4%)	88/275 (32.0%)	130/265 (49.1%)	0.000
Albumin ≤35 g/L		320/541 (59.1%)	126/275 (45.8%)	194/266 (72.9%)	0.000
Alanine aminotransferase >40 U/L		125/541 (23.1%)	61/275 (22.3%)	64/266 (24.1%)	0.683
Aspartate aminotransferase >40 U/L		179/540 (33.1%)	64/275 (23.3%)	115/265 (43.4%)	0.000
Total bilirubin >21 μmol/L		24/541 (4.4%)	7/275 (2.3%)	17/266 (6.4%)	0.036
Conjugated bilirubin >8 μmol/L		50/541 (9.2%)	17/275 (6.3%)	33/266 (12.6%)	0.017
Blood urea nitrogen >7.5 mmol/L		85/539 (15.8%)	18/273 (6.6%)	67/266 (25.2%)	0.000
Creatinine >85 μmol/L		146/539 (27.1%)	61/273 (22.3%)	85/266 (32.0%)	0.015
IL-1β > 5 ng/L		51/306 (16.7%)	34/170 (20.0%)	17/136 (12.5%)	0.091
IL-2R >710 U/mL		164/309 (53.1%)	73/171 (42.7%)	91/138 (65.9%)	0.000
IL-6 >7 ng/L		221/312 (70.8%)	107/175 (61.1%)	114/137 (83.2%)	0.000
IL-8 >62 ng/L		24/309 (7.8%)	10/171 (5.9%)	14/137 (10.1%)	0.200
IL-10 >9.1 ng/L		83/307 (27.0%)	34/170 (20.0%)	49/170 (35.8%)	0.003
TNF-α >8.1 ng/L		182/309 (58.9%)	89/171 (52.1%)	93/138 (67.4%)	0.008
Proteinuria		200/330 (60.6%)	98/193 (50.8%)	102/137 (74.5%)	0.000

Data are expressed as median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. P values comparing nonsevere cases and severe cases are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. IL=Interleukin. TNF=Tumor necrosis factor.

* SARS-CoV-2 nucleic acid test was performed pre-admission.

Table 3. Complications and treatment during hospitalization and clinical outcomes of COVID-19 patients

	All patients (n=548)	Nonsevere (n=279)	Severe (n=269)	p value
Complications				
ARDS	210/548 (38.3%)	27/279 (9.7%)	183/269 (68.0%)	0.000
Cardiac injury	119/548 (21.7%)	25/279 (9.0%)	94/269 (34.9%)	0.000
Liver dysfunction	106/548 (19.3%)	44/279 (15.8%)	62/269 (23.0%)	0.040
Acute kidney injury	95/548 (17.3%)	33/279 (11.8%)	62/269 (23.0%)	0.001
Bacteremia	42/548 (7.7%)	4/279 (1.4%)	38/269 (14.1%)	0.000
DIC	42/548 (7.7%)	5/279 (1.8%)	37/269 (13.8%)	0.000
Hyperglycemia	182/548 (33.2%)	60/279 (21.5%)	122/269 (45.4%)	0.000
Administration of systemic corticosteroids	341/548 (62.2%)	145/279 (52.0%)	196/269 (72.9%)	0.000
Duration, days	4 (0-11)	1 (0-10)	5 (0-12)	0.000
Cumulative dose, mg	200 (0-450)	50 (0-400)	295 (0-575)	0.000
Administration of antiviral drugs				
Lopinavir/ritonavir	164/548 (29.9%)	91/279 (32.6%)	73/269 (27.1%)	0.163
Umifenovir	401/548 (73.2%)	222/279 (79.6%)	179/269 (66.5%)	0.001
Oseltamivir	221/548 (40.3%)	127/279 (45.5%)	94/269 (34.9%)	0.015
Ribavirin	29/548 (5.3%)	8/279 (2.9%)	21/269 (7.8%)	0.012
Interferon α nebulization	168/548 (30.7%)	97/279 (34.8%)	71/269 (26.4%)	0.041
Intravenous Immunoglobulin	213/548 (38.9%)	103/279 (36.9%)	110/269 (40.9%)	0.381
Vasopressor	79/548 (14.4%)	5/279 (1.8%)	74/269 (27.5%)	0.000
Oxygen therapy	355/548 (64.8%)	131/279 (47.0%)	224/269 (83.3%)	0.000
Nasal cannula or mask	228/548 (41.6%)	118/279 (42.3%)	110/269 (40.9%)	0.000
High-flow oxygen therapy	24/548 (4.4%)	2/279 (0.7%)	22/269 (8.2%)	
Noninvasive mechanical ventilation	78/548 (14.2%)	10/279 (3.6%)	68/269 (25.3%)	
Invasive mechanical ventilation	25/548 (4.6%)	1/279 (0.4%)	24/269 (8.9%)	
Continuous renal replacement therapy	2/548 (0.4%)	0	2/269 (99.3%)	0.241
Clinical outcomes				
Discharge from hospital	287/545 (52.7%)	202/277 (72.9%)	85/268 (31.7%)	0.000

In-hospitalization	168/545 (30.8%)	72/277 (26.0%)	96/268 (35.8%)
Death	90/545 (16.5%)	3/277 (1.1%)	87/268 (32.5%)

Data are expressed as median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. P values comparing nonsevere cases and severe cases are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. ARDS=acute respiratory distress syndrome. DIC=diffuse intravascular coagulation.

Table 4. Unadjusted and adjusted cox proportional hazards regression model for death among severe COVID-19 patients

Variable	Unadjusted HR	95% CI	p value	Adjusted HR	95% CI	p value
Sex, male vs. female	1.96	1.24-3.11	0.004	1.72	1.05-2.82	0.032
Age, ≥65 years vs. <65 years	1.69	1.09-2.59	0.018	1.72	1.09-2.73	0.021
Blood leukocyte count, >10×10 ·/L vs. ≤10×10 ·/L	3.85	2.50-5.93	0.000	2.04	1.26-3.31	0.004
Lactose dehydrogenase, > 445 U/L vs. ≤445 U/L	3.94	2.48-6.28	0.000	2.00	1.21-3.30	0.007
Complications						
Cardiac injury	3.89	2.52-6.01	0.000	2.92	1.80-4.76	0.000
Hyperglycemia	2.49	1.61-3.87	0.000	1.77	1.11-2.84	0.017
Treatment						
Corticosteroids			0.000			0.000
No steroid (ref)						
Low dose*	1.07	0.57-2.01	0.825	1.26	0.61-2.580	0.534
High dose#	3.32	1.85-5.97	0.000	3.50	1.79-6.86	0.000
Lopinavir/ritonavir	0.26	0.13-0.52	0.000	0.43	0.21-0.89	0.022
Umifenovir	0.46	0.30-0.71	0.000	0.54	0.34-0.84	0.007

P values are from cox proportional hazards regression model. The final model was adjusted for sex, age, blood leukocyte count, lactose dehydrogenase, cardiac injury, hyperglycemia, and administration of corticosteroids, lopinavir/ritonavir, and umifenovir. * Low dose of steroid indicates that the maximum dose was less than 1 mg/kg/d prednisone. # High dose of steroid indicates that the maximum dose was equivalent to or more than 1 mg/kg/d prednisone. CI=confidence interval. HR=hazard ratio.