Original Article

# Clinical characteristics and treatment of critically ill patients with COVID-19 in Hebei

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**Background:** In December, 2019, a novel coronavirus disease 2019 (COVID-19) emerged in Wuhan, China. We aimed to clarify the epidemiology, laboratory examinations, imaging findings, and treatment of critically ill patients with COVID-19 in Hebei province, China.

**Methods:** In this retrospective study, the demographic, laboratory and imaging, and treatment data of patients with severe COVID-19 treated in 13 designated hospitals in Hebei were collected and analyzed.

**Results:** A total of 319 severe COVID-19 patients were treated at the 13 designated hospitals between 22 January, 2020 and 25 March, 2020. Eventually, 51 critically ill (31 severe cases and 20 critically severe cases) patients were included in the analysis. The patients had an average age of 58.9±13.7 years, and 27 (52.9%) were men. Twenty-one (41.2%) were familial cluster, and 33 (64.7%) had chronic illnesses. The patients in critically severe group had longer duration from symptom to confirmation, more severe infections, more severe lung injury, and a lower percentage of lymphocytes. All 51 patients received antiviral drugs, 47 (92.2%) received antibacterial agents, 49 (96.1%) received traditional Chinese drugs, and 46 (90.2%) received methylprednisolone. The critically severe patients received more fluid and more diuretic treatment; 14 (70.0%) required invasive mechanical ventilation, and 13 (65.0%) developed extrapulmonary complications.

**Conclusions:** COVID-19 patients who had underlying diseases and longer confirmation times were more likely to progress to critically severe COVID-19. These patients also presented with a higher risk of respiratory depression, circulatory collapse, extrapulmonary complications, and infection.

**Keywords:** 2019 novel coronavirus; novel coronavirus disease 2019 (COVID-19); SARS-CoV-2; 2019-nCoV; critically ill

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## Introduction

In December 2019, an outbreak of pneumonia of unknown etiology emerged in Wuhan, the capital city of Hubei province in China. Eventually, the pathogen was confirmed to be a distinct clade of Betacoronavirus and officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); the disease was termed novel coronavirus disease 2019 (COVID-19) (1,2). As of 25 March, 2020, the disease had infected 413,467 people and killed 18,433 (4.46%) people in 186 countries.

According to Chinese Clinical Guidelines for COVID Pneumonia Diagnosis and Treatment (7th edition) COVID-19 cases are classified as mild, moderate, severe, or critically severe (3). Patients in Hubei experienced relatively severe symptoms and had a high mortality rate compared to patients in other Chinese provinces (4), which may be attributed to the demand for health care outstripping available resources (5). Early identification and efficient treatment are of paramount importance to reducing mortality among patients with severe COVID-19. Herein, we describe the epidemiological clinical features and treatment of patients with severe COVID-19 in Hebei province. Our experience may be of considerable value to the early identification and efficient treatment of patients with a high risk of progression to critically severe COVID-19. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1273).

## Methods

### *Study design and population*

A multicenter, retrospective, observational trial of critically ill patients with COVID-19 who received treatment at 13 designated hospitals in Hebei, China, between 22 January, 2020 and 25 March, 2020, was conducted. The patients were diagnosed by SARS-CoV-2 nucleic acid real-time polymerase chain reaction (RT-PCR) and the local health authority were categorized as severe or critically severe cases based on the Chinese Clinical Guidelines for COVID Pneumonia Diagnosis and Treatment ($7^{th}$ edition) (3). Cases meeting any of the following criteria were categorized as a severe: (I) respiratory distress: respiratory rate >30 breaths per minute; (II) percutaneous oxygen saturation ($SpO_2$) <93% when resting; and (III) partial pressure of oxygen ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) ≤300 mmHg. Cases meeting any of the following criteria were categorized as critically severe: (I) respiratory failure requiring mechanical ventilation; (II) shock; (III) other organ failure, and needed monitoring and treatment in intensive care unit (ICU). Patients aged ≤18 years, patients with a hospital stay of ≤48 hours, and pregnant patients were not included. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients. This study was approved by the Ethics Commission of the Fourth Clinical Medical College of Hebei Medical University (2020KS002).

### *Data collection*

Patient data, including demographic information, exposure history, underlying diseases, symptoms from onset to hospital admission, vital signs upon confirmation of the disease type, chest computed tomography (CT) images, laboratory values on categorization of the disease type, the Sequential Organ Failure Assessment (SOFA) score, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, treatment, and extrapulmonary comorbidities, were collected. Any missing data were obtained and uncertain records were clarified through direct communication with the managing physician.

### *Statistical analysis*

Continuous variables with a non-normal distribution were described as median (interquartile range, IQR) and analyzed with the nonparametric Mann-Whitney U test (6). Continuous variables with a normal distribution were expressed as the mean (standard deviation), and groups were compared using *t*-tests. Categorical variables were expressed as count (percentage) and compared with Pearson's chi-square test or Fisher's exact probability test. All statistical analyses were performed using IBM SPSS Statistics version 26.0. A two-sided P value of <0.05 was considered to be statistically significant.

## Results

### *Epidemiological characteristics*

By 25 March 2020, 319 cases of COVID-19 had been recorded in Hebei, including 56 (17.55%) critically ill patients. Of them, 51 patients (31 severe cases and 20 critically severe cases) were eventually included in this study.

 

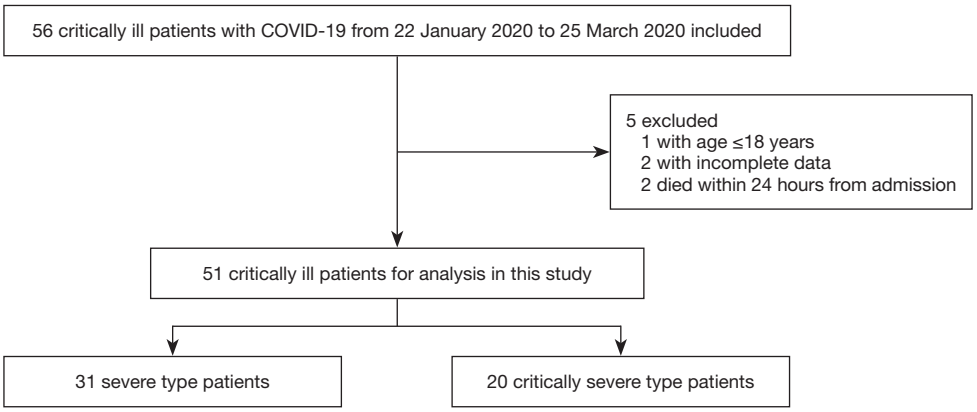


**Figure 1** Study flow diagram.

The other 5 patients were excluded for the following reasons: aged ≤18 years (n=1), lack of clinical data (n=2), and death within 24 hours (n=2) (*Figure 1*). The patients had an average age of 58.9±13.7 years old, and 27 (52.9%) were men. None of the patients had a history of exposure to Wuhan's Huanan seafood market. The majority (78.4%) of patients had a known contact history, and more than half (51.0%) were familial clusters (*Table 1*). There were 33 (64.7%) patients who had chronic illnesses including hypertension (21 cases, 41.2%), cardiovascular disease (12 cases, 23.5%), diabetes (11 cases, 21.6%), and pulmonary disease (8 cases, 15.7%). Few patients had other diseases or a smoking history. Sixteen (31.4%) patients had a surgical history (*Table 1*).

### *Symptoms from onset to hospital admission*

The most common symptoms experienced by patients were fever (94.1%), cough (66.7%), expectoration (37.3%), dyspnea (35.3%), fatigue (27.5%), myalgia (13.7%), and diarrhea (11.8%); however, headaches (7.8%) were rarely reported (*Table 2*). The duration from symptom onset to admission, symptom onset to laboratory confirmation, and symptom onset to classification was 3.0 (range, 1.0–6.0), 6.0 (range, 3.0–10.0), and 10.2±4.7 days, respectively. The differences in these durations between the two groups were not statistically significant (P>0.05) (*Table 2*). Compared to the severe group, a higher proportion of patients in the critically severe group had a confirmation time of longer than 10 days (P=0.010).

### *Vital signs, and laboratory and imaging findings*

The critically severe group had a higher maximum daily temperature and respiratory rate than the severe group, but lower blood pressure. Therefore, vasoconstrictive agents were more frequently used in critically severe patients (12, 60.00%) (*Tables 3*,*4*).

The critically severe group had lower $PaO_2/FiO_2$ (<150 mmHg) and received higher $FiO_2$ levels to maintain $SpO_2$ ≥93% than the severe group (*Table 3*). Both groups had a mild elevation of lactate concentration but without significant difference. The white blood cell (WBC) count, percentage of neutrophils, and the levels of C-reactive protein and procalcitonin of the critically severe group were significantly elevated compared with those of the severe group; conversely, the percentage of lymphocytes was significantly lower (P<0.05) (*Table 3*). The critically severe group also had a higher erythrocyte sedimentation rate (ESR) than the severe group, but the difference between the groups was not statistically significant (P>0.05) (*Table 3*). Additionally, the critically severe patients had mild coagulation disorders with slightly prolonged prothrombin time (PT), and slightly elevated levels of blood urea nitrogen (BUN) and creatine kinase (P<0.05); as a result, their APACHE II and SOFA scores were higher than those of the severe patients (*Table 3*).

The counts of cluster of differentiation CD4+, CD8+, and CD3+ cells were measured in 13 patients (5 critically severe cases and 8 severe cases), and the ratio of CD4+ to CD8+cells (CD4+/CD8+) was calculated.

Patients with critically severe disease tended to have lower levels of CD4+ cells and CD4+/CD8+, but the difference between the groups was not statistically significant (P>0.05) (*Table 3*).

In the severe group, all but 2 (96.1%) patients had bilateral infiltrates on chest CT, and most patients showed

 

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

| Variables | All patients (n=51) | Severe (n=31) | Critically severe (n=20) | P value |
|---|---|---|---|---|
| Age, years | 58.9±13.7 | 58.3±13.6 | 60.0±14.1 | 0.686 |
| Male | 27 (52.9) | 19 (61.3) | 8 (40.0) | 0.137 |
| Exposure | 40 (78.4) | 23 (74.2) | 17 (85.0) | 0.570 |
| Exposure to Huanan seafood market | 0 (0.0) | 0 (0.0) | 0 (0.0) | – |
| Travel to Wuhan | 12 (23.5) | 9 (29.0) | 3 (15.0) | 0.415 |
| Exposure to people who had travelled to Wuhan | 7 (13.7) | 5 (16.1) | 2 (10.0) | 0.838 |
| Exposure to patients* | 22 (43.1) | 11 (35.5) | 11 (55.0) | 0.169 |
| Clustering onset† | 26 (51.0) | 15 (48.4) | 11 (55.0) | 0.645 |
| Chronic medical illness | 33 (64.7) | 16 (51.6) | 17 (85.0) | 0.015 |
| Hypertension | 21 (41.2) | 8 (25.8) | 13 (65.0) | 0.005 |
| Diabetes | 11 (21.6) | 7 (22.6) | 4 (20.0) | 1.000 |
| Chronic cardiac disease | 12 (23.5) | 3 (9.7) | 9 (45.0) | 0.010 |
| Chronic pulmonary disease | 8 (15.7) | 4 (12.9) | 4 (20.0) | 0.775 |
| Cerebrovascular disease | 5 (9.8) | 2 (6.5) | 3 (15.0) | 0.603 |
| Chronic kidney disease | 2 (3.9) | 0 (0.0) | 2 (10.0) | 0.290 |
| Chronic liver disease | 3 (5.9) | 1 (3.2) | 2 (10.0) | 0.693 |
| Malignancy | 1 (2.0) | 0 (0.0) | 1 (5.0) | 0.823 |
| Surgery history | 16 (31.4) | 8 (25.8) | 8 (40.0) | 0.286 |
| Smoking | 4 (7.8) | 2 (6.5) | 2 (10.0) | 1.000 |

The results were described as mean (standard deviations) or counts (percentages). *, patients who have confirmed COVID-19 infection or are highly suspected of being infected; †, 2 or more cases of fever and/or respiratory symptoms within 2 weeks in enclosed spaces such as the home, office, school/classroom, etc. COVID-19, novel coronavirus disease 2019.

localized infiltrates. In the critically severe group, chest CT demonstrated diffuse, extensive interstitial, and alveolar infiltrates (*Figure 2*), making these patients more likely to experience shortness of breath (*Table 2*).

### *Treatment, extrapulmonary comorbidities, and outcomes*

All of the patients were treated with antiviral therapy: 50 (98.0%) with interferon, 49 (96.1%) with lopinavir/ritonavir, 37 (72.5%) with arbidol, and 11 (21.6%) with oseltamivir). Many of the patients (47, 92.2%) were also treated with antibacterial agents, including azithromycin, levofloxacin, moxifloxacin, cefoperazone sodium, sulbactam sodium/tazobactam sodium, and piperacillin sodium and tazobactam sodium (*Table 4*). Combined antibiotic therapy was more commonly received by the critically severe patients than the severe patients. Methylprednisolone was used to treat 46 (90.2%) patients, and the treatment duration tended to be longer in the critically severe group (P=0.095). Approximately one-half of the patients were treated with the immunizing agents Xuebijing and albumin, 49 (96.1%) were treated with traditional Chinese drugs, and approximately one-quarter received blood transfusion (*Table 4*).

All participants developed acute respiratory distress syndrome (ARDS), and the patients with critically severe COVID-19 had more severe dyspnea and lower oxygenation than the patients with severe disease (*Table 3*). In the severe group, 23 (74.2%) patients were treated with a nasal cannula, and 6 (19.4%) received a high-flow nasal cannula. In the critically severe group, 14 (70.00%) patients were treated with invasive mechanical ventilation, 11 (55.0%) with prone-position ventilation, 4 (20.0%) with noninvasive mechanical ventilation, 3 (15.0%) with continuous renal

 

**Table 2** Symptoms of critically ill patients with COVID-19 from onset to hospital admission

| Variables | All patients (n=51) | Severe (n=31) | Critically severe (n=20) | P value |
|---|---|---|---|---|
| Symptoms | | | | |
| Fever | 48 (94.1%) | 30 (96.8%) | 18 (90.0%) | 0.693 |
| Cough | 34 (66.7%) | 18 (58.1%) | 16 (80.0%) | 0.105 |
| Expectoration | 19 (37.3%) | 11 (35.5%) | 8 (40.0%) | 0.745 |
| Dyspnea | 18 (35.3%) | 7 (22.6%) | 11 (55.0%) | 0.018 |
| Myalgia | 7 (13.7%) | 5 (16.1%) | 2 (10.0%) | 0.838 |
| Fatigue | 14 (27.5%) | 8 (25.8%) | 6 (30.0%) | 0.743 |
| Diarrhea | 6 (11.8%) | 3 (9.7%) | 3 (15.0%) | 0.896 |
| Headache | 4 (7.8%) | 3 (9.7%) | 1 (5.0%) | 0.942 |
| Duration from symptom onset to admission, days | 3.0 (1.0, 6.0) | 3.0 (0.0, 6.0) | 3.0 (1.0, 4.8) | 0.946 |
| Duration from symptom onset to confirmation, days | 6.0 (3.0, 10.0) | 5.0 (3.0, 8.0) | 6.5 (3.3, 11.0) | 0.274 |
| Confirmation time ≥10 d | 13 (25.5%) | 4 (12.9%) | 9 (45.0%) | 0.010 |
| Duration from symptom onset to classification, days | 10.2±4.7 | 9.8±5.0 | 10.9±4.1 | 0.301 |
| No. of positive COVID-19 nucleic acid tests, times | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) | 1.0 (1.0, 1.0) | 0.656 |

The results were described as median (interquartile ranges), mean (standard deviations), or counts (percentages), as appropriate. COVID-19, novel coronavirus disease 2019.

**Table 3** Vital signs and laboratory and imaging findings of critically ill patients with COVID-19 within 24 hours of the final clinical classification (severe or critically severe type)

| Variables | All patients (n=51) | Severe (n=31) | Critically severe (n=20) | P value |
|---|---|---|---|---|
| Vital signs | | | | |
| Temperature, ℃ | 37.8±1.1 | 37.5±1.0 | 38.3±1.0 | 0.011 |
| Heart rate, beats per min | 86±20 | 84±15 | 91±26 | 0.284 |
| Respiratory rate, breaths per min | 22 [19, 25] | 20 [18, 22] | 25 [22, 33] | <0.001 |
| $SpO_2$, % | 95.0 (92.0,98.0) | 95.0 (93.0,98.0) | 94.0 (88.3,98.0) | 0.303 |
| Systemic blood pressure, mmHg | 121±19 | 127±15 | 112±21 | 0.004 |
| Diastolic blood pressure, mmHg | 73±13 | 76±12 | 67±13 | 0.018 |
| Mean arterial pressure, mmHg | 88±15 | 93±12 | 81±16 | 0.005 |
| Arterial blood gas | | | | |
| PH | 7.45±0.05 | 7.44±0.05 | 7.46±0.05 | 0.095 |
| $PaO_2$, mmHg | 75.2 (62.0, 86.0) | 74.0 (63.6, 87.2) | 78.0 (60.0, 86.2) | 0.646 |
| $PaCO_2$, mmHg | 34.1±5.3 | 35.5±4.8 | 31.9±5.5 | 0.023 |
| $FiO_2$, % | 39 [33, 59] | 33 [29, 37] | 70 [50, 85] | <0.001 |
| Oxygenation index | 185 [138, 243] | 231 [193, 286] | 131 [85, 161] | <0.001 |
| Lactate concentration, mmol/L | 2.4±1.3 | 2.1±0.9 | 2.9±1.8 | 0.106 |
| Blood routine | | | | |
| White blood cell count, $\times 10^9$/L | 6.74 (4.59, 10.76) | 5.25 (3.50, 7.20) | 9.73 (6.77, 13.29) | <0.001 |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Variables | All patients (n=51) | Severe (n=31) | Critically severe (n=20) | P value |
|---|---|---|---|---|
| Neutrophilic percentage, % | 85.30 (75.88, 90.93) | 82.00 (66.60, 88.00) | 90.40 (85.70, 94.14) | <0.001 |
| Lymphocyte percentage, % | 9.25 (5.70, 15.85) | 12.40 (6.70, 24.10) | 6.80 (3.80, 11.00) | 0.004 |
| Lymphocyte count, $\times10^9$/L | 0.65 (0.37, 0.81) | 0.63 (0.37, 0.91) | 0.66 (0.35, 0.73) | 0.639 |
| Platelet count, $\times10^9$/L | 187±72 | 184±54 | 193±95 | 0.714 |
| ESR, mm/h* | 48±29 | 41±31 | 60±21 | 0.128 |
| C-reactive protein, mg/L | 53.00 (19.70, 84.68) | 39.76 (14.96, 65.03) | 72.55 (33.29, 140.00) | 0.020 |
| Procalcitonin, ng/mL | 0.15 (0.05, 0.34) | 0.10 (0.05, 0.22) | 0.28 (0.10, 0.89) | 0.018 |
| Coagulation function | | | | |
| Prothrombin time, s | 12.8±1.7 | 12.4±2.1 | 13.4±1.8 | 0.041 |
| Activated partial thromboplastin time, s | 33.6 (29.3, 37.9) | 32.6 (29.8, 37.4) | 33.8 (29.0, 38.8) | 0.690 |
| Blood biochemistry | | | | |
| Albumin, g/L | 34.23±5.13 | 35.29±5.37 | 32.41±4.25 | 0.057 |
| Direct bilirubin, mmol/L | 5.10 (3.36, 8.60) | 4.50 (2.88, 6.90) | 7.10 (4.50, 9.29) | 0.064 |
| Indirect bilirubin, mmol/L | 8.22 (5.00, 11.20) | 8.26 (4.82, 10.63) | 7.70 (6.57, 14.00) | 0.438 |
| Creatinine, μmol/L | 67.35 (59.00, 86.75) | 66.45 (55.85, 80.25) | 70.50 (59.98, 120.48) | 0.094 |
| Blood urea nitrogen, mmol/L | 5.69 (3.92,7.96) | 4.84 (3.59, 6.70) | 8.20 (5.29, 12.48) | 0.004 |
| Blood glucose, mmol/L | 8.92 (6.53, 13.10) | 8.16 (6.28, 11.85) | 9.97 (7.51, 16.38) | 0.137 |
| Creatine kinase, U/L | 59.50 (36.00, 206.75) | 54.15 (30.68, 113.83) | 185.55 (57.00, 325.00) | 0.005 |
| Potassium, mmol/L | 3.94±0.58 | 3.83±0.60 | 4.12±0.51 | 0.182 |
| Sodium, mmol/L | 136.13±3.94 | 135.55±3.67 | 137.09±4.28 | 0.087 |
| APACHE-II | 10±4 | 8±3 | 14±4 | <0.001 |
| SOFA | 3 [2, 5] | 3 [2, 3] | 5 [4, 10] | <0.001 |
| $CD4^+$ T cells count, /μL† | 228±120 | 273±128 | 156±64 | 0.087 |
| $CD8^+$ T cells count, /μL† | 149 [101, 242] | 98 [60, 153] | 101 [92, 114] | 0.833 |
| $CD3^+$ T cells count, /μL† | 435 [272, 590] | 320 [252, 438] | 234 [224, 292] | 0.435 |
| $CD4^+/CD8^+$† | 1.45±0.72 | 1.70±0.73 | 1.07±0.56 | 0.131 |
| Imaging findings | | | | |
| Bilateral involvement | 49 (96.1%) | 29 (93.5%) | 20 (100.0%) | 0.674 |
| Interlobular thickening | 5 (9.8%) | 2 (6.5%) | 3 (15.0%) | 0.603 |
| Consolidation | 17 (33.3%) | 8 (25.8%) | 9 (45.0%) | 0.156 |
| Ground-glass opacity | 44 (86.3%) | 24 (77.4%) | 20 (100.0%) | 0.061 |
| Reticular pattern | 20 (39.2%) | 5 (16.1%) | 15 (75.0%) | <0.001 |
| Pleural effusion | 5 (9.8%) | 2 (6.5%) | 3 (15.0%) | 0.603 |
| Pulmonary edema | 6 (11.8%) | 0 (0.0%) | 6 (30.0%) | 0.005 |

The results were described as median (interquartile ranges), mean (standard deviations), or counts (percentages), as appropriate. *, data available for 24 patients; †, data available for 13 COVID-19 patients (8 severe cases and 5 critically severe cases). COVID-19, novel coronavirus disease 2019; $SpO_2$, percutaneous oxygen saturation; $PaO_2$, arterial oxygen pressure; $PaCO_2$, partial pressure of carbon dioxide; $FiO_2$, oxygen concentration; ESR, erythrocyte sedimentation rate; CD, cluster of differentiation; APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

 

**Table 4** Treatments, extrapulmonary comorbidities, and outcomes of critically ill patients with COVID-19

| Variables | All patients (n=51) | Severe (n=31) | Critically severe (n=20) | P value |
|---|---|---|---|---|
| Oxygen support | | | | <0.001 |
| Nasal cannula | 23 (45.1%) | 23 (74.2%) | 0 (0.0%) | – |
| High-flow nasal cannula | 8 (15.7%) | 6 (19.4%) | 2 (10.0%) | – |
| Non-invasive mechanical ventilation | 6 (11.8%) | 2 (6.5%) | 4 (20.0%) | – |
| Invasive mechanical ventilation | 14 (27.5%) | 0 (0.0%) | 14 (70.0%) | – |
| Prone position ventilation | 11 (21.6%) | 0 (0.0%) | 11 (55.0%) | <0.001 |
| ECMO | 2 (3.9%) | 0 (0.0%) | 2 (10.0%) | 0.290 |
| CRRT | 3 (5.9%) | 0 (0.0%) | 3 (15.0%) | 0.107 |
| Antiviral treatment | 51 (100.0%) | 31 (100.0%) | 20 (100.0%) | – |
| Oseltamivir | 11 (21.6%) | 7 (22.6%) | 4 (20.0%) | 1.000 |
| Lopinavir/ritonavir | 49 (96.1%) | 29 (93.5%) | 20 (100.0%) | 0.674 |
| Arbidol | 37 (72.5%) | 23 (74.2%) | 14 (70.0%) | 0.743 |
| Interferon | 50 (98.0%) | 31 (100.0%19) | 19 (95.0%) | 0.823 |
| Antibiotic treatment | 47 (92.2%) | 28 (90.3%) | 19 (95.0%) | 0.942 |
| Combined use of antibiotics | | | | <0.001 |
| Single antibiotic treatment | 18 (35.3%) | 17 (54.8%) | 1 (5.0%) | – |
| Combination of two antibiotics | 13 (25.5%) | 7 (22.6%) | 6 (30.0%) | – |
| Combination of three or more antibiotics | 16 (31.4%) | 4 (12.9%) | 12 (60.0%) | – |
| Antifungal treatment | 4 (7.8%) | 0 (0.0%) | 4 (20.0%) | 0.039 |
| Glucocorticoids | | | | |
| Methylprednisolone | 46 (90.2%) | 26 (83.9%) | 20 (100.0%) | 0.159 |
| Duration, days* | 5.0 (3.0, 8.0) | 5.0 (2.0, 7.0) | 6.0 (4.0, 10.5) | 0.095 |
| Daily dosage, mg* | 80 [40, 80] | 80 [40, 80] | 80 [40, 160] | 0.282 |
| Hydrocortisone | 2 (3.9%) | 0 (0.0%) | 2 (10.0%) | 0.290 |
| Intravenous immunoglobulin therapy | 28 (54.9%) | 13 (41.9%) | 15 (75.0%) | 0.021 |
| Human albumin | 26 (51.0%) | 11 (35.5%) | 15 (75.0%) | 0.006 |
| Blood transfusion | 15 (29.4%) | 2 (6.5%) | 13 (68.4%) | <0.001 |
| Thymalfasin | 27 (52.9%) | 14 (45.2%) | 13 (65.0%) | 0.166 |
| Diuretic | 29 (56.9%) | 12 (38.7%) | 17 (85.0%) | 0.001 |
| Xuebijing injection | 30 (58.8%) | 18 (58.1%) | 12 (60.0%) | 0.891 |
| Traditional Chinese medicine | 49 (96.1%) | 30 (96.8%) | 19 (95.0%) | 1.000 |
| rhBNP | 6 (11.8%) | 0 (0.0%) | 6 (30.0%) | 0.005 |
| Levosimendan | 5 (9.8%) | 0 (0.0%) | 25 (10.0%) | 0.014 |
| Vasoactive drugs | 12 (23.5%) | 0 (0.0%) | 12 (60.0%) | <0.001 |
| Dopamine | 7 (13.7%) | 0 (0.0%) | 7 (35.0%) | 0.002 |

**Table 4** (*continued*)

**Table 4** (*continued*)

| Variables | All patients (n=51) | Severe (n=31) | Critically severe (n=20) | P value |
|---|---|---|---|---|
| Noradrenaline | 12 (23.5%) | 0 (0.0%) | 12 (60.0%) | <0.001 |
| Sedatives | 15 (29.4%) | 1 (3.2%) | 14 (70.0%) | <0.001 |
| Propofol | 13 (25.5%) | 0 (0.0%) | 13 (65.0%) | <0.001 |
| Dexmedetomidine | 10 (19.6%) | 1 (3.2%) | 9 (45.0%) | 0.001 |
| Midazolam | 14 (27.5%) | 1 (3.2%) | 13 (65.0%) | <0.001 |
| Analgesic | 14 (27.5%) | 0 (0.0%) | 14 (70.0%) | <0.001 |
| Fentanyl | 13 (25.5%) | 0 (0.0%) | 13 (65.0%) | <0.001 |
| Dezocine | 1 (2.0%) | 0 (0.0%) | 1 (5.0%) | 0.823 |
| Neuromuscular blocking agents | 7 (13.7%) | 0 (0.0%) | 7 (35.0%) | <0.001 |
| Total liquid input in 5 days, mL[†] | 10,910 [9,447, 13,681] | 10,296 [7,950, 12,255] | 12,265 [10,387, 16,265] | 0.020 |
| Total liquid output in 5 days, mL[†] | 11,220 [8,510, 14,640] | 9,650 [7,400, 13,600] | 14,025 [9,738, 15,788] | 0.014 |
| Total liquid balance in 5 days, mL[†] | 340 [–1,543, 1,540] | 340 [–1,543, 1,550] | –21 [–1,750, 1,374] | 0.606 |
| Daily liquid balance, mL[†] | 68 [–309, 308] | 68 [–309, 310] | –4 [–350, 275] | 0.635 |
| Extrapulmonary comorbidities | 16 (31.4%) | 3 (9.7%) | 13 (65.0%) | <0.001 |
| Cardiac injury | 10 (19.6%) | 1 (3.2%) | 9 (45.0%) | 0.001 |
| Acute kidney injury | 5 (9.8%) | 0 (0.0%) | 5 (25.0%) | 0.014 |
| Liver dysfunction | 4 (7.8%) | 2 (6.5%) | 2 (10.0%) | 1.000 |
| Gastrointestinal hemorrhage | 7 (13.7%) | 1 (3.2%) | 6 (30.0%) | 0.022 |
| Clinical outcome | | | | 0.006 |
| Remained in hospital | 2 (3.9%) | 0 (0.0%) | 2 (10.0%) | – |
| Discharged | 46 (90.2%) | 31 (100.0%) | 15 (75.0%) | – |
| Died | 3 (5.9%) | 0 (0.0%) | 3 (15.0%) | – |
| Length of hospital stay, days | 20.0 (16.0, 26.0) | 20.0 (16.0, 23.0) | 24.5 (17.0, 31.5) | 0.091 |

The results were described as median (interquartile ranges), mean (standard deviations), or counts (percentages), as appropriate. *, data available for 38 patients; [†], data available for 47 patients. CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; rhBNP, lyophilized recombinant human brain natriuretic peptide.

replacement therapy (CRRT), 2 (10.0%) with a high-flow nasal cannula, and 2 (10.0%) with extracorporeal membrane oxygenation (ECMO) therapy (*Table 4*). The critically severe group, more cases received sedation, analgesics, vasoconstrictors, fluid and diuretics than in the severe group (*Table 4*).

Thirteen (65.0%) patients with critically severe disease had extrapulmonary organ injury: 9 (45.0%) had cardiac injury, 6 (30.0%) had gastrointestinal bleeding, 5 (25.0%) had acute kidney injury, and 2 (10.0%) had liver dysfunction (*Table 4*). The critically severe patients had worse clinical outcomes. Only 3 (15.0%) patients died in the critically severe group. The length of hospital stay was longer in the critically severe group, but the difference between the groups was not statistically significant (P=0.091).

## Discussion

Since December, 2019, COVID-19 has spread around the world, carrying with it considerable morbidity and mortality. The management of severe patients is the key point of treatment. We described the epidemiological,

 

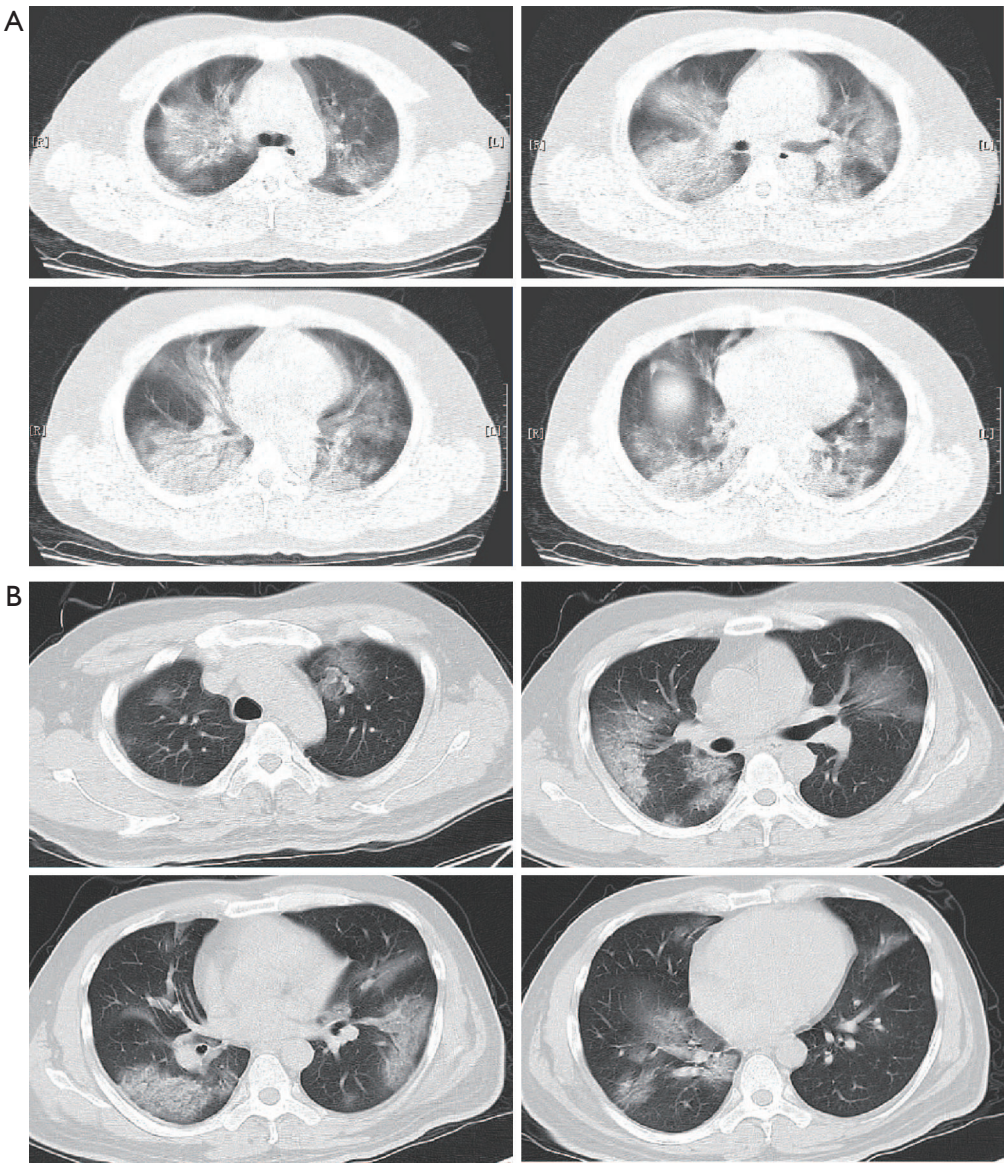


**Figure 2** Chest computed tomography of critically ill COVID-19 patients. (A) In most critically severe cases, chest computed tomogram scans demonstrated bilateral diffuse ground-glass opacities, reticular pattern, and consolidation; (B) in most severe cases, the main patterns of abnormality on chest computed tomogram included localized ground-glass opacity of both lungs.

clinical characteristics, and treatment status of these patients, with the aim of providing a valuable reference for other colleagues.

Half of the critically ill patients in this study were >60 years old, which is similar to the findings from Zhejiang province and wuhan area (4,7). Among the critically ill patients in Hebei, familial clusters accounted for almost half of cases, while none of these patients had a history of exposure to the Huanan seafood market. These results differ from findings in Wuhan but are similar to those in Zhejiang. The data in this study confirm significant human-to-human transmission of COVID-19 through close contact, which supports the restrictions introduced to minimize virus transmission by preventing people gathering in large groups. Similar to the findings of Huang *et al.*, gender, age distribution, and exposure history were similar in the two groups, but patients with underlying diseases had a higher risk of developing critically severe disease (8).

The rate of underlying diseases among critically ill patients, which is consistently predictive of a worse prognosis, was higher in Hebei than in Wuhan (5). Moreover, patients with critically severe COVID-19 had a longer duration from symptom onset to confirmation than those with severe disease.

Among the cardinal clinical symptoms like fever, cough, and expectoration was similar in both groups, while dyspnea was more common among patients with critically severe disease.

In terms of vital signs, the patients with critically severe COVID-19 had higher temperature, faster respiratory frequency, and more severe hypotension than those with severe disease, thus they required more respiratory and vasoactive support.

In patients with COVID-19, leucopenia and lymphopenia are common (7,8). However, Huang *et al*. (8) found that ICU patients had higher WBC and inflammatory cytokine levels than non-ICU patients, indicating that the severity of COVID-19 is associated with cytokine storm. An autopsy study (9) reported that the counts of peripheral CD4+ and CD8+ cells were markedly decreased in critically ill patients with COVID-19. Our laboratory results showed similar results; critically severe patients had higher WBC, neutrophil percentage, and C-reactive protein and procalcitonin levels, and lower lymphocyte percentage, T cell subsets, and $PaO_2/FiO_2$, which indicated stronger inflammatory response and more severe lung injury. Severe immune dysfunction in patients with critically severe COVID-19 may result in them receiving more broad-spectrum antibiotics. Patients in the critically severe group had mild coagulation disorders with slightly prolonged PT, and slightly elevated BUN and creatine kinase levels. Extrapulmonary complications, especially heart or kidney injury were common in the critically severe group, which was in line with the findings of previous studies (7,8). Patients with critically severe disease also had higher APACHE II and SOFA scores (7,8), and received more immunizing agents, albumin, and blood transfusions, as a result of the impact of the laboratory results.

Pan *et al*. (10) reported that only one or two lobes of the lung were damaged in early stages of COVID-19, with lung function remaining normal. As the disease progressed, the consolidations were gradually absorbed, resulting in ground-glass opacity or fiber-cord focus. In our study, chest CT imaging of patients with critically severe disease showed more ground-glass opacities, reticular pattern, and pulmonary edema, which is also similar with the findings of previous studies (10,11). Pulmonary edema may result from a severe increase in capillary permeability.

All of the patients in our study received antiviral therapy. Lopinavir/ritonavir, interferon, and arbidol are recommended in Chinese Clinical Guidelines for COVID Pneumonia Diagnosis and Treatment (7th edition). Arbidol is also recommended as antiviral treatment for influenza infection in Russia and China (12). The effect of interferon has previously been evaluated in clinical studies on Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), but its benefits are still under discussion (13,14). There are proven benefits of using traditional Chinese drugs to treat patients with mild COVID-19 (15), but their efficacy in the treatment of severe patients still needs to be studied.

Twenty (100%) of the patients with critically severe disease and 26 (83.9%) of the patients with severe disease received similar low doses of methylprednisolone, but the duration of treatment tended to be longer in the critically severe group. The use of corticosteroids for treating COVID-19 also presents a challenging problem. Because there is no clinical benefit in using corticosteroids to treat influenza, MERS, or SARS, the routine usage of corticosteroids for treating ARDS or shock associated with COVID-19 is not recommended by the World Health Organization (16). High-dose corticosteroids carry several potential risks, such as secondary infections, prolonged virus shedding, and long-term complications. However, the overwhelming inflammation in critically ill patients can lead their pneumonia to rapidly progress, and a physiologic or low dose of corticosteroids could alleviate the pulmonary fibrosis and prevent progressive pathological deterioration in patients with advanced ARDS, while also bringing earlier reversal of shock and a shorter length of ICU stay and mechanical ventilation (17-19). Moreover, a low-to-moderate dose of corticosteroids could reduce mortality in severe patients with influenza A ($PaO_2/FiO_2$ <300 mmHg) (20). Thus, in China, low-dose and short-course methylprednisolone (≤1–2 mg/kg per day, for 3–5 days) is recommended for patients with severe COVID-19. In addition, the use of corticosteroids should be cautiously applied in patients who have chronic hypoxemia or who receive regular corticosteroid therapy, due to underlying diseases (21).

Severe ARDS is the result of the pathophysiologic processes underlying severe COVID-19 infection, which is similar to SARS and MERS (5,22-25). The majority of patients with severe COVID-19 presented with mild ARDS,

 

and the patients with critically severe disease presented with more severe ARDS. Unfortunately, despite decades of research, the treatment of severe ARDS has remained focused on respiratory support, such as low tidal-volume mechanical ventilation, prone-position ventilation, and ECMO (26,27). In our study, 70% of patients with critically severe COVID-19 received invasive mechanical ventilation, more than 50% received prone-position ventilation, and 2 received ECMO. Lower plasma $PCO_2$ in patients with critically severe disease may indicate an unsatisfactory condition resulting from ventilator settings, sedation, or analgesia.

Fluid management is also important and challenging in ARDS. Compared with liberal fluid management, conservative fluid management may significantly decrease the severity of pulmonary edema, the duration of mechanical ventilation and ICU stay, and mortality in patients with ARDS (28,29). Our results showed that patients with critically severe COVID-19 received more fluids and more diuretics than patients with severe disease, suggesting that it may be difficult to follow a conservative liquid management strategy because of the severity of the disease.

Clinical outcome was worse in patients with critically severe COVID-19; they had a mortality rate of 15%, while no patients in the severe group died. Also, the length of hospital stay tended to be longer in the critically severe group. Further research is needed to explore the risk factors associated with worse outcome.

There are several limitations in the current study. First, the sample size of this study was small, which may only represent the characteristics of the patient population in Hebei, although it can also reflect some issues (e.g., characteristics of the patient group, treatment, etc.). Second, clinical data were limited in this retrospective study; thus, further evaluations in other regions need to be carried out.

## Conclusions

Overall, patients with underlying diseases and longer confirmation times were more likely to develop to critically severe COVID-19. The patients in the critically severe group also had a higher risk of respiratory depression, circulatory collapse, extrapulmonary complications, and infection.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients. This study was approved by the Ethics Commission of the Fourth Clinical Medical College of Hebei Medical University (2020KS002).



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