

Research Article

Clinical Features of 49 Critically Ill Patients Infected with SARS-CoV-2 Outside Wuhan

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Background

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses and belong to the family Coronaviridae and the order Nidovirales, of which two coronaviruses, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [1,2] and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [3] have caused recent pandemics of respiratory infectious diseases with high mortality rates of 10% for SARS-CoV [4] and 37% for MERS-CoV [5].

On Jan 7, 2020, a novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) from the lower respiratory tract sample of a patient, and subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO) [6]. Since the first case was reported in December 2019 in Wuhan, China, the outbreak of the disease is currently continuously spreading all over the world.

The disease caused by SARS-CoV-2 that is named as Coronavirus Disease 2019 (COVID-19) by WHO could induce symptoms including fever, dry, cough, dyspnea, fatigue, and lymphopenia in infected patients, with some patients rapidly developing Acute

Respiratory Distress Syndrome (ARDS), acute respiratory failure, or multiple organ failure and even death [7]. Mechanical ventilation is usually required in critically ill patients with ARDS or acute respiratory failure. At present, although many articles have established the epidemiology and clinical features of patients with SARS-CoV-2 infection [7-10], the information regarding clinical manifestations and laboratory findings in critically ill patients with COVID-19 has not been reported yet. In the present study, we investigated the clinical features of critically ill patients with COVID-19 and identified the independent risk factors for death of these patients in Huanggang City and Xiaogan City, Hubei province outside Wuhan.

Methods

Patients

We retrospectively analyzed the medical records from critically ill patients with COVID-19 admitted to Dabie Mountain Medical Center and the First People's Hospital of Xiaochang County, Hubei Province from February 1 to March 25, 2020. The two hospitals, which are located in Huang gang City and Xiaogan City respectively, Hubei Province, about 80-90 km away from Wuhan, China, are the designated hospitals for the hospitalization of patients with COVID-19. SARS-CoV-2 pneumonia was diagnosed based on

Table 1: Demographics and baseline characteristics of critically ill patients with COVID-19.

	All patients (n=49)	Survivors (n=33)	Deceased (n=16)	P-value
Age-yrs	63 (53-73)	58 (50-74)	67 (60-72)	0.267
Sex-n (%)				
Female	17 (35)	12 (36)	5 (31)	0.724
Male	32 (65)	21 (64)	11 (69)	
Exposure history-n (%)				
Familiar/cluster infections	26 (53)	16 (48)	10 (63)	0.357
Community infections	23 (47)	17 (52)	6 (37)	0.357
Occupation-n (%)				
Agricultural worker	13 (27)	9 (27)	4 (25)	0.867
Employee	11 (22)	8 (24)	3 (19)	0.669
Retired	25 (51)	16 (49)	9 (56)	0.610
Smokers-n (%)	18 (37)	11 (33)	7 (44)	0.478
Chronic systemic diseases-n (%)	36 (73%)	22 (67)	14 (88)	0.174
Hypertension	22 (45%)	13 (39)	9 (56)	0.266
Chronic heart disease	16 (33%)	10 (30)	6 (38)	0.614
Diabetes	11 (22%)	6 (18)	5 (31)	0.456
Chronic obstructive pulmonary disease	11 (22%)	8 (24)	3 (19)	1.000
Cerebrovascular disease	9 (18%)	4 (12)	5 (31)	0.130
Chronic liver disease	5 (10%)	4 (12)	1 (6)	1.000
Chronic renal disease	2 (4%)	1 (3)	1 (6)	1.000
Malignancy	2 (4%)	1 (3)	1 (6)	1.000
Two or more of the above diseases	28 (57)	15 (45)	13 (81)	0.018
Days from disease onset to admission-days	7.0 (4.5-10.0)	6.0 (4.0-10.0)	8.0 (6.3-10.8)	0.534
Days from admission to critical condition-days	4.0 (2.5-8.0)	6.0 (3.5-8.5)	2.5 (1.0-4.0)	0.001

Data are shown as median (IQR) or n (%). P values comparing survivors and deceased are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. COVID-19, coronavirus disease 2019; IQR, interquartile range

clinical symptoms with typical changes in chest CT and positive for the nucleic acids of SARS-CoV-2. Severity of COVID-19 was defined according to the diagnostic and treatment guideline for SARS-CoV-2 issued by Chinese National Health Committee (version 3-6). Critically ill patients with COVID-19 was designated when the patients had one of the following criteria: (a) respiratory failure with mechanical ventilation; (b) shock; (c) combination with other organ failure, with ICU monitoring and treatment.

Data collection

Epidemiological, demographic, clinical, laboratory, and medical imaging data from patients' medical records were collected by Qi Liu and Liangfei Deng who is a doctor of critical medicine and rush to the rescue of Dabie Mountain Medical Center on February 1, 2020. If data were missing from the records or clarification was needed, we obtained data by direct communication with attending doctors and patients or their families. The nucleic acid testing for SARS-CoV-2 was performed using quantitative RT-PCR on samples from the respiratory tract by Huanggang CDC and Xiaogan CDC, which are the designated laboratory for SARS-CoV-2 test.

Statistical analysis

Categorical data were expressed as number (%) and evaluated by

χ^2 or Fisher's exact test; continuous data were expressed as median (Interquartile Range (IQR)) and evaluated by Mann-Whitney U test. To explore the risk factors associated with death of critically ill patients, a multivariable logistic regression model was used. A two-sided α of less than 0.05 was considered statistically significant. All the statistical analyses were performed with SPSS (version 26.0).

Results

Demographics and clinical characteristics

A total of 49 critically ill patients with COVID-19, who all were admitted to Intensive Care Unit (ICU) and required oxygen therapy, were included in this study (32 men, 17 women), with median age of 63 years (IQR 53-73). 33 patients discharged and 16 patients were deceased. Among them, there were 26 patients with familiar/cluster exposure history and 23 cases with community exposure history. 73% patients had comorbid chronic systemic diseases, including hypertension (45%), chronic heart disease (33%), diabetes (22%), chronic obstructive pulmonary disease (22%), cerebrovascular disease (18%), chronic liver disease (10%), chronic renal disease (4%), and malignant tumor (4%), of who 57% patients had two or more of the comorbidities. The median intervals from disease onset to admission and from admission to critical condition were 7.0 days (IQR 4.5-

Table 2: Clinical manifestations of critically ill patients with 2019-nCoV pneumonia.

	All patients (n=49)	Survivors (n=33)	Deceased (n=16)	P-value
Fever-n (%)	40 (82)	28 (85)	12 (75)	0.449
Cough-n (%)	39 (80)	27 (82)	12 (75)	0.709
Fatigue-n (%)	28 (57)	21 (64)	7 (44)	0.187
Muscle ache-n (%)	9 (18)	5 (15)	4 (25)	0.449
Headache-n (%)	5 (10)	2 (6)	3 (19)	0.313
Sore throa-n (%)t	4 (8)	2 (6)	2 (13)	0.588
Chill-n (%)	3 (6)	1 (3)	2 (13)	0.245
Chest tightness/dyspnea-n (%)	22 (45)	13 (39)	9 (56)	0.266
Gastrointestinal symptoms-n (%)	23 (47)	10 (30)	12 (75)	0.003
Nausea or vomiting	15 (31)	8 (24)	7 (44)	0.198
Diarrhea	11 (22)	5 (15)	6 (38)	0.141
Anorexia	8 (16)	3 (9)	5 (31)	0.094
Abdominal pain	3 (6)	1 (3)	2 (13)	0.245

Data are shown as n (%). P values comparing survivors and deceased are from χ^2 test, or Fisher's exact test. COVID-19, coronavirus disease 2019; IQR, interquartile range

10.0) and 4.0 days (IQR 2.5-8.0), respectively. The deceased patients were more often associated with two or more of comorbidities and shorter time from admission to critical condition compared with the survivors, whereas there were no significant differences between the survivors and deceased groups with respect to age, sex, exposure history, occupation, smokers etc (Table 1).

The most common symptoms at disease onset were fever (82%), cough (76%), fatigue (57%), gastrointestinal symptoms (47%), and Chest tightness/dyspnea (45%). Gastrointestinal symptoms included nausea or vomiting (31%), diarrhea (22%), anorexia (16%), and abdominal pain (6%). The gastrointestinal symptoms were more common in the deceased patients compared with the survivors, whereas there were no significant differences between the survivors and deceased groups about the other symptoms (Table 2).

Laboratory and imaging findings

On admission, leucocytes were within the normal range in most of the patients (59%), with 35% increased and 6% decreased numbers. Neutrophils were above the normal range in 39% patients, and nearly half of patients (47%) had increased neutrophil percentage. Lymphopenia was common, and lymphocytes and lymphocyte percentage were below the normal range in 71% and 65% of the patients, respectively. Platelets and haemoglobin were below the normal range in 20% patients and 45% patients, respectively. Most patients had increased levels of C-Reactive Protein (CRP) (86% cases) and Procalcitonin (PCT) (55% cases), with median CRP level 37.4mg/L (IQR 16.0-62.4) and median PCT level 0.6 ng/mL (IQR 0.1-3.8) (Table 3).

On admission, most patients showed normal prothrombin time, and all patients showed normal activated partial thromboplastin time. D-dimer level was above the normal range in 59% patients, with median D-dimer level 0.6 μ g /mL (IQR 0.2-1.3) (Table 3).

The median Fasting Blood Glucose (FBG) level of the patients was 6.9mmol/L (IQR 5.7-9.7), with FBG \geq 7.0 mmol/L in 49% patients on admission. The patients had liver function abnormality, with 57%

decreased albumin level, 8% increased Alanine Aminotransferase (ALT) or 14% increased Aspartate Aminotransferase (AST) level, and 22% increased total bilirubin level. The patients had abnormal myocardial zymogram, which showed the elevation of Creatine Kinase (CK) in 31% patients, the elevation of MB isoenzyme of Creatine Kinase (CKMB) in 16% patients, and the elevation of Lactate Dehydrogenase (LDH) in 76% patients. The patients had renal function damage, with elevated blood urea nitrogen in 22% patients and elevated serum creatinine in 22% patients (Table 3).

On admission, all patients showed bilateral viral pneumonia in chest CT images. The representative chest CT findings of a deceased patient and a discharged patient showed bilateral ground glass opacity (Table 3 and Supplementary Figure 1).

The deceased patients had higher median neutrophil percentage, lower median lymphocytes and lymphocyte percentage, higher median C-reactive protein level and procalcitonin level, higher median fasting blood glucose level, and higher median lactate dehydrogenase level compared with the survivors, whereas there were no significant differences between the survivors and deceased groups concerning the other blood routine, coagulation function, other blood biochemistry parameters (Table 3).

Treatment regimen

According to the diagnostic and treatment guideline for COVID-19 issued by Chinese National Health Committee (version 3-6), all patients received antiviral therapy, including combination of interferon- α (5 million U, twice daily, inhalationally) and lopinavir/ritonavir tablets (500mg, twice daily, orally) or combination of interferon- α (5 million U, twice daily, inhalationally and abidol (200mg, three times daily, orally). The duration of treatment was 4-10 days. 61% patients were given corticosteroid treatment (methylprednisolone or dexamethasone) for 4-7 days. 49% patients were administered with empirical antibiotic treatment (cephalosporins, quinolones, or carbapenems) for 5-12 days. 4 (8.2%) patients were also treated with antifungal drugs (voriconazole) (Supplementary Table 1).

Table 3: Laboratory characteristics of critically ill patients with with COVID-19.

	All patients (n=49)	Survivors (n=33)	Deceased (n=16)	P-value
Blood routine				
Leucocytes ($\times 10^9/L$; normal range 3.5-9.8)	5.8 (4.1-10.1)	5.5 (4.2-9.8)	10.3 (3.7-14.7)	0.277
Increased-n (%)	17 (35)	9 (27)	8 (50)	0.117
Decreased-n (%)	3 (6)	2 (6)	1 (6)	1.000
Neutrophils ($\times 10^9/L$; normal range 1.8-6.3)	4.1 (2.8-9.5)	3.9 (2.7-6.0)	9.5 (3.0-13.5)	0.050
Increased-n (%)	19 (39)	10 (30)	9 (56)	0.08
Neutrophil percentage-(%) (normal range 40-75)	74.6 (65.6-87.6)	70.3 (61.4-78.7)	88.8 (82.3-93.0)	0.000
Increased-n (%)	23 (47)	10 (30)	13 (81)	0.001
Lymphocytes ($\times 10^9/L$; normal range 1.1-3.2)	0.8 (0.6-1.4)	1.0 (0.7-1.6)	0.6 (0.4-0.8)	0.002
Decreased-n (%)	35 (71)	20 (61)	15 (94)	0.019
Lymphocyte percentage-(%) (normal range 20-50)	15.6(8.7-25.1)	19.8 (11.3-26.6)	8.7 (3.4-11.7)	0.000
Decreased-n (%)	32 (65)	17 (52)	15 (94)	0.004
Platelets ($\times 10^9/L$; normal range 125-350)	178 (131-226)	130 (115-145)	147 (120-201)	0.150
Decreased-n (%)	10 (20)	6 (18)	4 (25)	0.709
Haemoglobin (normal range 115-150 g/L)	131 (115-145)	130 (115-145)	134 (113-146)	0.991
Decreased-n (%)	22 (45)	16 (48)	6 (38)	0.468
Infection biomarkers				
C-reactive protein (mg/L; normal range 0.0-8.0)	37.4 (16.0-62.4)	31.2 (10.0-56.0)	58.3 (26.7-90.0)	0.047
Increased-n (%)	42 (86)	27 (82)	15 (94)	0.402
Procalcitonin (ng/mL; normal range 0.0-0.5)	0.6 (0.1-3.8)	0.2 (0.1-1.2)	3.0 (0.6-7.5)	0.004
Increased-n (%)	27 (55)	14 (42)	13 (81)	0.010
Coagulation function				
Prothrombin time (s; normal range 9.0-15.0)	13.2 (12.2-14.2)	13.2 (11.8-13.9)	13.7 (13.0-14.5)	0.088
Increased-n (%)	7 (14)	4 (12)	3 (19)	0.668
Activated partial thromboplastin time (s; normal range 22.0-45.0)	30.3 (28.2-33.0)	30.3 (28.6-32.4)	31.2 (26.1-35.6)	0.749
D-dimer ($\mu g/mL$; normal range 0.0-0.5)	0.6 (0.2-1.3)	0.6 (0.2-1.1)	0.8 (0.1-2.2)	0.654
Increased-n (%)	29 (59)	19 (58)	10 (63)	0.742
Blood biochemistry				
Fasting blood glucose (mmol/L; normal range 3.9-6.1)	6.9 (5.7-9.7)	6.1 (5.3-7.9)	8.3 (7.1-12.7)	0.003
Increased (≥ 7.0 mmol/L)-n (%)	24 (49)	11(33)	13 (81)	0.002
Albumin (g/L; normal range 35.0-52.0)	34.1(29.5-37.7)	34.7 (29.2-39.2)	33.7 (29.8-36.8)	0.587
Decreased-n (%)	28 (57)	17 (52)	11 (69)	0.253
Alanine aminotransferase (U/L; normal range 9-50)	20.0 (14.5-33.0)	19.0 (1.5-32.5)	21.5 (14.0-36.8)	0.579
Increased-n (%)	4 (8)	3 (9)	1 (6)	1.000
Aspartate aminotransferase (U/L; normal range 15-40)	23.0 (1.08-34.9)	22.0 (18.0-34.5)	26.5 (17.7-35.3)	0.685
Increased-n (%)	7 (14)	5 (15)	2 (13)	1.000
Total bilirubin ($\mu mol/L$; normal range 5.1-23.0)	14.4 (9.3-22.1)	13.5 (8.8-19.0)	15.2 (10.8-32.8)	0.365
Increased-n (%)	11(22)	5 (15)	6 (38)	0.141
Creatine kinase (U/L; normal range 26-174)	113.0 (58.5-196.0)	108.0 (58.5-191.0)	118.5 (58.3-225.8)	0.550
Increased-n (%)	15 (31)	10 (30)	5 (31)	0.946
Creatine kinase-MB (U/L; normal range 3-25)	13.5(9.0-23.2)	12.1 (8.4-27.0)	16.4 (10.1-22.5)	0.354
Increased-n (%)	8 (16)	5 (15)	3 (19)	1.000
Lactate dehydrogenase (U/L; normal range 109-245)	315.6 (216.5-449.0)	268.6 (201.6-367.6)	443.4 (279.7-528.5)	0.016
Increased-n (%)	37 (76)	23 (70)	14 (88)	0.290

Serum creatinine ($\mu\text{mol/L}$; normal range 32-106)	69.5(61.0-96.4)	68.9 (57.7-88.0)	86.6 (64.3-112.5)	0.147
Increased-n (%)	11 (22)	6 (18)	5 (31)	0.466
Blood urea nitrogen (mmol/L; normal range 1.5-7.5)	5.5 (4.4-7.1)	5.5 (4.4-7.1)	5.4 (4.5-9.7)	0.815
Increased-n (%)	11 (22)	7 (21)	4 (25)	1.000
Bilateral involvement of chest CT images-n (%)	49 (100)	33 (100)	16 (100)	-

Data are shown as median (IQR) or n (%). P values comparing survivors and deceased are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. COVID-19, coronavirus disease 2019; IQR, interquartile range

All patients received respiratory support for 5-18 days, with 45% non-invasive ventilation and 55% invasive ventilation, of whom, a patient was given combination of invasive ventilation and Extracorporeal Membrane Oxygenation (ECMO). 4 patients treated with Continuous Renal Replacement Therapy (CRRT) in deceased patients. Moreover, 90% patients were administered with traditional Chinese medicine (Lianhua Qingwen granules orcapsules). There were no significant differences between the survivors and deceased groups about the above treatment regimens except for CRRT (Supplementary Table 1).

The independent risk factors for poor prognosis

To investigate the risk factors for poor prognosis in our cohort of 49 critically ill patients with SARS-CoV-2 infection, we performed a multivariable logistic regression analysis by the forward method using clinical manifestations and laboratory parameters which showed significant differences between the survivors and deceased groups. The result indicated that gastrointestinal symptoms, decreased lymphocytes, and increased fasting blood glucose were the independent risk factors for death of critically ill patients (Table 4).

Discussion

According to the diagnostic and treatment guideline for COVID-19 issued by Chinese National Health Committee (version 3-6) (<http://www.nhc.gov.cn/>), the clinical classification of severity of COVID-19 includes into four types: mild, common, severe, and critical. In this study, we reported clinical features of 49 critically ill patients with COVID-19 confirmed by clinical and laboratory results, who needed mechanical ventilation therapy in ICU. These patients came from Huanggang City and Xiaogan City, Hubei Province, 80-90 kms away from Wuhan, who may be second or third generation cases by humantohuman transmission of SARS-CoV-2.

In our cohort, 33% (16) patients were deceased, and the mortality was lower than that of the first generation cases reported by Huang et al. in Wuhan, who showed that 38% (5 cases) died in 13 ICU patients with SARS-CoV-2 pneumonia. The median time from admission to critical condition were 4 days, which was longer than that (2 days) between hospital admission and ARDS by reported by Huang et al. [8]. The deceased patients had shorter median time from admission to critical condition compared with the survivors. These findings suggest that pathogenicity of SARS-CoV-2 seem to decrease with the increase of its generations, and the shorter the time from admission to critical condition, the more serious the illness. 65% of the patients were male, and this percentage was also lower than that of ICU patients (85%) reported by Huang et al. [8]. The median age of all patients was 63 years, which was older than those reported by Chen et al (55.5 years) [7], Huang et al. (49 years) [8], Wang et al (56 years) [9], Liu et al. (57 years) [11], and Zhang et al. (57 years) [12]. In our

Table 4: Multivariable logistic regression analysis.

Variables	P-value	OR	95% CI
Gastrointestinal symptoms (≥ 1 symptoms)	0.009	13.4	1.9-94.8
Lymphocytes ($< 1.1 \times 10^9/\text{L}$)	0.020	25.5	1.6-394
Fasting blood glucose (≥ 7.0 mmol/L)	0.016	11.7	1.6-85.5

study, 73% (36) patients had comorbid chronic systemic diseases, and hypertension (45%), chronic heart disease (33%), diabetes (22%), and chronic obstructive pulmonary disease (22%) were the most common comorbidities, whose percentages were higher than those of other reports [7-9, 11,12]. These discrepancies may be due to 100% of critical COVID-19 patients in our series. Importantly, we found that the percentage of two or more of comorbid chronic systemic diseases in the deceased patients was higher than that in the survivors, which was consistent with the report by Guan et al. who have verified the significantly escalated risk of poor prognosis in patients with two or more comorbidities as compared with those who had no or only a single comorbidity [13].

In the present study, the most common symptoms included fever (82%), cough (76%), fatigue (57%), and Chest tightness/dyspnea (45%), which was in accordance with the previous reports [10-15]. Moreover, it was noteworthy that the incidence of gastrointestinal symptoms was 47% in our cohort, including nausea or vomiting (31%), diarrhea (22%), anorexia (16%), and abdominal pain (6%), and gastrointestinal symptoms were more common in the deceased patients than that in the survivors. Consistent with our result, Zhang et al. showed that gastrointestinal symptoms were observed in 39.6% of the patients, and 42.1% of the severe patients with COVID-19 [12]; Wang et al found that more than 60% of the patients with COVID-19 had gastrointestinal symptoms, and the gastrointestinal symptoms were more common in the ICU patients than those in the non-ICU patients [9]; of patients with COVID-19 with gastrointestinal symptoms, 30% had severe/critical types, significantly higher than those without gastrointestinal symptoms (8%) [16]. These results suggest that gastrointestinal symptoms are a potential indicator for severity of COVID-19.

In our cohort, abnormal blood routine results mainly included decreased lymphocytes and lymphocyte percentage, and increased neutrophil percentage. Noticeably, abnormalities of the above parameters were more prominent in the deceased patients than those in the survivors. Infection biomarkers showed that increased level of CRP and PCT was found in 86% and 55% of the patients, respectively, and the level of CRP and PCT was higher in the deceased patients compared with the survivors. These changes of CRP and PCT may represent more prominent inflammation, whereas higher neutrophil percentage and PCT may be due to more significant secondary bacterial infection in the deceased patients. Numerous studies have

showed that lymphopenia is common in patients with COVID-19 [7-12, 14]. Huang et al showed that lymphopenia was more prominent in the ICU patients than that in the non-ICU patients [8]; Zhang et al. reported that lymphocyte percentage was lower in severe patients compared with nonsevere patients [12].

Increased neutrophil has been rarely reported in patients with COVID-19. Huang et al showed that the median neutrophil count was significantly higher in the ICU patients than that in the non-ICU patients [8]; Chen et al indicated that increased neutrophils was found in 38% of the patients with COVID-19 [7]. Increased level CRP is often reported in recent studies about COVID-19 [7,11,12], whereas increased PCT is rarely observed [12]. Zhang et al reported CRP and PCT concentrations were significantly higher in severe patients with COVID-19 compared with nonsevere patients with COVID-19; Chen et al found that PCT level > 0.5ng/mL was one of independent risk factors associated with fatal outcome in patients with COVID-19 [14]. The above findings were roughly consistent with our results.

Significant abnormal blood biochemistry findings were increased FBG \geq 7.0mmol/L, decreased albumin, and increased LDH levels, whereas other liver function, myocardial zymogram, and renal function indexes were within the normal range in most of the patients. In addition, the level of FBG and LDH was higher in the deceased patients than that in the survivors. Increased LDH level is common in patients with COVID-19 [7-10,17]. Two reports indicated that LDH level was higher in the ICU patients than that in the non-ICU patients [8,9]. Few studies have reported hyperglycemia in patients with SARS-CoV-2 infection. Chen et al showed that increased FBG was found in 52% of the patients with 2019-nCoV infection [7]; Li et al reported that hyperglycemia (>7.1 mmol/L under fasting state) was detected in 56.5% (13/23) severe cases with COVID-19 and 21.4% (9/42) mild cases with COVID-19 [18]. The above results suggest that higher FBG and LDH levels are the important laboratory indexes for patients with COVID-19.

In our cohort of 49 critically ill patients with COVID-19, all patients showed bilateral viral pneumonia in chest CT images, and there were no significant differences in treatment regimens between the deceased patients and the survivors, including antiviral treatment, corticosteroid treatment, antibacterial treatment, antifungal treatment, respiratory support, and traditional chinese medicine, which were consistent with the other reports [7-12].

In our study, some independent risk factors for fatal outcome were found by using a multivariable logistic regression analysis. Gastrointestinal symptoms, decreased lymphocytes, and increased FBG were the independent predictive factors for death of critically ill patients with COVID-19.

The multi-organ nature of COVID-19 has been demonstrated in a latest autopsy studies [19]. The sequence of SARS-CoV-2 receptor-binding domain is similar to SARS-CoV, and Angiotensin-Converting Enzyme 2 (ACE2) is its receptor. ACE2 is highly expressed not only in the lung, but also in other organs including the heart, the kidney, and the gastrointestinal tract [20-25]. SARS-CoV-2 may mediate the invasion into gastrointestinal epithelium cells by binding to ACE2 receptor, leading to malabsorption, unbalanced intestinal secretion and activated enteric nervous system, in turn resulting in

gastrointestinal symptoms and electrolyte disturbance [16,20,22]. In this way, the patients with gastrointestinal symptoms trend towards the critical type of the disease and a poor prognosis [16].

SARS-CoV-2 might mainly act on lymphocytes, especially T lymphocytes like SARSCoV. The virus induces a cytokine storm, generates a series of immune responses, and consumes many immune cells that results in the decrease in lymphocytes and cellular immune deficiency [7,9]. Damage to T lymphocytes might be an important factor leading to exacerbations of the patients [26].

Hyperglycemia caused by respiratory pathogenic virus infection has been reported. SARSCoV causes acute pancreatic islet injury by binding to ACE2 receptor, resulting in hyperglycemia in patients with SARSCoV infection [27]; the report by Wang et al indicated that high FBG is an independent predictor for severity of H1N1 pneumonia [28]. Therefore, it is reasonable to think that SARS-CoV-2 may invade islet cells through ACE2 receptor and causes hyperglycemia. Increased glucose level inhibits T lymphocyte proliferation, which aggravates lymphopenia and cellular immune dysfunction leading to the deterioration of the disease [29,30]. Indeed, Jin et al. showed that increased glucose level was the independent risk factors for severe/critical COVID-19 in patients with gastrointestinal symptoms [16], which is similar to our result. Thus, high attention should be paid to rescue this process to prevent the further deterioration of COVID-19.

Our study has several limitations. First, the sample size of this study is small. Second, although the risk factors for death of critically ill patients with COVID-19 were identified according to the data on admission, there is still a lack of a predictive model for disease progression. Third, cytokine storm is found in the disease [8]; thus, it would be better if cytokine changes were detected in this study.

Conclusion

In this study, we reported for the first time that COVID-19 patients with more than 60 years old of age and two or more comorbidities are more likely to develop to fatally critical condition, and gastrointestinal symptoms, decreased lymphocytes, and increased FBG are the independent risk factors for death of critically ill patients with COVID-19. The early identification of these risk factors is urgently necessary to facilitate appropriate intensive care.

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Authors' Contributions

Xiaojuan Peng, Yanfang Chen, Liangfei Deng, Qi Liu, and Qing Li contributed equally to this paper. Xiaojuan Peng, Yanfang Chen, and Qing Li helped design the study, analyzed the study data, helped draft the manuscript, made critical revisions of the manuscript, and provided final approval of the version. Liangfei Deng and Qi Liu helped design the study, acquired epidemiological, demographic, clinical, and laboratory data, analyzed the study data, made critical revisions of the manuscript, and provided final approval of the version. Jie Xiong and Ying Shi analyzed the study data, helped draft the manuscript, and provided final approval of the version. Shaohui Tang designed the study, analyzed study data, drafted the manuscript,

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Availability of Data and Materials

Data sharing will be considered only on a collaborative basis with the principal investigators, after evaluation of the proposed study protocol and statistical analysis plan.

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