

# Clinical Characteristics of Severe COVID-19 in China: A Case Series and Meta-analysis

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## Research

**Keywords:** COVID-19, severe, case series, clinical characteristics

**DOI:** <https://doi.org/10.21203/rs.3.rs-186426/v1>

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## Abstract

**Background:** There have been inconsistent reports regarding the unique manifestations of severe coronavirus disease 2019 (COVID-19) occurring in China. This study analyzed the clinical manifestation of 13 severe COVID-19 cases at a single institution and compared the data to previously reported characteristics of severe COVID-19 in China.

**Methods:** This retrospective case study included patients with severe COVID-19 who were admitted to the isolation ward of the Shandong Chest Hospital from January 2020 to February 2020. The clinical signs and symptoms, laboratory examination results, imaging features, treatment strategies, and patient prognoses were summarized. A database search was then conducted for studies published through December 2020 documenting characteristics of severe COVID-19 cases in China. The pooled results for severe COVID-19 patients in China were calculated by using the random-effects model.

**Results:** A total of 4 severe and 9 critical patients were included from Shandong Chest Hospital. The average patient age was 55.3 (range 23-88) years, and 61.5% of patients were male. Chest computed tomography for all patients showed multiple lesions as ground-glass shadows in both lungs. All patients presented bacterial infection and various degrees of liver and myocardial injury. The treatment strategies for patients included antibiotics, immunoglobulin, and glucocorticoids, and mechanical ventilation was used in all patients for respiratory failure. Two patients died, and 11 recovered. In the pooled data for severe COVID-19 patients, the most common comorbidities were hypertension, diabetes mellitus, and coronary heart disease. The common signs in these patients were fever, cough, fatigue, chest tightness, and a leukocyte count > 10.

**Conclusions:** Older males with hypertension, diabetes mellitus, and coronary heart disease may be at higher risk of developing severe COVID-19. Patients should be assessed for concomitant bacterial infections. Cardiac and liver enzymes, fever, cough, fatigue, chest tightness, and leukocytosis should be monitored for signs of disease progression.

## Introduction

Coronavirus disease 2019 (COVID-19) is an acute infectious disease caused by infection with the novel coronavirus “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), that has affected more than 200 countries and has now caused a second wave of pandemic [1]. The global epidemic for COVID-19 remains severe, although the disease in China is well controlled [2]. The confirmed cases in China were primarily older patients with comorbidities at the early stage of the epidemic, and the number of severe cases rapidly increased [3]. Severe COVID-19 patients may progress into acute respiratory distress syndrome (ARDS) or multiple organ failure, which is associated with an increased likelihood of admission to the intensive care unit and the risk of mortality [4, 5].

The clinical symptoms of COVID-19 are widely varied, from asymptomatic to mild, severe, and critical [6, 7]. The majority of COVID-19 cases present mild symptoms, including dry cough, fever, sore throat, nasal congestion, and muscle pain [6, 7]. Severe COVID-19 is characterized by severe pneumonia, and critical cases include respiratory failure, septic shock, or multiple organ failure [6, 7]. Studies have already found that nearly 18% of COVID-19 cases were diagnosed with severe or critical disease, and around 5% of cases required intensive care management, irrespective of mechanical ventilation status [8]. Therefore, a classification of the characteristics of severe COVID-19 could benefit the clinical management of the disease and further improve patient prognosis. This study aimed to assess the clinical manifestation of severe COVID-19 in China.

## Materials And Methods

### Study design

This study involved a retrospective case series of patients with severe COVID-19 in the Shandong Provincial Chest Hospital from January 2020 to February 2020, and a subsequent meta-analysis including studies documenting the characteristics of severe COVID-19 patients in China. The diagnostic criteria for COVID-19 followed the Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (trial version 5) released by the National Health Commission. This study was approved by the institutional ethics board of Shandong Provincial Chest Hospital (2021XKYYEC-01).

### Data collection

Data collected from the electronic medical records system included age, sex, epidemiological history, symptoms from onset to hospital admission, hospital stay, comorbidity, weakness, fever, chest distress, cough, smoking status, imaging results, laboratory examinations, treatment strategies, and the prognosis of COVID-19. The meta-analysis was performed by searching the PubMed and EmBase databases for studies reporting the clinical manifestations for patients with severe COVID-19 in China through December 2020.

### Statistical analysis and meta-analysis

This study was based on descriptive analyses, and the mean (deviation) or rate (proportion) were calculated for continuous and categorical variables, respectively. All pooled analyses were calculated using the random-effects model, which considers the underlying variables across studies [9]. Moreover, the heterogeneity among included studies was assessed by using  $I^2$  and Q statistics. All statistical analyses were performed using SPSS Version 20.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA) and STATA Release 10 (Stata Statistical Software, StataCorp, College Station, TX, USA).

## Results

### Demographic features of case series patients

The clinical characteristics of the 13 Shandong Provincial Chest Hospital patients are shown in Table 1. According to the diagnostic criteria, 4 cases were severe, and 9 cases were critical. Of the included patients, 8 were males and 5 were females. The patients were aged 23–88 years with an average age of 55.3 (20.8) years. Ten of the patients had no history of smoking, and the remaining 3 patients had current or previous smoking history. Among the 13 patients, 4 had hypertension, 1 had diabetes, 1 had a cerebral infarction, 1 had hyperlipidemia, and 6 were healthy without underlying disease.

Table 1  
Clinical characteristics of patients

Case	Type	Sex	Age (years)	Hospital stay (days)	Comorbidity	Fatigue	Fever	Chest tightness	Cough and expectoration	Smoking status	Chest CT	CRP
1	Critical	Female	84.0	13	Hypertension	No	Yes	Yes	Yes	No	Multiple ground glass shadows in both lungs, bilateral thoracoscopic effusion	28.3
2	Critical	Female	82.0	7	Hypertension, CHD, and DM	Yes	Yes	Yes	Yes	No	Multiple plaques and ground glass shadows in both lungs	< 5
3	Severe	Male	34.0	19	Hypertension	Yes	Yes	Yes	Yes	Yes	Multiple lamellae in both lungs	105
4	Severe	Male	23.0	20	None	No	Yes	No	Yes	Yes	External ground glass for both lungs	16.8
5	Severe	Male	51.0	10	None	Yes	Yes	No	Yes	Yes	Multiple ground glass and plaque in both lungs	9.68
6	Critical	Female	46.0	35	DM	Yes	Yes	Yes	Yes	No	Both lungs diffuse sheet ground glass shadow	23.47
7	Critical	Male	51.0	39	Hyperlipidaemia	Yes	Yes	Yes	Yes	No	Large ground glass shadows in both lungs without pleural effusion	Increase
8	Critical	Female	64.0	7	None	Yes	Yes	Yes	Yes	No	Both lungs diffuse sheet ground glass shadow	79.0
9	Critical	Male	35.0	26	None	Yes	Yes	Yes	Yes	No	Double lung plaques, ground glass shadow	112.4
10	Severe	Male	65.0	27	None	Yes	Yes	Yes	Yes	No	Ground glass shadows and lamellae in both lungs	66.3
11	Critical	Male	36.0	33	None	No	Yes	No	Yes	No	Bilateral lung outer film flocculation	Increase
12	Critical	Male	60.0	24	Hypertension, arrhythmia	No	Yes	Yes	Yes	No	Patchy high-density shadows in both lungs	63.7
13	Critical	Female	88.0	7	Cerebral infarction, hiatus hernia	No	Yes	Yes	Yes	No	Ground glass shadows and lamellae in both lungs	19.4

## Clinical characteristics of case series patients

Epidemiological history and disease course

Of the 13 patients, 7 had been in direct contact with patients in Wuhan in Hubei Province, 2 cases resulted from family contact, 2 had a history of contact with another confirmed COVID-19 patient, and 2 were local farmers for whom no specific contacts were found. The average time from exposure to onset of symptoms in the 13 patients was 5.1 (range 1–10) days. The patients entered a designated isolation area for treatment immediately after testing positive in the SARS-CoV-2 nucleic acid test. The duration of treatment was 7–39 days, with an average of 20.5 ± 11.2 days.

#### Imaging features and laboratory examination

Chest computed tomography (CT) for all patients showed bilateral lung lesions and early ground-glass opacities; with the progression of disease, these lesions became dense. For one case, the lesions increased in size during treatment and later gradually decreased in size, and in one case with pleural effusion, the number of lesions was low. The C-reactive protein levels were higher than normal in all patients. The white blood cell counts were significantly elevated in 4 patients, neutrophil proportions and absolute neutrophil numbers were significantly elevated in 10 patients, and lymphocyte counts were decreased in 9 patients. A spectrum of myocardial enzymes were elevated in 10 patients, D2 dimer levels were elevated in 4 patients, liver enzyme indexes were elevated in 11 patients, and all patients had elevated bilirubin levels and hypercoagulation. The T cell proportions were lower than normal in 7 patients, and albumin levels were low in 11 patients.

#### Clinical manifestations

All patients presented cough and expectoration accompanied by fever. Eight patients presented fatigue, and 10 patients had chest tightness. The disease progressed rapidly in a short time, and blood oxygen saturations decreased significantly. The patients showed typical hypoxemia. ARDS and hypoproteinemia were found in the critically ill patients.

#### Treatment and prognosis

All 13 patients were treated with antiviral therapy and oxygen inhalation as well as prone position ventilation. Eleven patients were treated with antibiotics due to bacterial infection; 2 patients were treated for fungal infection with antifungal drugs; 10 patients were treated with glucocorticoids, and all patients were treated with the traditional Chinese herbal drug Xuebijing. Eleven patients were treated with immunoglobulin.

## Meta-analysis

A total of 14 studies were selected for final meta-analysis [3, 10–22], and the pooled results for characteristics and patient prognosis are shown in Table 2. The pooled proportion of males and current smokers were 0.61 (95% CI: 0.57–0.65), and 0.25 (95% CI: 0.05–0.45), respectively. The most prevalent comorbidities were hypertension (0.34; 95% CI: 0.25–0.44), diabetes mellitus (0.16; 95% CI: 0.12–0.20), and coronary heart disease (0.14; 95% CI: 0.09–0.19). The incidences of fever, cough, fatigue, chest tightness, and leukocyte count > 10 were 0.89 (95% CI: 0.83–0.94), 0.66 (95% CI: 0.54–0.79), 0.53 (95% CI: 0.43–0.63), 0.48 (95% CI: 0.34–0.62), and 0.27 (95% CI: 0.03–0.50), respectively.

Table 2  
Summary results for the characteristics of patients

Outcomes	No. of studies	Incidence and 95%CI	P value	Heterogeneity (%)	P value for heterogeneity
Male	14	0.61 (0.57–0.65)	< 0.001	0.0	0.583
Current smoker	5	0.25 (0.05–0.45)	0.014	92.3	< 0.001
Hypertension	11	0.34 (0.25–0.44)	< 0.001	75.0	< 0.001
Diabetes mellitus	11	0.16 (0.12–0.20)	< 0.001	24.9	0.207
Arrhythmia	2	0.07 (0.01–0.13)	0.020	0.0	0.922
Coronary heart disease	12	0.14 (0.09–0.19)	< 0.001	55.0	0.011
Cerebrovascular disease	6	0.05 (0.02–0.08)	0.002	31.6	0.198
Fever	14	0.89 (0.83–0.94)	< 0.001	55.8	0.016
Cough	14	0.66 (0.54–0.79)	< 0.001	89.6	< 0.001
Fatigue	13	0.53 (0.43–0.63)	< 0.001	75.8	< 0.001
Chest tightness	11	0.48 (0.34–0.62)	< 0.001	87.1	< 0.001
Leukocyte > 10	3	0.27 (0.03–0.50)	0.027	79.1	0.008
Mortality	7	0.20 (0.09–0.30)	< 0.001	83.7	< 0.001

## Discussion

An outbreak of highly contagious COVID-19 began at the end of 2019, and its incubation period was unclear. A small number of cases with an incubation period of up to 28 days have since been reported [23]. The disease progresses rapidly, and significant worsening can be seen on chest CT within 2 days. The clinical manifestations of COVID-19 are not specific, and most patients are asymptomatic at the early stage of the disease. As the disease progresses, patients develop fever, cough, chest tightness and respiratory failure, and their conditions range from mild to severe. The prognosis of mild COVID-19 with common

clinical treatment is generally good, and most patients are cured, with few sequelae. However, due to insufficient understanding of the disease and in patients with underlying disease, mild disease can develop into severe COVID-19, which is associated with poor prognosis.

This study presented the clinical characteristics of severe and critical cases of COVID-19. Based on the patients treated in our hospital, critical patients generally exhibit underlying diseases, mainly hypertension and diabetes, which is consistent with previous reports by other researchers [8]. As with previous studies, the majority of COVID-19 cases were found to have clear epidemiological connections [24–26]. Of the 13 patients examined, 7 had been in contact with a COVID-19 patient in Wuhan. COVID-19 was first discovered in Wuhan, China, after which many articles began to refer to COVID-19 as Wuhan pneumonia [3, 27, 28].

This study also supports previous findings that severe COVID-19 cases are more common in males [3, 29]. A potential reason for this could be that COVID-19 was first found in a seafood market in Wuhan, and most of the workers there were men. The treatment courses for severe COVID-19 are varied, and the duration of treatment ranged from 7–39 days in our study. The shorter hospital stays could be explained by the rapid progression of the disease, and patients who died because of failure to receive timely treatment. Moreover, most patients presented with chest tightness, which could be explained by the rapid progression of the disease, and patients showed obvious short-term hypoxemia that developed into respiratory failure. Mechanical ventilation was often required because oxygen and antiviral treatments could not ease the symptoms.

The symptoms of severe COVID-19 were not restricted to viral infection, and bacterial or fungal infections were also observed. In our study, 10 patients presented with an increased neutrophil percentage and absolute neutrophil count, indicating a need for antimicrobial therapy. The two patients who died had fungal infections contributing to increased lesions in the lungs. Therefore, pulmonary fungal infection should be prevented in patients with COVID-19 to reduce the risk of mortality, and the risk factors for pulmonary aspergillosis should be monitored [30].

Most patients also presented with elevated cardiac and liver enzymes, which could be explained by destruction of cardiomyocytes and hepatocytes by the SARS-CoV-2 virus. These enzyme elevations were more evident in patients with severe COVID-19 than in those with milder disease. In addition, 4 patients in our study showed high D2 polymer levels and blood viscosity, which could be caused by damage to the coagulation system and trigger an emergency status in patients with COVID-19 [31].

Furthermore, lower immune status has been shown to be a risk factor for the onset of COVID-19 and the development of more severe disease [2, 10, 32–34]. Immune status may be the key to the relatively high incidence of hypertension, diabetes mellitus, and coronary heart disease found in patients with severe COVID-19 in this study. Studies have already found that patients with hypertension, diabetes mellitus, and coronary heart disease showed lower immunity status than healthy individuals [35–37].

The most common symptoms of severe COVID-19 patients were fever, cough, fatigue, chest tightness, and leukocytosis, and these signs should be carefully monitored to prevent the progression of COVID-19. The treatment regimens for severe COVID-19 patients in our hospital were based on the National Health and Construction Commission guidelines [38]. In addition, traditional Chinese medicine and symptomatic support was combined with antiviral treatment. We noted that most patients presented with bacterial infection, and antibiotics were added into the conventional regimens. Glucocorticoids were administered to prevent infection for patients without bacterial infection [39]. One study found that the use of glucocorticoids could inhibit an excessive inflammatory response in the body and reduce lung injury [40]. Moreover, glucocorticoids may promote the absorption of pulmonary lesions in the acute stage and reduce the risk of pulmonary fibrosis in the later stage, leading to a shorter duration of mechanical ventilation [5, 41]. Therefore, glucocorticoids should be administered for severe COVID-19 patients presenting with progression of oxygenation indexes. However, glucocorticoids may inhibit lymphocytes and reduce immune function, which are significantly related to the disease course and prognosis of COVID-19. Therefore, glucocorticoids should be combined with immunoglobulin and albumin as an important supportive treatment for patients with COVID-19. Finally, mechanical ventilation should be considered, depending on the patient's respiratory function, and the early use of a ventilation device could improve patients' oxygenation, reduce pulmonary interstitial edema, and reduce the mortality risk for severe COVID-19.

Several limitations in this study should be acknowledged. The retrospective case series only included 13 patients, and there was no control group of patients with non-severe disease or comparison of characteristics and prognosis between those with mild and severe disease. The risk factors for the prognosis of severe COVID-19 were not identified, and the potential confounders were not adjusted.

## Conclusions

This study provides a comprehensive overview of the clinical characteristics and prognosis for patients with severe COVID-19 in China. Although older males with a history of hypertension, diabetes mellitus, and coronary heart disease may be at higher risk of developing severe COVID-19, all patients should be assessed for cardiac and liver enzyme elevations, and symptoms of fever, cough, fatigue, chest tightness, and leukocytosis should be monitored for signs of disease progression. Further study should be conducted to construct a prognostic model for COVID-19 patients at different disease stages.

## Declarations

### Ethics approval and consent to participate

This study was approved by the institutional ethics board of Shandong Provincial Chest Hospital. Consent waiver was granted by the ethics committee for the collection and use of participants' health and personal information.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that there is no conflict of interest.

## Funding

None.

## Acknowledgements

None.

## Authors' contributions

Study conception and design were contributed by GT, HH. GT, JW collected the data. GT, XW, HZ analyzed and interpreted the results. GT, YC prepared the draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

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