Clinical features and risk factors associated with severe COVID-19 patients in China

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Abstract

Background: Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread throughout the world. In this study, we aimed to identify the risk factors for severe COVID-19 to improve treatment guidelines.

Methods: A multicenter, cross-sectional study was conducted on 313 patients hospitalized with COVID-19. Patients were classified into two groups based on disease severity (nonsevere and severe) according to initial clinical presentation. Laboratory test results and epidemiological and clinical characteristics were analyzed using descriptive statistics. Univariate and multivariate logistic regression models were used to detect potential risk factors associated with severe COVID-19.

Results: A total of 289 patients (197 nonsevere and 92 severe cases) with a median age of 45.0 (33.0, 61.0) years were included in this study, and 53.3% (154/289) were male. Fever (192/286, 67.1%) and cough (170/289, 58.8%) were commonly observed, followed by sore throat (49/289, 17.0%). Multivariate logistic regression analysis suggested that patients who were aged ≥ 65 years (OR: 2.725, 95% confidence interval [CI]: 1.317–5.636; $P = 0.007$), were male (OR: 1.878, 95% CI: 1.002–3.520, $P = 0.049$), had comorbid diabetes (OR: 3.314, 95% CI: 1.126–9.758, $P = 0.030$), cough (OR: 3.427, 95% CI: 1.752–6.706, $P < 0.001$), and/or diarrhea (OR: 2.629, 95% CI: 1.109–6.231, $P = 0.028$) on admission had a higher risk of severe disease. Moreover, stratification analysis indicated that male patients with diabetes were more likely to have severe COVID-19 (71.4% *vs.* 28.6%, $\chi^2 = 8.183$, $P = 0.004$).

Conclusions: The clinical characteristics of those with severe and nonsevere COVID-19 were significantly different. The elderly, male patients with COVID-19, diabetes, and presenting with cough and/or diarrhea on admission may require close monitoring to prevent deterioration.

Keywords: Clinical feature; Coronavirus disease 2019; Diabetes; Risk factor; Severe acute respiratory syndrome coronavirus 2

Introduction

Coronavirus disease 2019 (COVID-19) refers to an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has resulted in huge economic losses and already become a global threat. Most patients diagnosed with COVID-19 present with fever and cough, which are the most common symptoms.[1-3] The clinical spectrum of COVID-19 appears to be wide, encompassing severe pneumonia, acute respiratory distress syndrome, or multiple organ failure and death.[1] Although the disease is mild in most cases, the proportion with severe COVID-19 is 24.3%.[4] As of July 22, 2020, the global mortality rate was estimated to be 4.1% according to the WHO,[5] far below that reported with severe acute respiratory syndrome (SARS; more than 10%) and the Middle East respiratory syndrome (>35%).[6] Previous studies of COVID-19 have included single site studies, such as in Wuhan,[1,2,7,8]

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Beijing,[9] and Shenzhen,[10] and multi-center studies,[3,11-13] primarily focusing on epidemiological and clinical features. Few publications have focused on severe cases specifically. The rapidly increasing number of patients, especially those with severe or critical COVID-19, has created a major public health challenge. It is therefore urgent that critical patients be studied and identified early, medical resources be allocated rationally, and treatment plans be adjusted in a timely manner to enhance the efficacy and reduce the risk of death resulting from COVID-19.

Therefore, this multi-center cross-sectional study was conducted. We analyzed the laboratory test results and epidemiological and clinical characteristics of 313 patients hospitalized with COVID-19 across 12 provinces/municipalities in China to identify risk factors and clinical features associated with severe COVID-19, with the intention of providing guidance for early diagnosis and timely treatment.

Methods

Ethical approval

The protocol for this study was approved by the Institutional Ethics Review Board of Peking University People's Hospital (No. 2020PHB051–01). Written informed consent was waived by the Ethics Review Board due to the urgent need for clinical data collection and investigation.

Study design and participants

In this retrospective study, the sample size was calculated based on the assumed proportion of severe cases among all COVID-19 subjects (assumed to be 0.25 based on a previous study),[4] with a type I error level of 0.05.[14,15] Hence, the sample size was estimated to be 306 for this study.

From February 22 to March 29, 2020, we collected information of 313 patients hospitalized for COVID-19 from 25 designated hospitals across 12 provinces/municipalities in China. During the study period, the management of COVID-19 patients was more standardized than during the onset of the disease, including diagnosis, laboratory tests, and daily documents (*eg*, case report form). All participants recruited from the hospitals were laboratory-confirmed cases with positive high-throughput sequencing or real-time reverse-transcription polymerase chain reaction (RT-PCR) assay results from respiratory secretions.[16] Patients were classified into four groups (mild, moderate, severe, and critical) according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia Version 6 (Trial)" established by the National Health Commission of the People's Republic of China.[16]

Data collection

Patient data were extracted from electronic medical records using a standardized data collection form, the modified translated version of the WHO/International Severe Acute Respiratory and Emerging Infection Consortium case record form for severe acute respiratory infections.[8] These data, including demographics, clinical features (including smoking history, exposure history, comorbidities, and signs and symptoms), laboratory findings, and radiological characteristics, were collected on the day of hospital admission. Information concerning the treatments applied during hospitalization was collected, and the outcomes were defined as of March 29, 2020.

To secure data validity and quality, the study team and tools were established. A coordinator was designated to manage the local medical records in each hospital. All information was extracted from the medical records by the coordinator and entered into SO JUMP (https://www.wjx.cn/), a professional online platform for designing, distributing, and collecting data. All data were cross-checked by a team of experienced respiratory clinicians. If any core data were missing, a query was immediately sent to the coordinator, who would then contact the patient's attending clinicians and update the data in SO JUMP.

Laboratory procedures and treatments

SARS-CoV-2 RNA was detected by the local centers for disease control and prevention, health institutions, and hospitals. Laboratory confirmation was conducted using real-time RT-PCR.[2] Sputum and throat swab specimens collected from patients were analyzed using real-time RT-PCR for SARS-CoV-2 RNA within three hours. Virus detection was performed twice at least 24 h apart.

Laboratory examinations included a complete blood count, a blood chemistry (including liver and renal function, creatine kinase, and glucose), myocardial enzymes, procalcitonin, and C-reactive protein. Radiological assessments were conducted using chest X-rays or computed tomography (CT). Each patient was examined on the day of admission to the designated hospital.

Noninvasive and invasive ventilation were applied based on the severity of hypoxemia. Other treatments, including the administration of inotropes/vasopressors, neuromuscular blocking agents, renal replacement therapy and the use of extracorporeal membrane oxygenation (ECMO) were also applied for some patients.

Definitions

To better understand the clinical features, and to provide guidance for the early diagnosis and timely treatment of severe COVID-19, we combined mild and moderate cases into the nonsevere group and the severe and critical cases into the severe group. According to the "Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia Version 6 (Trial)",[16] the criteria for discharge were as follows: absence of fever for at least three days, substantial improvement in both lungs on chest CT, clinical remission of respiratory symptoms, and two lower respiratory tract specimens negative for SARS-CoV-2 RNA obtained at least 24 h apart. Exposure history was defined as exposure to live/dead animals, exposure to

people with COVID-19 infection, or exposure to people who had recently visited Wuhan.

Statistical analysis

For continuous variables, the Shapiro-Wilk normality test was performed for each. Normally distributed continuous variables are presented as means and standard deviations. Continuous variables that are not normally distributed are presented as medians (Q_1, Q_3). The *t* tests or Wilcoxon rank-sum tests were then applied. Categorical variables are summarized as counts and percentages, and χ^2 or Fisher exact tests were used. Univariate and multivariate logistic regression models were performed to detect potential risk factors associated with severe COVID-19. The statistically significant risk factors from the univariate logistic regression analysis, along with sex and age, were included in the final multivariate models. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were included in the univariate and multivariate regression analyses. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The statistical significance level was set at 0.05.

Results

Demographic and clinical characteristics

By March 29, 2020, a total of 313 laboratory-confirmed COVID-19 patients were recruited from 25 hospitals across 12 provinces/municipalities in China. For this study, three with duplicated information, four with missing data (*eg*, sex, age), and 17 who did not meet the clinical classification criteria were excluded from the final analysis. Therefore, 289 patients were included in this retrospective study [Figure 1].

The demographic and clinical features of the patients are shown in Table 1. The patients were aged from one month to 91 years, the median age was 45.0 (33.0, 61.0) years, 20.4% (59/289) were aged ≥ 65 years, and there were slightly more male patients (154/289, 53.3%). Of the 289 patients, 98 (33.9%) were residents of Wuhan, Hubei province, 8 (2.8%) were from other areas in Hubei province, and 183 (63.3%) were from outside of Hubei province. A history of recent travel to an epidemic area, contact with confirmed cases of COVID-19, and contact with wildlife was documented in 56.5% (157/278), 50.0% (97/194), and 1.0% (2/208) of the patients, respectively. The most common symptoms in the laboratory-confirmed patients were fever (192/286, 67.1%) and cough (170/289, 58.8%), followed by sore throat (49/289, 17.0%), shortness of breath (42/289, 14.5%), fatigue/malaise (42/289, 14.5%), diarrhea (38/289, 13.1%), myalgia (35/289, 12.1%), headache (30/289, 10.4%), runny nose (23/289, 8.0%), vomiting/nausea (21/289, 7.3%), chest pain (19/289, 6.6%), arthralgia (15/289, 5.2%), wheezing (11/289, 3.8%), bleeding (6/289, 2.1%), and abdominal pain (5/289, 1.7%). Only one patient (1/289, 0.3%) developed altered consciousness. Moreover, the most common comorbidity was diabetes (25/289, 8.7%), followed by chronic cardiovascular disease (18/289, 6.2%) and chronic pulmonary disease (12/289, 4.2%).

As indicated in Table 1, 197 (68.2%) and 92 (31.8%) of the patients were classified into the nonsevere and severe group, respectively. Between the two groups, the following parameters were significantly different: age (40.0 [30.0, 50.0] years *vs.* 60.0 [45.5, 69.5] years, $Z = 43.912$, $P < 0.001$); region of residence ($P = 0.001$); prevalence of contact with confirmed cases (54.9% *vs.* 31.7%, $\chi^2 = 6.958$, $P = 0.008$); presence of cough (50.3% *vs.* 77.2%, $\chi^2 = 18.763$, $P < 0.001$), shortness of breath (10.2% *vs.* 23.9%, $\chi^2 = 9.561$, $P = 0.002$), and diarrhea (10.2% *vs.* 19.6%, $\chi^2 = 4.866$, $P = 0.027$); arterial oxygen saturation (SaO_2) > 93% (100.0% *vs.* 64.4%, $\chi^2 = 60.797$, $P < 0.001$); and arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) > 300 mm Hg (100.0% *vs.* 16.1%, $\chi^2 = 51.142$, $P < 0.001$). Compared to the nonsevere group, the patients in the severe group more commonly had comorbidities, including diabetes (17.4% *vs.* 4.6%, $\chi^2 = 13.049$, $P < 0.001$), chronic cardiac disease (14.1% *vs.* 2.5%, $\chi^2 = 14.430$, $P < 0.001$), chronic kidney disease (4.3% *vs.* 0.5%, $P = 0.037$), and chronic hematologic disease (3.3% *vs.* 0, $P = 0.032$). Tachypnea (respiratory rate > 24 breaths per min) (19.8% *vs.* 1.2%, $\chi^2 = 29.090$, $P < 0.001$) and a history of smoking (5.4% *vs.* 1.0%, $P = 0.035$) were also more common in the severe group than in the nonsevere group.

Laboratory and radiological findings

The laboratory and radiological findings of patients diagnosed with COVID-19 are listed in Table 2. Most patients (164/239, 68.6%) had normal peripheral white blood cell counts [(4–9.9)× 10^9/L] on admission. Lymphopenia was observed in 40.8% (95/233) of the patients. Procalcitonin < 0.5 ng/mL and C-reactive protein ≥ 10 mg/mL occurred in 76.4% (84/110) and 57.0% (90/158) of the patients, respectively. Severe cases had more prominent laboratory abnormalities, such as reduced hemoglobin levels (64.9% *vs.* 45.8%, $\chi^2 = 6.397$, $P = 0.011$), lymphopenia (54.2% *vs.* 33.3%, $\chi^2 = 9.650$, $P = 0.002$) and elevated creatinine (11.6% *vs.* 2.1%, $P = 0.019$), blood urea nitrogen (18.4% *vs.* 5.2%, $P = 0.038$), glucose (42.9% *vs.* 25.3%, $\chi^2 = 4.166$, $P = 0.041$), procalcitonin (40.8% *vs.* 9.8%, $\chi^2 = 14.449$, $P < 0.001$), and C-reactive protein (71.2% *vs.* 48.5%, $\chi^2 = 7.772$, $P = 0.005$) levels, as compared with nonsevere cases.

Although there were no statistically significant differences in chest CT or radiography results between the severe and nonsevere cases, for patients infected with COVID-19, the most common patterns on chest CT were ground-glass opacities (184/211, 87.2%) and infiltration (136/184, 73.9%), followed by air bronchogram (59/184, 32.1%) and interlobular septal thickening (57/185, 30.8%). The chest CTs of two patients are shown in Supplementary Figure 1, http://links.lww.com/CM9/A524.

Treatments and outcomes

In our study, three kinds of anti-infection medications were used to treat patients with COVID-19 [Table 3]. Antivirals, antibiotics, and antifungals were used in 95.8% (253/264), 62.2% (155/249) and 8.1% (20/247) of patients, respectively. Antibiotics (67.4% *vs.* 49.3%, $\chi^2 = 7.091$,

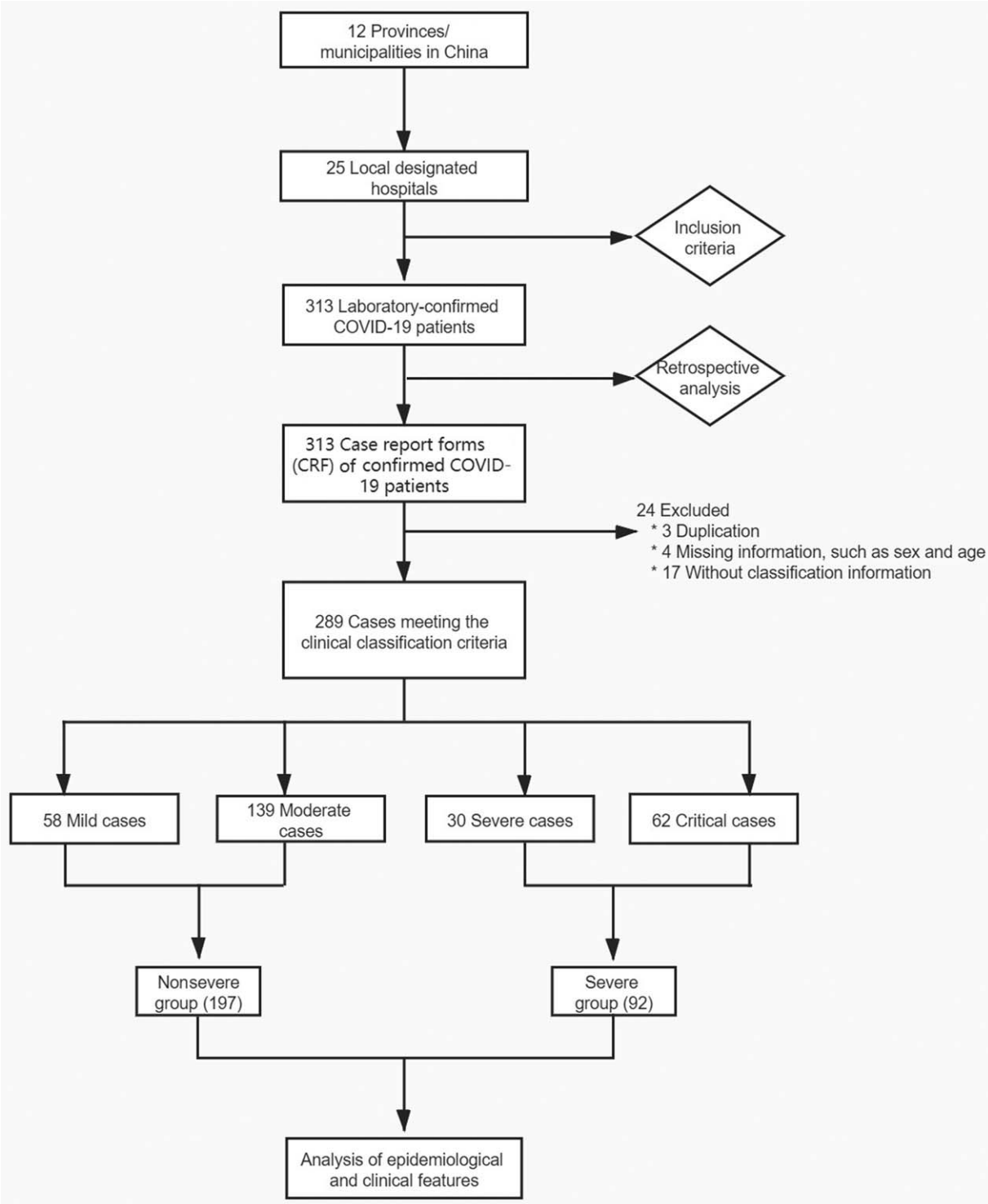

Figure 1: Recruitment flowchart of COVID-19 patient. COVID-19: Coronavirus disease 2019.

$P = 0.008$) were used more often in nonsevere group, while antifungal agents (21.6% *vs.* 2.3%, $\chi^2 = 25.969$, $P < 0.001$) were used more often in the severe group. In addition, noninvasive and invasive mechanical ventilation, renal replacement therapy, inotropes/vasopressors, neuromuscular blocking agents, and ECMO were only used in the severe group.

As of March 29, 2020, five patients had died during hospitalization, 154 patients were discharged, 51 patients were still hospitalized, and eight patients were transferred to other designated hospitals [Table 3]. The percentages of patients who were discharged in nonsevere and severe groups were 75.7% (112/148) and 60.0% (42/70), respectively, while the percentages of patients who were

Table 1: Characteristics of patients with COVID-19.

Characteristics	All patients ($n = 289$)	Nonsevere ($n = 197$)	Severe ($n = 92$)	Statistics	P
Age (years)	45.0 (33.0, 61.0)	40.0 (30.0, 50.0)	60.0 (45.5, 69.5)	43.912*	<0.001
Age (years)				–	<0.001
0–14	8 (2.8)	7 (3.6)	1 (1.1)		
15–29	48 (16.6)	41 (20.8)	7 (7.6)		
30–49	115 (39.8)	93 (47.2)	22 (23.9)		
50–64	59 (20.4)	35 (17.8)	24 (26.1)		
≥ 65	59 (20.4)	21 (10.7)	38 (41.3)		
Sex				3.117†	0.077
Male	154 (53.3)	98 (49.7)	56 (60.9)		
Female	135 (46.7)	99 (50.3)	36 (39.1)		
Smoking history	7 (2.4)	2 (1.0)	5 (5.4)	–	0.035
Healthcare worker	23/233 (9.9)	22/177 (12.4)	1/56 (1.8)	5.417†	0.020
Region of residence				–	0.001
Wuhan	98 (33.9)	58 (29.4)	40 (43.5)		
Other cities in Hubei Province	8 (2.8)	2 (1.0)	6 (6.5)		
Cities outside Hubei Province	183 (63.3)	137 (69.5)	46 (50.0)		
Exposure history					
Recently visited epidemic area	157/278 (56.5)	102/192 (53.1)	55/86 (64.0)	2.833†	0.092
Contact with confirmed cases	97/194 (50.0)	84/153 (54.9)	13/41 (31.7)	6.958†	0.008
Contact with wildlife	2/208 (1.0)	2/155 (1.3)	0 (0)	–	1.000
Comorbidity					
Diabetes	25 (8.7)	9 (4.6)	16 (17.4)	13.049†	<0.001
Chronic cardiac disease	18 (6.2)	5 (2.5)	13 (14.1)	14.430†	<0.001
Chronic pulmonary disease	12 (4.2)	5 (2.5)	7 (7.6)	–	0.058
Chronic kidney disease	5 (1.7)	1 (0.5)	4 (4.3)	–	0.037
Malignant neoplasm	5 (1.7)	3 (1.5)	2 (2.2)	–	0.655
Chronic hematologic disease	3 (1.0)	0 (0)	3 (3.3)	–	0.032
Chronic liver disease	3 (1.0)	3 (1.5)	0 (0)	–	0.554
Obesity	3 (1.0)	2 (1.0)	1 (1.1)	–	1.000
Dementia	2 (0.7)	2 (1.0)	0 (0)	–	1.000
Malnutrition	1 (0.3)	0 (0)	1 (1.1)	–	0.318
Signs and symptoms					
Fever	192/286 (67.1)	141/194 (72.7)	53/92 (57.6)	6.497†	0.011
Cough	170 (58.8)	99 (50.3)	71 (77.2)	18.763†	<0.001
Sore throat	49 (17.0)	37 (18.8)	12 (13.0)	1.467†	0.226
Fatigue/malaise	42 (14.5)	29 (14.7)	13 (14.1)	0.018†	0.894
Shortness of breath	42 (14.5)	20 (10.2)	22 (23.9)	9.561†	0.002
Diarrhea	38 (13.1)	20 (10.2)	18 (19.6)	4.866†	0.027
Myalgia	35 (12.1)	21 (10.7)	14 (15.2)	1.224†	0.269
Headache	30 (10.4)	18 (9.1)	12 (13.0)	1.029†	0.310
Rhinitis	23 (8.0)	18 (9.1)	5 (5.4)	1.173†	0.279
Vomiting/nausea	21 (7.3)	15 (7.6)	6 (6.5)	0.111†	0.739
Chest pain	19 (6.6)	16 (8.1)	3 (3.3)	2.413†	0.120
Arthralgia	15 (5.2)	13 (6.6)	2 (2.2)	–	0.157
Wheezing	11 (3.8)	6 (3.0)	5 (5.4)	–	0.335
Bleeding	6 (2.1)	5 (2.5)	1 (1.1)	–	0.668
Abdominal pain	5 (1.7)	3 (1.5)	2 (2.2)	–	0.655
Altered consciousness	1 (0.3)	1 (0.5)	0 (0)	–	1.000
Heart rate (>100 beats per min)	45/256 (17.6)	28/170 (16.5)	17/86 (19.8)	0.428†	0.513
Respiratory rate (>24 breaths per min)	19/258 (7.4)	2/172 (1.2)	17/86 (19.8)	29.090†	<0.001
SaO_2 (>93%)	206/238 (86.6)	148/148 (100.0)	58/90 (64.4)	60.797†	<0.001
PaO_2/FiO_2 (>300 mmHg)	43/69 (62.3)	38/38 (100.0)	5/31 (16.1)	51.142†	<0.001

Data are presented as median (Q_1, Q_3), *n* (%), or *n*/*N* (%). COVID-19: Coronavirus disease 2019; PaO_2/FiO_2: Arterial partial pressure of oxygen/fraction of inspired oxygen; SaO_2: Arterial oxygen saturation; –: Not applicable. *Z values. †χ^2 values.

Table 2: Laboratory and radiological findings of patients with COVID-19.

Items	All patients ($n = 289$)	Nonsevere ($n = 197$)	Severe ($n = 92$)	χ^2	P
Laboratory findings					
Hemoglobin (g/L)				6.397	0.011
<130	97/181 (53.6)	49/107 (45.8)	48/74 (64.9)		
≥130	84/181 (46.4)	58/107 (54.2)	26/74 (35.1)		
White blood cell count ($\times 10^9$/L)				4.552	0.103
<4	57/239 (23.8)	44/158 (27.8)	13/81 (16.0)		
4–9.9	164/239 (68.6)	104/158 (65.8)	60/81 (74.1)		
≥10	18/239 (7.5)	10/158 (6.3)	8/81 (9.9)		
Lymphocyte count ($\times 10^9$/L)				9.650	0.002
<1	95/233 (40.8)	50/150 (33.3)	45/83 (54.2)		
≥1	138/233 (59.2)	100/150 (66.7)	38/83 (45.8)		
Neutrophil count ($\times 10^9$/L)				2.336	0.126
<1.8	29/209 (13.9)	22/132 (16.7)	7/77 (9.1)		
≥1.8	180/209 (86.1)	110/132 (83.3)	70/77 (90.9)		
Platelet count ($\times 10^9$/L)				–	0.070
<100	8/184 (4.3)	2/107 (1.9)	6/77 (7.8)		
≥100	176/184 (95.7)	105/107 (98.1)	71/77 (92.2)		
Alanine aminotransferase (U/L)				2.043	0.153
<40	147/196 (75.0)	92/117 (78.6)	55/79 (69.6)		
≥40	49/196 (25.0)	25/117 (21.4)	24/79 (30.4)		
Aspartate aminotransferase (U/L)				3.258	0.071
<40	144/178 (80.9)	88/103 (85.4)	56/75 (74.7)		
≥40	34/178 (19.1)	15/103 (14.6)	19/75 (25.3)		
Total bilirubin (μmol/L)				0.724	0.395
<17.1	136/170 (80.0)	79/96 (82.3)	57/74 (77.0)		
≥17.1	34/170 (20.0)	17/96 (17.7)	17/74 (23.0)		
Creatinine (μmol/L)				–	0.019
<133	153/163 (93.9)	92/94 (97.9)	61/69 (88.4)		
≥133	10/163 (6.1)	2/94 (2.1)	8/69 (11.6)		
Blood urea nitrogen (mmol/L)				–	0.038
<7.5	122/134 (91.0)	91/96 (94.8)	31/38 (81.6)		
≥7.5	12/134 (9.0)	5/96 (5.2)	7/38 (18.4)		
Glucose (mmol/L)				4.166	0.041
<7.0	92/133 (69.2)	68/91 (74.7)	24/42 (57.1)		
≥7.0	41/133 (30.8)	23/91 (25.3)	18/42 (42.9)		
Creatine kinase (U/L)				3.160	0.075
<185	133/151 (88.1)	81/88 (92.0)	52/63 (82.5)		
≥185	18/151 (11.9)	7/88 (8.0)	11/63 (17.5)		
Myoglobin (ng/mL)				2.854	0.091
<75	60/79 (75.9)	29/34 (85.3)	31/45 (68.9)		
≥75	19/79 (24.1)	5/34 (14.7)	14/45 (31.1)		
Troponin T (ng/mL)				0.315	0.574
<0.1	36/50 (72.0)	20/29 (69.0)	16/21 (76.2)		
≥0.1	14/50 (28.0)	9/29 (31.0)	5/21 (23.8)		
Procalcitonin (ng/mL)				14.449	<0.001
<0.5	84/110 (76.4)	55/61 (90.2)	29/49 (59.2)		
≥0.5	26/110 (23.6)	6/61 (9.8)	20/49 (40.8)		
C-reactive protein (mg/L)				7.772	0.005
<10	68/158 (43.0)	51/99 (51.5)	17/59 (28.8)		
≥10	90/158 (57.0)	48/99 (48.5)	42/59 (71.2)		
Radiological findings					
Ground-glass opacity	184/211 (87.2)	133/151 (88.1)	51/60 (85.0)	0.365	0.546
Infiltration	136/184 (73.9)	97/135 (71.9)	39/49 (79.6)	1.117	0.291
Air bronchogram	59/184 (32.1)	43/136 (31.6)	16/48 (33.3)	0.048	0.827
Interlobular septal thickening	57/185 (30.8)	41/137 (29.9)	16/48 (33.3)	0.193	0.660
Reversed halo sign	27/182 (14.8)	24/136 (17.6)	3/46 (6.5)	3.367	0.066
Mosaic sign	16/183 (8.7)	14/137 (10.2)	2/46 (4.3)	–	0.365
Tractive bronchiectasis	8/184 (4.3)	7/136 (5.1)	1/48 (2.1)	–	0.683

Data are presented as *n*/*N* (%). COVID-19: Coronavirus disease 2019; –: Not applicable.

Table 3: Treatments and outcomes of patients with COVID-19.

Items	All patients ($n = 289$)	Nonsevere ($n = 197$)	Severe ($n = 92$)	χ^2	P
Treatments					
Antiviral treatment	253/264 (95.8)	168/177 (94.9)	85/87 (97.7)	–	0.348
Antibiotic treatment	155/249 (62.2)	120/178 (67.4)	35/71 (49.3)	7.091	0.008
Antifungal treatment	20/247 (8.1)	4/173 (2.3)	16/74 (21.6)	25.969	<0.001
Noninvasive ventilation	62/270 (23.0)	0 (0)	62/89 (69.7)		
Invasive ventilation	6/270 (2.2)	0 (0)	6/89 (6.7)		
Renal replacement therapy	4/270 (1.5)	0 (0)	4/89 (4.5)		
Inotropes/vasopressors	4/270 (1.5)	0 (0)	4/89 (4.5)		
Neuromuscular blocking agents	4/270 (1.5)	0 (0)	4/89 (4.5)		
ECMO	2/270 (0.7)	0 (0)	2/89 (2.2)		
Outcomes				–	0.002
Discharged alive	154/218 (70.6)	112/148 (75.7)	42/70 (60.0)		
Hospitalization	51/218 (23.4)	30/148 (20.3)	21/70 (30.0)		
Transfer to other facility	8/218 (3.7)	6/148 (4.1)	2/70 (2.9)		
Death	5/218 (2.3)	0/148 (0)	5/70 (7.1)		

Data are presented as *n*/*N* (%). COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; –: Not applicable.

still hospitalized were 20.3% (30/148) *vs.* 30.0% (21/70), who had transferred to other facilities were 4.1% (6/148) *vs.* 2.9% (2/70), and who had died were 0 *vs.* 7.1% (5/70), respectively, in nonsevere group and severe group.

Risk factors for patients with severe COVID-19

The univariate analysis results [Table 4] showed that older age (≥ 65 years; OR, 5.898; 95% CI: 3.192–10.900; $P < 0.001$), and smoking history (OR, 5.603; 95% CI: 1.066–29.450; $P = 0.042$) were associated with severe COVID-19, and being a health care worker (OR, 0.128; 95% CI: 0.017–0.973; $P = 0.047$), being a resident in cities outside Hubei province (OR, 0.487; 95% CI: 0.289–0.822; $P = 0.007$), having close contact with confirmed patients (OR, 0.381; 95% CI: 0.184–0.792; $P = 0.010$) were less likely to be associated with severe COVID-19. Patients with chronic cardiac disease (OR, 6.319; 95% CI: 2.180–18.310; $P = 0.001$) and diabetes (OR, 4.398; 95% CI: 1.863–10.380; $P = 0.001$) were also more likely to be in the severe group. In addition, the presence of fever (OR, 0.511; 95% CI: 0.304–0.859; $P = 0.011$), cough (OR, 3.347; 95% CI: 1.909–5.867; $P < 0.001$), respiratory rate > 24 breaths per min (OR, 20.933; 95% CI: 4.711–93.067; $P < 0.001$), and some laboratory results, including higher hemoglobin (OR, 0.458; 95% CI: 0.249–0.842; $P = 0.012$) and lymphocyte count (OR, 0.422; 95% CI: 0.244–0.731; $P = 0.002$) were associated with the severity of COVID-19; and elevated glucose (OR, 2.218; 95% CI: 1.024–4.802; $P = 0.043$), blood urea nitrogen (OR, 4.110; 95% CI: 1.216–13.890; $P = 0.023$), creatinine (OR, 6.033; 95% CI: 1.239–29.370; $P = 0.026$), procalcitonin (OR, 6.322; 95% CI: 2.286–17.480; $P < 0.001$), and C-reactive protein levels (OR, 2.625; 95% CI: 1.320–5.221; $P = 0.006$) were associated with severe COVID-19.

To further analyze the risk factors for severe COVID-19, multivariate regression models were used. The results indicated that being ≥ 65 years old (OR, 2.725; 95% CI: 1.317–5.636; $P = 0.007$), male (OR, 1.878; 95% CI: 1.002–3.520; $P = 0.049$), having comorbid diabetes (OR, 3.314; 95% CI: 1.126–9.758; $P = 0.030$) or chronic cardiac disease (OR, 3.533; 95% CI: 0.989–12.642; $P = 0.052$, marginal significance), and presenting with cough (OR, 3.427; 95% CI: 1.752–6.706; $P < 0.001$) and/or diarrhea (OR, 2.629; 95% CI: 1.109–6.231; $P = 0.028$) on admission were significantly positively correlated with severe COVID-19. Moreover, COVID-19 patients with and without comorbid diabetes were stratified by sex for both groups [Supplementary Table 1, http://links.lww.com/CM9/A524], and male patients with diabetes were found to be more likely to develop severe COVID-19 (71.4% *vs.* 28.6%; $\chi^2 = 8.183$; $P = 0.004$).

Discussion

This multi-center retrospective study covered 313 laboratory-confirmed COVID-19 patients from 25 hospitals across 12 provinces/municipalities in China. Our study included patients from a vast area of China, not only Wuhan, and the definition of COVID-19 from Diagnosis and Treatment Protocol for Novel Coronavirus Infection-Induced Pneumonia Version 6 (Trial) was used. However, the cases were divided into two groups instead of four (severe *vs.* nonsevere) according to our study objective, which was to better understand the clinical features of COVID-19 and provide guidance to improve early diagnosis and timely treatment of severe cases.

A total of 40.8% of patients in this study were aged ≥ 50 years. This finding is consistent with previous studies, which have shown that older age is as an important predictor of severe illness or even death in COVID-19[1,8,17] and is similar to the findings with SARS[18] and Middle East Respiratory Syndrome.[19] Since the majority of the elderly population have weak immune function, proinflammatory responses may be prolonged and the risk of serious outcomes may be increased.[20] Among the 289 cases included in this study, we also observed that COVID-19 was more frequently diagnosed in male than in female, consistent with recent COVID-19 cases.[3,7] Additionally, Jaillon *et al*[21] have reported that the X chromosome and

Table 4: Risk factors associated with severe COVID-19.

Parameters	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Baseline characteristics						
Age (≥ 65 years *vs.* < 65 years)	5.898	3.192–10.900	<0.001	2.725	1.317–5.636	0.007
Sex (male *vs.* female)	1.571	0.950–2.599	0.078	1.878	1.002–3.520	0.049
Smoking history (yes *vs.* no)	5.603	1.066–29.450	0.042	2.252	0.360–14.090	0.385
Healthcare worker (yes *vs.* no)	0.128	0.017–0.973	0.047			
Region of residence						
Wuhan	1.000	–	–			
Other cities in Hubei Province	4.350	0.835–22.660	0.081			
Cities outside Hubei Province	0.487	0.289–0.822	0.007			
Exposure history						
Recently visited epidemic area (yes *vs.* no)	1.565	0.927–2.642	0.093	1.638	0.870–3.084	0.126
Contact with confirmed patients (yes *vs.* no)	0.381	0.184–0.792	0.010			
Comorbidities						
Diabetes (yes *vs.* no)	4.398	1.863–10.380	0.001	3.314	1.126–9.758	0.030
Chronic cardiac disease (yes *vs.* no)	6.319	2.180–18.310	0.001	3.533	0.989–12.642	0.052
Chronic pulmonary disease (yes *vs.* no)	3.162	0.976–10.250	0.055			
Chronic kidney disease (yes *vs.* no)	8.909	0.982–80.860	0.052			
Malignant neoplasm (yes *vs.* no)	1.437	0.236–8.751	0.694			
Obesity (yes *vs.* no)	1.072	0.096–11.970	0.955			
Signs and symptoms						
Fever (yes *vs.* no)	0.511	0.304–0.859	0.011	0.541	0.278–1.051	0.070
Cough (yes *vs.* no)	3.347	1.909–5.867	<0.001	3.427	1.752–6.706	<0.001
Sore throat (yes *vs.* no)	0.649	0.321–1.312	0.228			
Fatigue/malaise (yes *vs.* no)	0.954	0.470–1.933	0.895			
Shortness of breath (yes *vs.* no)	2.781	1.429–5.411	0.003	1.326	0.557–3.156	0.523
Diarrhea (yes *vs.* no)	2.153	1.077–4.301	0.030	2.629	1.109–6.231	0.028
Myalgia (yes *vs.* no)	1.504	0.727–3.112	0.271			
Headache (yes *vs.* no)	1.492	0.686–3.243	0.313			
Rhinitis (yes *vs.* no)	0.572	0.205–1.590	0.284			
Vomiting/nausea (yes *vs.* no)	0.847	0.317–2.257	0.739			
Chest pain (yes *vs.* no)	0.381	0.108–1.343	0.133			
Arthralgia (yes *vs.* no)	0.315	0.070–1.424	0.133			
Wheezing (yes *vs.* no)	1.830	0.544–6.158	0.329			
Bleeding (yes *vs.* no)	0.422	0.049–3.664	0.434			
Abdominal pain (yes *vs.* no)	1.437	0.236–8.751	0.694			
Respiratory rate (>24 breaths per min *vs.* ≤24 breaths per min)	20.933	4.711–93.067	<0.001			
Heart rate (>100 beats per min *vs.* ≤100 beats per min)	1.249	0.641–2.436	0.513			
Laboratory parameters						
Hemoglobin (≥130 g/dL *vs.* <130 g/dL)	0.458	0.249–0.842	0.012			
WBC count (4.0×10^9–9.9×10^9/L *vs.* <4.0×10^9/L)	1.953	0.974–3.915	0.059			
WBC count (≥10.0×10^9/L *vs.* <4.0×10^9/L)	1.387	0.519–3.704	0.514			
Lymphocyte count (≥1×10^9/L *vs.* <1×10^9/L)	0.422	0.244–0.731	0.002			
Neutrophil count (≥1.8×10^9/L *vs.* <1.8×10^9/L)	2.000	0.812–4.928	0.132			
Platelet count (≥100×10^9/L *vs.* <100×10^9/L)	0.225	0.044–1.149	0.073			
Alanine aminotransferase (≥40 U/L *vs.* <40 U/L)	1.606	0.836–3.083	0.155			
Aspartate aminotransferase (≥40 U/L *vs.* <40 U/L)	1.990	0.935–4.236	0.074			
Total bilirubin (≥17.1 mmol/L *vs.* <17.1 mmol/L)	1.386	0.652–2.945	0.396			
Creatinine (≥133 μmol/L *vs.* <133 μmol/L)	6.033	1.239–29.370	0.026			
Blood urea nitrogen (≥7.5 mmol/L *vs.* <7.5 mmol/L)	4.110	1.216–13.890	0.023			
Glucose (≥7.0 mmol/L *vs.* <7.0 mmol/L)	2.218	1.024–4.802	0.043			
Creatine kinase (≥185 U/L *vs.*<185 U/L)	2.448	0.892–6.718	0.082			
Myoglobin (≥75 ng/mL *vs.* <75 ng/mL)	2.619	0.838–8.188	0.098			
Troponin T (≥0.1 ng/mL *vs.* <0.1 ng/mL)	0.694	0.194–2.487	0.575			
Procalcitonin (≥0.5 ng/mL *vs.* <0.5 ng/mL)	6.322	2.286–17.480	<0.001			
C-reactive protein (≥10 mg/L *vs.* <10 mg/L)	2.625	1.320–5.221	0.006			

CI: Confidence interval; COVID-19: Coronavirus disease 2019; OR: Odds ratio; WBC: White blood cell; –: Not applicable.

sex hormones play a role in reducing susceptibility to viral, bacterial, and fungal infections in female. In addition, 50% of patients diagnosed with COVID-19 in this study had a history of exposure to confirmed cases, which is consistent with previous studies showing that COVID-19 infection is spread by human-to-human transmission.[1,3,17]

Consistent with other studies,[7,8,17] severe COVID-19 was found to occur more often in those with comorbid chronic cardiac disease or diabetes in our study. It has also been associated with more serious outcomes in influenza and other respiratory viral infections.[22] Patients with diabetes usually have weaker immune function,[23] suggesting that daily blood glucose control and supportive immune system therapies should be maintained to effectively reduce the severity of this disease in these patients.

The most two common symptoms in this study were fever and cough, which is consistent with previous findings.[1,3] In our study, presenting with fever, cough, shortness of breath, diarrhea, and a higher respiratory rate (>24 breaths per min) were more frequently found in severe COVID-19 cases than in nonsevere cases. These results suggest that patients with these symptoms on admission should be closely monitored to achieve better outcomes.

In terms of laboratory tests, lymphopenia was more commonly observed in patients with severe COVID-19 in this study. This was consistent with a previous study,[17] which suggested that SARS-CoV-2 might selectively attack lymphocytes, initiating a series of immune responses. Moreover, higher levels of glucose, blood urea nitrogen, and creatinine were observed in severe COVID-19 cases, which was consistent with the finding that patients with diabetes are more likely to have severe COVID-19. Analogous to the report by Guan *et al*,[3] we found that patients with severe COVID-19 were more likely to have procalcitonin ≥0.5 ng/mL and C-reactive protein ≥10 mg/L, suggesting the potential for serious outcomes from severe COVID-19. Hence, early identification and timely treatment of severe cases is essential.

Antiviral drugs and antibiotics were more commonly used for patients with COVID-19 in this study, which was similar to some previous findings.[1,2,17] Antibiotics were used more often in nonsevere COVID-19 cases, whereas antifungal drugs were used more in severe COVID-19 cases. Other medications administered more in severe COVID-19 cases included inotropes/vasopressors and neuromuscular blocking agents. This suggests that these drugs should be available for prompt treatment in COVID-19 patients. Furthermore, Richardson *et al*[24] reported that baricitinib may be a potential treatment option for COVID-19, and Wang *et al*[25] found that remdesivir and chloroquine could effectively inhibit SARS-CoV-2 *in vitro*. However, Wang *et al*[26] carried out a randomized, double-blind, placebo-controlled, multicenter trial with severe COVID-19 patients and the results showed that remdesivir was not significantly associated with clinical benefits. In the current study, 62 patients with severe COVID-19 received noninvasive ventilation and 6 patients with severe COVID-19 received invasive ventilation, whereas no patients with nonsevere COVID-19 received either treatment. Renal replacement therapy and ECMO were also only used in severe COVID-19 patients. Based on the above results, we suggest that comprehensive therapies are necessary in patients with severe COVID-19.

This study, however, has some limitations. First, due to the heavy workload of front-line physicians, not all patients hospitalized for COVID-19 during the study period from these 25 hospitals were included. Additionally, a much more comprehensive understanding of COVID-19 could have been obtained if patients from other provinces/municipalities in China were included. Second, since our study was conducted soon after the onset of COVID-19, a full picture of the disease could not be obtained. Therefore, the 289 cases included in this study might not be generalizable, especially since there were few mild or asymptomatic cases included in this study. Hence, the study might be biased towards more severe COVID-19. Third, in this study, the valid response rates were 80.6% (233/289) and 67.1% (194/289) for whether being a healthcare worker and having closely contact with confirmed cases, respectively. There might be a potential bias for the analysis of those two risk factors. Therefore, interpretation of these two risk factors needs to be cautious. Further observations of the natural history of COVID-19 are needed, particularly from outbreaks outside of China, to obtain more information on the epidemiological and clinical features of COVID-19.

In conclusion, we identified that fever and cough were the most two common symptoms in patients with COVID-19, while the latter was more likely to be associated with severe COVID-19. Elevated procalcitonin level (≥0.5 ng/mL) and C-reactive protein (≥10 mg/L) were also potential risk factors for severe COVID-19. Patients with diabetes, especially men, more often developed severe COVID-19, potentially resulting in poor clinical prognosis. Therefore, further investigations that include rigorous observations and comprehensive therapies for patients diagnosed with severe COVID-19 are necessary.

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Conflicts of interest

None.

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