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Clinical features and risk factors for severe-critically ill COVID-19 adult patients in Jiangsu, China

A multiple-centered, retrospective study

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Abstract

Coronavirus disease 2019 (COVID-19) becomes a global pandemic in 2020. Early identification of severe ill patients is a top priority for clinicians. We aimed to describe clinical features and risk factors of severe-critically ill patients with COVID-19 in Jiangsu Province.

This multi-centered retrospective study collected the information of 631 laboratory-confirmed COVID-19 patients hospitalized at 28 authorized hospitals in Jiangsu province from January 23, 2019 to March 13, 2020.

A total of 583 adult patients with laboratory-confirmed COVID-19 were enrolled for final analysis, including 84 severe-critically ill patients and 499 mild-moderate patients. Median age of the severe-critically ill patients was 57.0 years old (interquartile range, 49.0–65.8), and 50 (59.5%) were males. Multisystemic laboratory abnormalities were observed on admission for severe-critically ill patients. These patients showed more noticeable radiologic abnormalities and more coexisting health issues as compared to the mild-moderate patients. Most of the severe-critically ill COVID-19 patients became deteriorated in 2 weeks after diagnosis. Age, D-dimer, and lymphocytes were independently associated with the progression of severe-critically illness.

Older age, higher D-dimer levels and less lymphocyte counts on admission are potential risk factors for COVID-19 patients to develop into severe and critically illness.

Abbreviations: ALT = alanine aminotransferase, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, AUC = areas under the curves, CI = confidence interval, COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease 2019, IQR = interquartile range, LDH = lactose dehydrogenase, MV = mechanical ventilation, PT = prothrombin time, ROC = receiver operating characteristic.

Keywords: coronavirus, coronavirus disease 2019, critically ill, risk factor, severe

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the most recently detected novel coronavirus, called SARS-CoV-2.[1] This coronavirus and disease remained unknown until its outbreak in Wuhan, China, in December 2019. An exponential growth of cases and its expanding transmission have raised international concerns. This disease has caused 10,710,005 infections and 517,877 deaths in the world as of July

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The datasets generated during and/or analyzed during the current study are publicly available.

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03, 2020.[2] At present, COVID-19 is a pandemic infectious disease recognized by the World Health Organization.[3]

So far, the transmission of COVID-19 almost ceased in China. Of the exceeding 80,000 reported cases in China, more than 90% have recovered and been discharged. Several studies have described the clinical characteristics and mortality of the COVID-19.[4–7] The disease can rapidly develop into severe pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure, and even death. The early identification of patients with severe-critically illness is a key point to provide correct treatments. Although multiple studies have reported the epidemiology, clinical features, and outcomes of COVID-19 patients with severe illness, the results differed from region to region.[7–11]

The first case of SARS-CoV-2 infection in Jiangsu province was found on January 22, 2020. By February 19, a total of 631 laboratory-confirmed local cases have been reported in Jiangsu province. From February 19 to March 30, no more local COVID-19 patient was reported. All of these 631 COVID-19 patients have been cured and discharged on March 14. At present, no specific information for clinicians to identify severely ill patients and risk factors for these patients in Jiangsu was reported. The objective of this study is to characterize the clinical characteristics of severely afflicted patients in Jiangsu province and to reveal the potential high-risk factors associated with serious illness.

2. Materials and methods

2.1. Study design and participants

Patients included in the study were recruited in Jiangsu province (30°45'–35°20' N, 116°18'–121°57' E) with an area of 107,200 km^2. This province consists of 13 municipalities and 96 counties (districts), and there are 80.70 million inhabitants at the end of 2019. Currently, 28 hospitals were authorized to accept and treat patients with COVID-19 and 541 medical institutions have fever clinics across Jiangsu. This multiple-centered, retrospective study was done at these 28 hospitals (Jiangsu, China). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Zhongda Hospital Affiliated to Southeast University (No. 2020ZDSYLL013–P01 and 2020ZDSYLL019–P01). A waiver of written informed consent was granted by the ethics commission due to emerging infectious disease.

Patients aged 18 years or older were admitted if their diagnostic specimen were positive on reverse-transcriptase-polymerase-chain-reaction assay for SARS-CoV-2. The clinical spectrums are categorized into mild to critically ill according to COVID-19 guidelines (the seventh version) made by National Health Commission of the People's Republic of China.[12] The mild ill patients had mild symptoms and normal radiological images in both lungs. The moderate ill patients had fever, cough, and other typical respiratory symptoms and radiological lung images suggesting pneumonia. The severe ill patients had any one of the following conditions, respiratory rates $\geq$ 30 per minute, pulse oxygen saturation $\leq$ 93% on ambient air, and partial pressure of oxygen/fraction of inspired oxygen $\leq$ 300 mm Hg. The critically ill patients had any one of the following conditions: respiratory failure in need of invasive ventilation, signs of shock, and failure of any other organ when ICU care is necessary. The patients were divided into 2 groups, study group that includes severe-critically ill patients, and the control group that includes mild-moderate patients.

2.2. Data collection

The epidemiological information, medical history, exposure history, clinical characteristics, laboratory results, comorbidities, radiological features, therapies, and outcomes of the COVID-19 patients were extracted from the electronic medical records between January 22 and March 11, 2020. Any data missing or ambiguousness will be asked from the involved health-care providers who subsequently will collect or communicate with patients' families.

We collected data about age, gender, smoking history, exposure history, coexisting disorders (hypertension, diabetes, chronic obstructive pulmonary disease (COPD), coronary heart disease, cerebrovascular disease, chronic renal diseases, hyperlipidemia, hepatitis B infection, connective tissue disease, cancer, pregnancy), symptoms and signs on admission (fever, cough, sputum production, hemoptysis, shortness of breath, sore throat, nasal congestion, rhinorrhea, headache, chest pain, fatigue, nausea, vomiting, diarrhea, mylgia, arthralgia, chill, throat congestion), radiographic imagings, laboratory test results (leukocyte, lymphocyte, neutrophils, platelet, hemoglobin, C-reactive protein (CRP), procalcitonin, lactose dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatine kinase (CK), urea nitrogen, creatinine, D-dimer, prothrombin time (PT), activated partial thromboplastin time, odium, potassium), complications (sepsis, septic shock, respiratory failure, ARDS, acute kidney injury, acute cardiac injury, secondary infections), and treatment (antiviral drugs, antibiotics, antifungal administration, systemic corticosteroids, oxygen therapy, mechanical ventilation (MV), extracorporeal membrane oxygenation, renal replacement therapy, and intravenous immunoglobin). For severe-critically ill patients, the acute physiology and chronic health evaluation II score and sequential organ failure assessment were determined to assess disease severity.

2.3. Definition

ARDS was diagnosed according to the Berlin definition.[13] Sepsis and septic shock were defined according to the third international consensus definition for sepsis and septic shock (sepsis-3) criteria.[14] Acute cardiac injury was diagnosed when serum levels of high-sensitive cardiac troponin I were above the 99th percentile upper reference limit.[4] Acute kidney injury was identified on the basis of the highest serum creatinine level and urine output.[15] Secondary infection was diagnosed when patients showed clinical symptoms or signs of hospital-acquired pneumonia or bacteraemia combined with a positive culture of a new pathogen from lower respiratory tract specimens (sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples obtained at least 48 hours after admission.[4] The date of disease onset was defined as the day when the symptom was first noticed. The changes in disease status from onset to hospital admission, severe disease, critically ill disease, and discharge were recorded.

2.4. Statistical analysis

Categorical variables were sorted according to frequencies and percentages, and then analyzed with Pearson Chi-squared test or Fisher exact test as appropriate. Continuous variables were described as median and 25%, 75% quartiles [median interquartile range (IQR)], and analyzed using *t* tests or Mann–Whitney test as

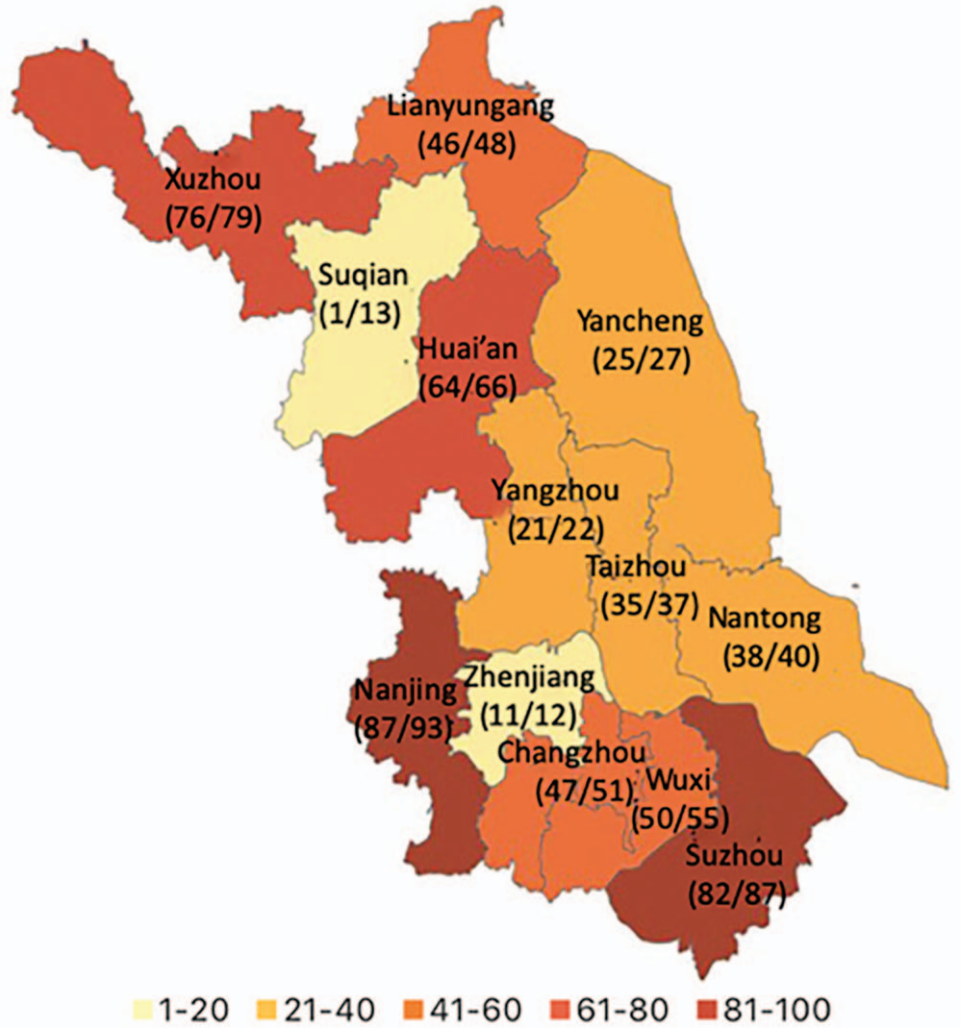

Figure 1. Distribution of local laboratory-confirmed coronavirus disease 2019 patients across Jiangsu Province. The numerator represents the number of patients finally included in the study, and the denominator represents the number of local confirmed patients in the 13 municipalities, according to the National Health Commission as March 31, 2020.

appropriate. Univariable and multivariable logistic regression models were used to assess the risk factors associated with severe-critically ill cases. To assess the discriminatory ability of the model, receiver-operating characteristic (ROC) curves were prepared, and the areas under the ROC curves (AUCs) were determined. Statistical analyses were performed using the SPSS (version 25.0; SPSS Inc., Chicago, IL) and GraphPad Prism (version 8.0, Graphpad Software, San Diego, CA, USA). $P < .05$ was considered as statistically significant.

3. Results

3.1. Demographic characteristics, clinical symptoms, and comorbidities

There were 631 hospitalized patients with COVID-19 in Jiangsu as of March 14, 2020. After excluding 14 patients without medical records and 34 patients below 18 years old, finally 583 adult patients from the 28 authorized hospitals were included in the present study (Fig. 1). In particular, 76 (13.0%) cases of mild, 423 (72.6%) moderate, 49 (8.4%) severe, and 35 (6.0%) critically ill were analyzed (Fig. 2).

Of those patients, 84 patients were assigned to the study group and 499 into the control group, respectively. The median age of the severe-critically ill patients was 57.0 (IQR 49.0–65.7) years (Table 1), whereas that of the mild-moderate ill patients was 47.0 (IQR 33.0–56.0) years. The median age of the former was significantly older than the later ($P < .001$). Patients at 50 years or older accounted for a higher proportion of the severe-critically ill patients (70.2% vs 40.3%). Among the severe-critically ill patients, 58.3% of them were males. No gender biased difference of COVID-19 was found between 2 groups. The smoking history was also similar in both groups.

In the severe-critically ill patients, the most frequently observed symptoms were fever (69.0%) and cough (57.1%) (Table 1). Other common symptoms included fatigue (38.1%), shortness of breath (31%), and sputum (23.8%). The severe-critically ill patients had a significantly higher percentage of shortness of breath than the control group (31% vs 7.4%, $P < .001$). The severe-critically ill patients tended to have coexisting diseases, and 57.1% (48/84) of them had 1 or more coexisting diseases (Table 1). The most common coexisting health issues for the severe-critically ill patients were hypertension (32.1%) and

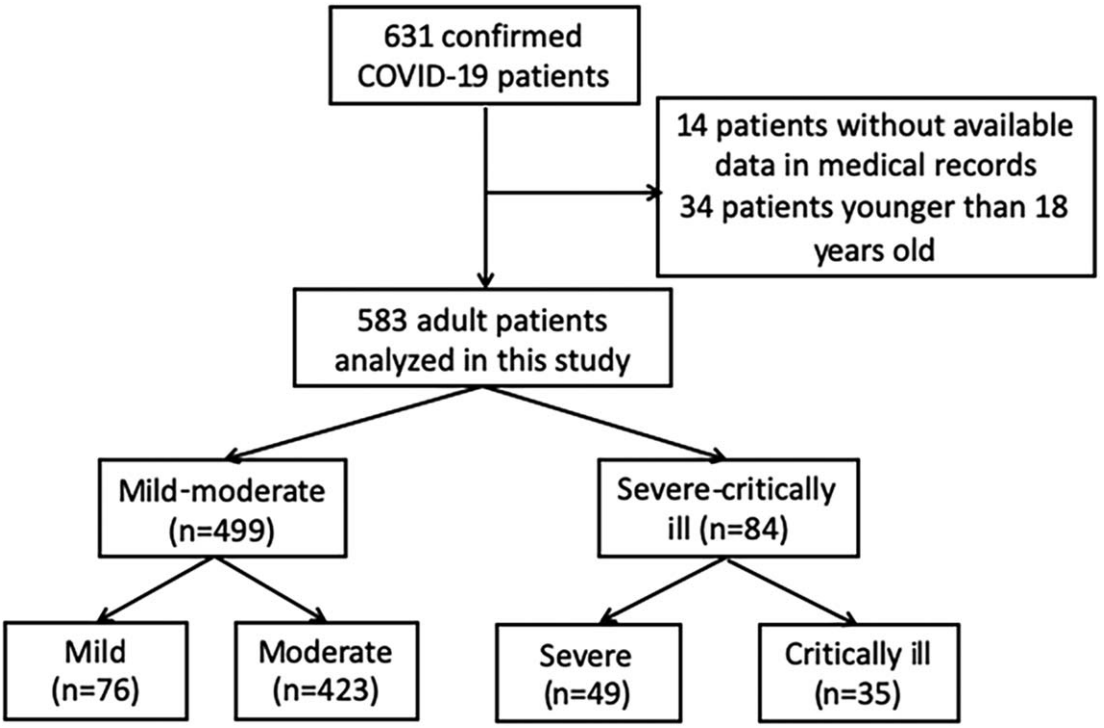

Figure 2. Flow chart for patients' enrollment in the study.

diabetes (29.8%). Compared with the mild-moderate patients, the severe-critically ill patients were more likely to suffer from coexisting diseases, including hypertension, diabetes, COPD, coronary heart disease, cerebrovascular disease, and cancer.

3.2. Radiological and laboratory examinations

All of the severe-critically ill patients had radiologic abnormalities on chest imaging, which were significantly more prominent than the mild-moderate patients ($P < .001$) (Table 2). 79.8% (67/84) of the severe-critically ill patients showed bilateral pneumonia, while only 58.3% (293/499) of the mild-moderate patients showed bilateral involvement ($P < .001$). Figure 3 shows CT findings of severe type confirmed COVID-19 pneumonia.

As shown in Table 2, there were numerous differences in laboratory findings between the mild-moderate and severe-critically ill patients. 86.9% (73/84) of the severe-critically ill patients had lymphopenia (lymphocyte counts $\leq 1.5 \times 10^9$/L) on admission, and the median lymphocyte counts of the severe-critically ill patients were significantly lower than those of the mild-moderate patients ($P = .022$). Hemoglobin levels, platelet counts and albumin values of severe-critically ill patients at admission were all lower than the mild moderate ill patients. The levels of ALT, AST, LDH, CRP, ESR, D-dimer, PT, and fibrinogen were all significantly higher in the severe-critically ill patients than the mild-moderate patients.

3.3. Complications, treatments and timeline of the disease progression

During hospitalization, the complications in severe-critically ill patients included respiratory failure (49, 58.3%), ARDS (12, 14.3%), secondary infection (14, 16.7%), acute renal injury (5, 6.0%), sepsis (74, 88.1%) and septic shock (5, 5.9%) (Table 3). The median Acute Physiology and Chronic Health Evaluation II and sequential organ failure assessment scores were 15 (12.5–18) and 4.5 (3.0–7.0), respectively.

In short, oxygen therapy, MV, renal replacement therapy, antibacterial agents, antifungal agents, systemic corticosteroids, and intravenous immunoglobin were administrated to 100%, 41.7%, 3.6%, 83.3%, 15.5%, 51.2%, and 26.2% of the severe-critically ill patients, respectively (Table 3). Of the 35 patients who received MV, 23 received non-invasive MV and 12 received invasive MV. In addition, 3 patients were treated with extracorporeal membrane oxygenation, and 2 underwent pulmonary transplant.

The median onset-admission interval was 5.8 (IQR 2.2–9.4) days for the severe-critically ill patients and 6.0 (IQR 2.3–10.7) days for the mild-moderate patients. There was no significant difference in the duration from symptom onset to hospital admission between these 2 groups. The mild-moderate patients had a shorter hospitalization time than the severe-critically ill patients [median (IQR), 22.0 (12.0–32.75) days vs 16.0 (9.75–25.0) days, $P = .018$]. The median time for COVID-19 to become severe disease was 7.0 (IQR, 4.0–9.5) days, and 10.0 (IQR, 7.5–12.0) days to critically ill disease.

3.4. Risk factors

Results of univariable analysis showed that the probability for the patients with shortness of breath, hypertension, diabetes, COPD, coronary heart disease, cerebrovascular disease, and cancer to develop into severe-critically illness increased. Age, bilateral patchy shadowing, lymphocytes, hemoglobin, platelet, ALT, AST, LDH, albumin, CRP, ESR, D-dimer, PT, and fibrinogen were also associated with the progression into severe-critically

Table 1

Demographic characteristics, Clinical symptoms, and Comorbidities of patients on admission.

Clinical characteristics	Severe-critically ill (n = 84)	Mild-moderate (n = 499)	*P* value
Age, yr	57.0 (49.0–65.7)	47.0 (33.0–56.0)	<.001
Age groups			<.001
<50	25 (29.8)	296 (59.3)	
50–64	37 (44.0)	146 (29.3)	
≥ 65	22 (26.2)	57 (11.4)	
Female	34 (40.5)	232 (46.5)	.306
Smokers	8 (9.5)	52 (10.4)	.802
Exposure			.447
Local residents of Wuhan	5 (5.9)	43 (8.6)	
Recently been to Wuhan	6 (7.1)	34 (6.8)	
Contacted with people from Wuhan	33 (39.3)	146 (29.3)	
Contacted with COVID-19 patients	39 (46.4)	241 (48.3)	
Unknown	1 (1.2)	35 (7.0)	
Symptoms on admission			
Fever	58 (69.0)	289 (57.9)	.054
The highest temperature (°C)			.126
<37.3	26 (31.0)	210 (42.1)	
37.3–37.5	14 (16.7)	89 (17.8)	
37.5-38	15 (17.9)	84 (16.8)	
38.1–39.0	17 (20.2)	79 (15.8)	
>39.0	12 (14.3)	37 (7.4)	
Cough	48 (57.1)	312 (62.5)	.348
Sputum	20 (23.8)	99 (20.3)	
Sore throat	6 (7.1)	39 (7.8)	.831
Nasal congestion	2 (2.4)	22 (4.4)	.557
Headache	5 (6.0)	20 (4.0)	.386
Hemoptysis	3 (3.6)	6 (1.2)	.127
Shortness of breath	26 (31.0)	37 (7.4)	<.001
Chest pain	2 (2.4)	5 (1.0)	.267
Fatigue	32 (38.1)	162 (32.5)	.311
Chill	8 (9.5)	43 (8.6)	.786
Nausea or vomiting	3 (3.6)	14 (2.8)	.723
Mylgia or arthralgia	14 (16.7)	50 (10.0)	.071
Diarrhea	9 (10.7)	30 (6.0)	.111
Throat congestion	4 (4.8)	35 (7.0)	.445
Comorbidities			
Any	48 (57.1)	186 (37.3)	.001
Hypertension	27 (32.1)	89 (17.8)	.002
Diabetes	25 (29.8)	45 (9.0)	<.001
COPD	7 (8.3)	10 (2.0)	.006
Coronary heart disease	6 (7.1)	12 (2.4)	.033
Cerebrovascular disease	5 (6.0)	5 (1.0)	.008
Arrhythmia	2 (2.4)	9 (1.8)	.664
Fatty liver	3 (3.6)	15 (3.0)	.734
Hyperlipidemia	1 (1.2)	7 (1.4)	1.000
Anemia	5 (6.0)	10 (2.0)	.51
Hepatitis B infection	1 (1.2)	16 (3.2)	.489
Chronic renal disease	1 (1.2)	3 (0.6)	.464
Cancer	6 (7.1)	4 (0.8)	.001
Connective tissue disease	2 (2.4)	3 (0.6)	.153
Pregnancy	1 (1.2)	2 (0.4)	.374
Timeline (d)			
Time from onset to admission	5.8 (2.2–9.4)	6.0 (2.3–10.7)	0.696
Hospital stay	22.0 (12.0–32.75)	16.0 (9.75–25.0)	0.003
Time from onset to severe disease	7.0 (4.0–9.5)		
Time from onset to critically ill disease	10.0 (7.5–12.0)		

Data are presented as median (25%, 75% quartiles) or number (%).
COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease 2019.

Table 2

Radiology and laboratory examinations of patients on admission.

Clinical characteristics	Severe-critically ill (n = 84)	Mild-moderate (n = 499)	*P* value
Radiology			
Abnormalities on chest imaging	84 (100)	423 (84.8)	<.001
Bilateral involved	67 (79.8)	293 (58.7)	<.001
Unilateral involved	17 (20.2)	130 (26.1)	.258
Laboratory examinations			
WBC ($\times 10^9$/L)	4.89 (3.87–5.79)	4.87 (3.90–6.11)	.32
Neutrophils ($\times 10^9$/L)	3.14 (2.31–4.31)	2.88 (2.16–3.83)	.970
Lymphocytes, ($\times 10^9$/L)	0.85 (0.62–1.10)	1.33 (0.98–1.70)	.022
Eosinophils ($\times 10^9$/L)	0.01 (0.0–0.02)	0.02 (0–0.05)	.245
Hemoglobin (g/L)	126 (117.25–140.0)	140 (128–153)	.026
Platelet ($\times 10^9$/L)	170.0 (128.25–193.75)	176.0 (145.75–219.0)	.001
ALT (U/L)	31 (22.25–54.3)	24.6 (17.0–36.0)	.003
AST (U/L)	33.0 (27.55–42.0)	23 (19–31)	<.001
LDH (U/L)	300.0 (251.0–456.0)	214.0 (171.25–294.0)	<.001
Albumin (g/L)	37.75 (33.03–41.40)	42.9 (40.0–45.9)	<.001
Total bilirubin (μmol/L)	10.30 (7.53–13.53)	11.0 (7.6–15.7)	.332
CK (μmol/L)	72.0 (54.25–145.25)	63.0 (43–94.75)	.477
Urea nitrogen (mmol/L)	4.40 (3.49–6.30)	3.86 (3.10–4.68)	.667
Creatinine (μmol/L)	66.50 (50.45–83.0)	62.0 (50.0–75.0)	.066
Sodium (mmol/L)	136.7 (133.0–139.8)	139.0 (136.25–141.3)	.618
Potassium (mmol/L)	3.69 (3.34–3.95)	3.83 (3.59–4.16)	.205
CRP (mg/L)	39.08 (10.0–76.99)	8.83 (2.03–15.71)	<.001
Procalcitonin (ng/mL)	0.05 (0.03–0.15)	0.03 (0.02–0.07)	.912
ESR (mm/h)	43.50 (14.0–62.50)	14 (7.0–28.0)	<.001
D-dimer (mg/L)	1.50 (0.34–162.50)	0.51 (0.23–90.0)	.020
PT (s)	12.50 (11.80–13.20)	12.40 (11.50–13.10)	.006
APTT (s)	32.90 (27.10–36.80)	32.0 (28.4–37.5)	.164
Fibrinogen (g/L)	4.45 (3.60–5.91)	3.51 (2.82–4.19)	<.001

Data are presented as median (25%, 75% quartiles) or number (%).
ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, CK = creatine kinase, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactose dehydrogenase, PT = prothrombin time.

illness (Table 4). Results of multivariable logistic regression analysis showed that age (odds ratios [OR] 1.08, 95% confidence interval [CI] 1.03–1.14), D-dimer (OR 3.21, 95%CI 1.39–7.40) and lymphocytes (OR 0.28, 95%CI 0.04–0.88) were independent risk factors for the progression into severe-critically illness (Table 4).

The ROC curves are shown in Figure 4. The AUC of age for predicting severe-critically illness was 0.68 (95% CI 0.62–0.74), while that of D-dimer was 0.79 (95% CI 0.73–0.85) and lymphocytes was 0.74 (95% CI 0.68–0.79). There was substantially superior performance for the combination of these 3 factors to predict the severe critically illness, and the AUC was 0.87 (95% CI 0.83–0.92). Therefore, the model performed well in predicting the development into severe-critically illness.

4. Discussion

In this study, we analyzed the clinical characteristics and risk factors for the adult COVID-19 patients to develop into severe-critically illness using the clinical records of 583 laboratory-confirmed patients hospitalized at the 28 authorized hospitals in Jiangsu province, China. The study of COVID-19 patients outside Wuhan is of paramount significance for an in-depth understanding of the clinical characteristics of COVID-19. The purpose of the study aims to further define the risk factors for the

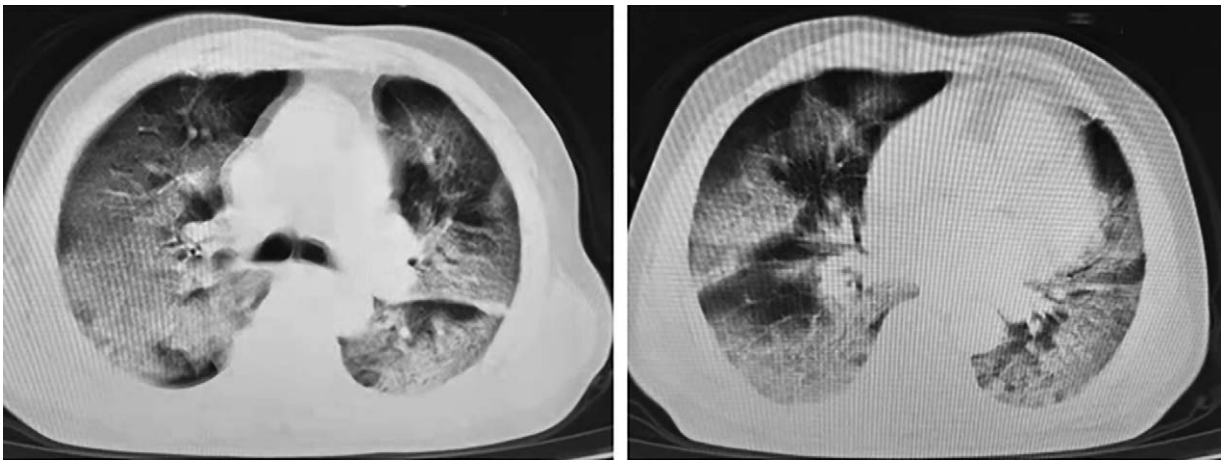

Figure 3. CT findings of severe type confirmed coronavirus disease 2019 pneumonia. A 66-year-old man with close contact history presenting with fever, cough and dyspnea. Chest CT showed diffusely subpleural distributed ground-glass opacities with consolidation of bilateral lungs.

progression into severe-critically illness. Our results showed that older age, higher D-dimer levels, and less lymphocyte counts are closely related to the development into serious illness.

Severe-critically illness occurred in 14.4% of the COVID-19 patients in Jiangsu Province, but no corresponding death has been reported so far. The percentage of severe-critically ill COVID-19 patients in Jiangsu was lower than that in Wuhan. The region-specific difference was caused by many factors. In the early stage of COVID-19 outbreak in Wuhan, the diagnostic capacity is limited. Some patients were not transferred to hospital until their conditions became deteriorated, and their medical treatments were delayed. At the start of the epidemic, there was a great shortage of medical staff and resources at hospitals in Wuhan, and medical workers were overloaded every day. Due to the shortage of sick beds in the hospitals, a majority of COVID-19 patients cannot receive medical treatment in hospitals and be effectively quarantined. In contrast, Jiangsu provincial government applied active surveillance in the early warning of the novel coronavirus. In particular, people with recent travel history to SARS-CoV-2 affected regions are under observation, and those in close contact with COVID-19 patients are traced. Thus, clinical cases could be found efficiently, which was reflected by a shorter onset-admission interval than those in Wuhan.[16]

Table 3

Complications and treatments of severe-critically ill patients.

Characteristics	Severe-critically ill patients (n = 84)
Complications	
Respiratory failure	49 (58.3)
ARDS	12 (14.3)
Secondary infection	14 (16.7)
Acute renal injury	5 (6.0)
Sepsis	74 (88.1)
Septic shock	5 (5.9)
Treatments	
Oxygen therapy	84 (100)
Non-invasive mechanical ventilation	23 (27.4)
Invasive mechanical ventilation	12 (14.3)
ECMO	3 (3.6)
Pulmonary transplant	2 (2.4)
Renal replacement therapy	3 (3.6)
Antibacterial agents	70 (83.3)
Antifungal agents	13 (15.5)
Systemic corticosteroids	43 (51.2)
Intravenous immunoglobin	22 (26.2)
APACHE-II	15 (12.5–18)
SOFA	4.5 (3.0–6.5)

Data are presented as median (25%, 75% quartiles) or number (%).
APACHE II = Acute Physiology and Chronic Health Evaluation II, ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation, SOFA = Sequential Organ Failure Assessment.

None of the severe-critically ill patient had an exposure history to Huanan seafood market, and nearly 85% of the patients did not travel or live in Wuhan. The majority of the diagnosed cases were the 2-generation cases, maybe third-generation cases, and even fourth-generation cases. Consistent with previous literatures, the most frequently observed symptoms on admission were fever and cough, and short of breath was quite common in severe-critically ill patients.[7,8,17] There were more evident lesions on chest radiographs in patients with severe-critically illness, suggesting a potential correlation between the extent of lung injury and the severity of illness. More than half of the severe-critically ill patients had 1 or more underlying diseases. Patients with pre-existing diseases, such as hypertension, diabetes, COPD, cardio-cerebrovascular diseases, and cancer, are vulnerable to the development of severe illness. A number of laboratory abnormalities were observed on admission in the severe-critically ill patients, including lower levels of lymphocytes, hemoglobin, platelet, albumin, and elevated content of ALT, AST, LDH, CRP, ESR, D-dimer, PT, fibrinogen. These results suggest that the severe-critically ill patients may be associated with more serious immune deficiency, coagulatory dysfunction, nutritional insufficiency, hepatic injury, and inflammatory reaction, indicating a multisystem involvement.

Patients with COVID-19 is likely to develop severe illness in 2 weeks after disease onset. Previously, older age was reported to indicate poor clinical outcomes of COVID-19.[5,6,10,11] In this study, we also found that the seniors were associated with the development of severe illness.

Declined immunocompetence is relatively common in the older patients who are more prone to severe infection. The incidence of severe-critically illness will be increased by 3.21 times, with

Table 4

Risk factors associated with severe-critically illness development.

Variables	Univariate analysis			Multivariate logistic regression analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Age	<.001	11.43	7.96–14.91	.004	1.08	1.03–1.14
Shortness of breath	<.001	5.97	3.16–9.91	.250		
Bilateral involved	<.001	2.04	1.32–3.16	.472		
Lymphocytes	.022	0.46	0.12–0.79	.034	0.28	0.04–0.88
Hemoglobin	.026	9.37	1.15–17.59	.597		
Platelet	.001	5.29	2.66–9.63	.073		
ALT	.003	1.53	3.66–17.39	.507		
AST	<.001	1.12	6.32–13.92	.317		
LDH	<.001	5.76	2.70–6.81	.085		
Albumin	<.001	5.27	3.78–6.76	.355		
CRP	<.001	4.31	2.08–6.53	.823		
ESR	<.001	2.11	1.46–4.75	.209		
PT	.020	1.45	1.25–1.85	.424		
D-dimer	.006	4.43	1.61–8.46	.024	3.21	1.39–7.40
Fibrinogen	<.001	1.46	1.11–1.75	.613		
Hypertension	.002	2.18	1.31–3.64	.504		
Diabetes	<.001	4.26	2.44–7.48	.104		
COPD	.006	4.45	1.64–12.03	.703		
Coronary heart disease	.033	3.12	1.14–8.56	.258		
Cerebrovascular disease	.008	6.25	1.77–22.09	.578		
Cancer	.001	9.52	2.63–34.49	.061		

ALT = alanine aminotransferase, AST aspartate aminotransferase, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactose dehydrogenase, PT = prothrombin time.

increment of 1 standard deviation in D-dimer. It was reported early that D-dimer can be a significant prognostic factor in patients with infection or sepsis.[18] Activation of coagulation system is an early and common event in patients with infection,[19] which could be reflected by D-dimer values. Therefore, D-dimer levels remain important as D-dimer can be potential therapeutic targets to resolve the coagulation disorder. Lymphocyte count was found to be an independent protective factor for severe-critically illness. For every 1 standard deviation increase in the lymphocyte level, the risk for developing into severe-critically illness will be decreased by about 72%. Earlier studies implied that depressed lymphocyte is a prominent feature of critically ill patients with SARS-CoV and MERS infection.[20,21] SARS-CoV-2 was reported to use the same cellular entry receptor as SARS-CoV.[22] Thus, we hypothesized that coronavirus particles may invade lymphocytes, damage the cytoplasmic component and cause their destruction. Patients with lymphocytopenia are thought to have a lower rigorous immune response against SARS-CoV-2 and an enhanced susceptibility to severe infection.

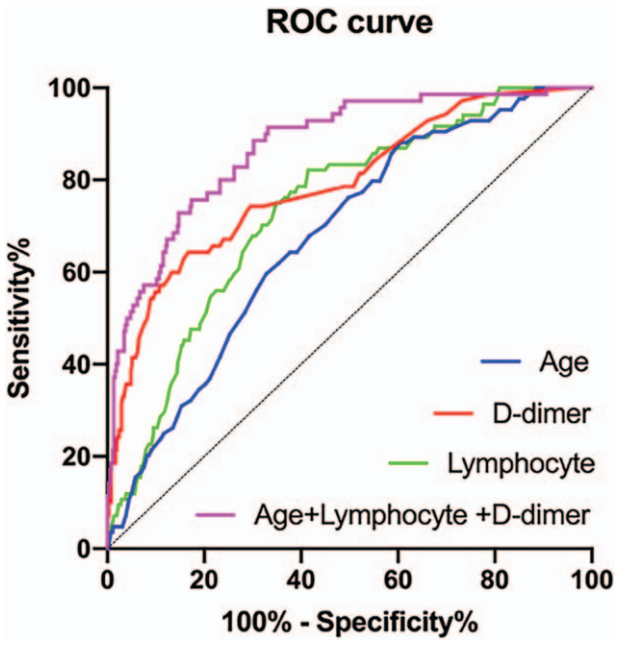

Figure 4. Receiver operating characteristic curves of factors for predicting severe-critically ill patients. Areas under the receiver operating characteristic curve: age was 0.68 (95% confidence interval [CI] 0.62–0.74), D-dimer was 0.79 (95% CI 0.73–0.85), and lymphocytes was 0.74 (95% CI 0.68–0.79). All $P < .001$. CI = confidence interval, ROC = receiver operating characteristic.

All of the severe-critically ill COVID-19 patients in this study were given antiviral agents. Currently, there are several ongoing clinical trials to investigate the efficacy and safety of those drugs. Nearly half of the patients were treated with intravenous corticosteroids. The use of corticosteroids at low-to-moderate dose in patients with coronavirus infection was supported.[11,23] The treatment with methylprednisolone tended to reduce the death risk in COVID-19 patients with ARDS.[11] Until now, no specific therapy has been recommended for severe and critically ill patients except for the meticulous supportive treatments. Notably, double lung transplants for 2 COVID-19 patients were successfully performed in Wuxi, Jiangsu Province, China. The transplanted lungs functioned well in oxygenation, and 2 patients got improved and discharged.

Our study, however, has some limitations. First, this is a retrospective study. The uncertainty of recall bias and variation of electronic medical record different hospitals might have unavoidably affected our evaluation. Second, not all of the laboratory indicators were tested in every patient, such as CD3,

CD4, CD8 T cells, IL-6, and IL-8. Especially, previous studies have revealed that CD3, CD4, and CD8 T cells played vital roles in coronavirus pneumonia.[11,24,25] The roles of these laboratory indicators were underestimated in predicting the progression of severe-critically ill patients. Third, the data on radiographical examination were not well described in detail. The imagines of some patients are merely left, right or bilateral pneumonia. Some specific information, such as ground-glass opacities, patchy shadow, and interstitial abnormalities, was missing.

5. Conclusions

This study conducted a comprehensive analysis of the clinical characteristics and risk factors of the severe-critically ill COVID-19 patients in Jiangsu province, China. The factors closely related to the progression of severe-critically illness are older age, elevated D-dimer values and declined lymphocyte cell contents. Our results may facilitate to establish targeted interventions and to reduce the mortality of COVID-19.

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Author contributions

Jiangnan Zhao and Yi Shi take responsibility for the study design, accuracy of the data analysis and drafting the manuscript. Meiying Zhu, Xin Su, Mao Huang, Yi Yang, Jianan Huang, Songshi Ni, Quan Cao, Qin Gu, Jun Li, Jiashu Li, Wenjing Zhao, and Bin Shi were responsible for the revision of the manuscript. All authors read and approved the final manuscript.

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