Original Article

Clinical diagnosis, treatment and outcome of critically ill patients with coronavirus disease 2019 infected by SARS-CoV-2 in Wuhan and Shenyang, China: A dual-center, retrospective, observational study

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ABSTRACT

Background and Objective: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is currently circulating worldwide. Our purpose was to describe the clinical diagnosis, treatment and outcome of severe cases of SARS-CoV-2 infection. **Methods:** In this study, we collected 86 critically ill adult patients with COVID-19 treated in ICU of Wuhan Red Cross Hospital and the Sixth People's Hospital of Shenyang from December 24, 2019 to February 10, 2021. Patients were divided into death group and survival group. The primary endpoint is the 28-day mortality rate, and the secondary endpoints were the incidence of acute respiratory distress syndrome (ARDS) and the proportion of patients requiring mechanical ventilation. **Results:** The average age of patients was 67.8 years, of whom 62 patients (72.1%) were male, 58 patients (67.4%) suffered from chronic diseases, and 84 patients (97.7%) had fever. The 28-day mortality rate was 53.5% (46/86 cases), and the average time from admission to ICU to clinical death was 7 days (IQR 3–11). There were 60 patients (69.7%) who occurred ARDS. There were 62 patients (72.1%) who required mechanical ventilation. And 37 patients (43.0%) received convalescent plasma treatment. Moreover, 30 patients (34.9%) were injected with tocilizumab. **Conclusions:** The mortality rate of critically ill patients with COVID-19 is high. The survival time of death cases is generally 1–2 weeks after entering the ICU. Old age, combined underlying diseases and ARDS are risk factors that increase the risk of death. Most critically ill patients require mechanical ventilation. Convalescent plasma and anti-IL-6 receptor monoclonal antibody may be effective immunotherapy methods.

Key words: severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, critically ill cases, acute respiratory distress syndrome, hypoxemia, mechanical ventilation

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) infection is a new infectious disease which is continuing to erupt globally.[1,2] As of February 10, 2021, 106,125,682 cases had been diagnosed globally and 2,320,497 patients (2.2%) were dead, moreover, fatality rate of critically ill cases is much higher than it.[3,4] Our research on the clinical diagnosis, treatment and outcome of critical COVID-19 cases is of great significance for early identification and treatment in order to reduce mortality of critical cases.

MATERIAL AND METHODS

Our dual-center, retrospective study was completed in Wuhan Red Cross Hospital and the Sixth People's Hospital of Shenyang, both of which are designated hospitals for COVID-19 treatment by the government. We retrospectively analyzed the confirmed critically ill cases of COVID-19 from December 24, 2019 to February 10, 2021 according to WHO interim guidelines and China's new coronavirus pneumonia diagnosis and treatment guideline.[5,6] The diagnostic criteria for critical cases are those who meet one of the following conditions: those with respiratory failure and requiring mechanical ventilation, those with shock, and those with other organ failure requiring ICU monitoring and treatment.[7,8] The data was evaluated and collected using the revised version of the International Severe Acute Respiratory and Emerging Infection Consortium medical record report template.[9]

The most important observation indicator was the 28-day mortality after entering the ICU. The secondary observation indicators are the incidence of acute respiratory distress syndrome (ARDS) and the proportion of patients requiring mechanical ventilation. The diagnosis of ARDS is based on the WHO guidelines for COVID-19.[5] The diagnosis of acute kidney injury is based on the increase of serum creatinine (SCr) by 0.5 mg/dL.[10] The diagnostic criteria for myocardial injury is that the serum troponin I (TNI) exceeds the upper limit of the normal reference value (> 0.5 ng/mL). The diagnosis for liver damage is that serum glutamyl transpeptidase (ALT) exceeds the upper limit of the normal reference value (> 40 U/L). Laboratory tests were carried out in the medical examination centers of Wuhan Red Cross Hospital and the Sixth People's Hospital of Shenyang. For the surviving cases as of February 10, 2021, their survival status were followed up until February 24, 2021.

For descriptive data, the mean ± standard deviation (SD) and median (IQR) were used to represent continuous variables, and the percentage (%) was used to represent categorical variables. When comparing the death group and survival group, two independent sample *t*-test or Wilcoxon rank sum test was used for parametric data or nonparametric data of continuous variables, and chi-square test was used for categorical variables.

Table1. Demographics and baseline characteristics of critically ill patients with COVID-19

Characteristics	Survivors (*N* = 40)	Non-Survivors (*N* = 46)	All patients (*N* = 86)
Age, years	50.6 ± 12.9*	70.4 ± 11.2	67.8 ± 15.3
Age range, *N* (%)			
30–39 years	4 (10.0)	2 (4.3)	6 (6.9)
40–49 years	3 (7.5)	1 (2.2)	4 (4.6)
50–59 years	3 (7.5)	3 (6.5)	6 (6.9)
60–69 years	13 (32.5)	13 (28.2)	26 (30.2)
70–79 years	7 (17.5)	15 (32.6)	22 (25.6)
≥80 years	8 (20.0)	14 (16.3)	22 (25.6)
Sex, *N* (%)			
Female	14 (35.0)	10 (21.7)	24 (27.9)
Male	30 (75.0)	32 (69.5)	62 (72.1)
Exposure, *N* (%)			
Exposure to patients[#]	17 (42.5)	23 (50.0)	40 (46.5)
Chronic medical illness	18 (45.0)*	40 (86.9)	58 (67.4)
Chronic cardiac disease	7 (17.5)	16 (34.8)	23 (26.7)
Chronic pulmonary disease	4 (10.0)	10 (21.7)	14 (16.3)
Diabetes	5 (12.5)	8 (17.4)	13 (15.1)
Cerebrovascular disease	2 (5.0)	3 (6.5)	5 (5.8)
Malignancy	0	3 (6.5)	3 (3.5)
Aplastic anemia	1 (2.5)	0	1 (1.2)
Infective endocarditis	1 (2.5)	0	1 (1.2)
Smoking	15 (37.5)	14 (30.4)	29 (33.7)

[#]Patients who have confirmed SARS-CoV-2 infection or are highly suspected of being infected. *$P < 0.05$ *vs.* non-survivors cases. COVID-19: coronavirus disease 2019.

SPSS version 26.0 (SPSS Inc., Chicago, USA) was used for analysis, and less than 0.05 is considered statistically different.

The Ethics Committee of Wuhan Red Cross Hospital and the Sixth People's Hospital of Shenyang agreed to this study. (No. KY-LW-2021-04-01) Due to the sudden epidemic of this infectious disease, written informed consent was exempted.

RESULTS

As of February 10, 2021, Wuhan Red Cross Hospital and Sixth People's Hospital of Shenyang have admitted 86 critical cases of COVID-19. The average age of the patients was 67.8 ± 15.3 years, and 70 patients (82.5%) were over 60 years old (Table 1). There were 62 male patients (72.1%). There were 40 patients (46.5%) who had contact history with confirmed or highly suspected patients. And 58 patients (67.4%) had chronic underlying diseases, of which 23 patients (26.7%) suffered from cardiovascular diseases.

The most common symptom was fever (97.7%), followed by cough (77.9%), and dyspnea (72.1%) (Table 2). Of the 86 severe cases, 6 (6.9%) developed fever 2–8 days after the onset of other symptoms. In all cases, lung X-ray or CT showed exudates from both lungs and typical ground glass shadows. The median time from onset of clinical symptoms to imaging manifestations of pneumonia, to entering ICU was 4.1 days (IQR 3.0–7.0) and 8.2 days (IQR 6.0–12.0), respectively.

Table 2. Symptoms, comorbidities, and treatments of critically ill patients with COVID-19

Items	Survivors (*N* = 40)	Non-Survivors (*N* = 46)	All patients (*N* = 86)
Symptoms, *N* (%)			
Fever	39 (97.5)	45 (97.8)	84 (97.7)
Cough	35 (87.5)	34 (73.9)	67 (77.9)
Dyspnoea	30 (75.0)	32 (69.5)	62 (72.1)
Malaise	18 (45.0)	24 (52.2)	42 (48.8)
Myalgia	14 (35.0)	13 (28.2)	27 (31.4)
Rhinorrhoea	11 (27.5)	9 (19.6)	20 (23.2)
Arthralgia	8 (20.0)	7 (15.2)	15 (17.4)
Chest pain	7 (17.5)	8 (17.4)	15 (17.4)
Headache	6 (15.0)	8 (17.4)	14 (16.3)
Vomiting	5 (12.5)	5 (10.8)	10 (11.6)
Comorbidities, *N* (%)			
Acute respiratory distress syndrome	20 (50.0)*	40 (86.9)	60 (69.7)
Acute kidney injury	19 (47.5)	27 (58.7)	36 (41.9)
Cardiac injury	18 (45.0)	28 (60.9)	36 (41.9)
Liver dysfunction	15 (37.5)	15 (32.6)	30 (34.9)
Hospital-acquired infection	10 (25.0)	17 (36.9)	27 (31.4)
Pneumothorax	2 (5.0)	1 (2.2)	3 (3.5)
Treatments, *N* (%)			
Mechanical ventilation	18 (45.0)*	44 (95.6)	62 (72.1)
Non-invasive	13 (32.5)	21 (45.6)	34 (39.5)
Invasive	11 (27.5)	17 (36.9)	28 (32.5)
Prone position ventilation	27 (67.5)	25 (54.3)	52 (60.5)
High flow nasal cannula	25 (62.5)	21 (45.6)	46 (53.5)
Extracorporeal membrane oxygenation	3 (7.5)	10 (21.7)	13 (15.1)
Antibacterial agents	36 (90.0)	44 (95.6)	80 (93.0)
Glucocorticoids	29 (72.5)	32 (69.5)	61 (70.9)
Antiviral agents	26 (65.0)	24 (52.2)	50 (58.1)
lopinavir/ritonavir	15 (37.5)	19 (41.3)	34 (39.5)
Remdesivir	11 (27.5)	5 (10.9)	16 (18.6)
Immunoglobulin	17 (42.5)	30 (65.2)	47 (54.6)
Convalescent plasma	27 (67.5)*	10 (21.7)	37 (43.0)
Vasoconstrictive agents	12 (30.0)	20 (43.5)	32 (37.2)
Tocilizumab Injection	23 (57.5)*	7 (15.2)	30 (34.9)
Blood purification	7 (17.5)	10 (21.7)	27 (31.4)
Renal replacement therapy	4 (10.0)	13 (28.2)	17 (19.7)

*$P < 0.05$ *vs.* non-survivors cases. COVID-19: coronavirus disease 2019.

The median Acute Physiology and Chronic Health Evaluation II (APACHE II) score of all the critical cases enrolled was 24 points (IQR 21–27), and the median SOFA score was 8 points (IQR 6–11). For death group and survival group, the median APACHE II scores were 26 points (IQR 24–29) and 21 points (IQR 19–24), respectively, and the median SOFA scores were 9 points (IQR 7–11) and 5 points (IQR 4–6), there is no significant difference between two groups (Table 3). The lymphocyte counts of 73 patients (84.9%) decreased. The death group and the survival group were 0.53×10^9/L and 0.7×10^9/L, respectively, and no statistical difference between them (Table 3).

Hospital acquired infections occurred in 27 patients (31.4%), which was based on the culture results of blood, sputum, urine, PICC tip and bronchoalveolar lavage fluid. Nine different microorganisms were detected, including multi-drug-resistant Acinetobacter baumannii (MDR-AB strain and CR-aba strain), extended-spectrum β-Lactamase (ESBL)-positive K pneumonia, carbapenem-resistant Klebsiella oxytoca (CRE strain), ESBL-positive and quinolone-resistant Escherichia coli (ESBL QNR-ECO strain),methicillin-resistant coagulase-negative Staphylococcus hominis, Methicillin-resistant Staphylococcus aureus (MRSA strain), high-levul-aminoglycoside -resistant Enterococcus faecalis (HLAR strain), methicillin-resistant coagulase-negative Staphylococcus capitis (Mrcon strain) and candida albicans.

Organ function damage occurred in most cases, including 60 patients (69.7%) of ARDS, 36 patients (41.9%) of acute kidney injury, 36 patients (41.9%) of myocardial damage, 30 patients (34.9%) of liver damage and 3 patients (3.5%) of pneumothorax (Table 2). The median value of Scr, TNI, ALT, IL-6, CRP and D-dimer was 89.8 μmol/L, 2.6 ng/mL, 72 U/L, 33.7 pg/mL, 110.3 mg/L and 35.8 mg/L, respectively. There was no statistical difference in above six indicators between death group and survival group (Table 3).

Among the patients, 62 patients (72.1%) received mechanical ventilation, 52 patients (60.5%) received prone position ventilation, 46 patients (53.5%) received high-flow nasal cannula oxygen, and 13 patients (15.1%) received extracorporeal membrane oxygenation (ECMO). Antibiotics were given to 80 patients (93.0%). Intravenous glucocorticoids were given to 61 patients (70.9%). There were 50 patients (58.1%) who received antiviral therapy, among which, 34 patients (39.5%) were given lopinavir/ritonavir, and 16 patients (18.6%) were given Remdesivi. Immunoglobulin therapy was given to 47 patients (54.6%). Convalescent plasma was received in 37 patients (43.0%). Vasoconstrictors were given to 32 patients (37.2%). Tocilizumab injection was given to 30 patients (34.9%). Blood purification therapy was given to 27 patients (31.4%). And there were 17 patients (19.7%) who received renal replacement therapy (Table 2). The criteria for these treatment therapies were based on two planes of China.[11,12]

Among 40 surviving cases, 28 patients were discharged from the

Table 3. Differences in intensive care measures and vital signs between survivors and non-survivors of critically ill patients with COVID-19

Items	Survivors (*N* = 40)	Non-Survivors (*N* = 46)	All patients (*N* = 86)
Duration from onset of symptoms to radiological confirmation of pneumonia, days	6.5 (3.0–9.0)	2.9 (2.0–6.0)	4.1 (3.0–7.0)
Duration from onset of symptoms to ICU admission, days	12.1 (7.0–14.0)	5.3 (3.0–9.0)	8.2 (6.0–12.0)
Heart rate, beat/min	89 (61–101)	95 (59–111)	92 (65–111)
Systolic blood pressure, mmHg	123 (90–149)	139 (88–150)	130 (92–157)
Ratio of PaO_2 to FiO_2, mmHg	105.2 (66.6–136.7)	57.9 (42.0–74.1)	83.1 (49.9–200.1)
APACHE II score on day 1	21 (19–24)	26 (24–29)	24 (21–27)
SOFA score on day 1	5 (4–6)	9 (7–11)	8 (6–11)
Lymphocyte count, $\times10^9$/L	0.7 (0.5–1.3)	0.5 (0.1–1.1)	0.6 (0.1–1.2)
IL-6, pg/mL	29.9 (21.1–42.1)	42.9 (29.9–65.2)	33.7 (26.8–49.6)
CRP, mg/L	99.8 (79.3–149.2)	130.1 (95.3–210.1)	110.3 (87.1–231.9)
D-dimer, mg/L	32.3 (20.9–51.1)	41.8 (30.5–60.1)	35.8 (20.6–49.7)
Prothrombin time, s	11.1 (8.1–14.7)	12.8 (9.7–16.9)	12.1 (9.6–17.3)
Glutamyltranspetidase, U/L	66 (23–109)	76 (30–262)	72 (27–262)
Serum creatinine concentration, μmol/L	77.5 (39.0–117.1)	91.7 (48.6–170.3)	89.8 (56.7–189.5)
Troponin I, ng/mL	2.1 (0.3–3.8)	2.5 (0.3–5.2)	2.6 (0.4–3.9)
Lactate concentration, mmol/L	1.3 (0.9–1.6)	3.0 (1.5–3.5)	2.3 (0.9–5.2)

Data are median (IQR). COVID-19: coronavirus disease 2019, APACHE II: acute physiology and chronic health evaluation II, FiO_2: fraction of inspired oxygen, PaO_2: partial pressure of oxygen, SARS-CoV-2: severe acute respiratory coronavirus 2, SOFA: sequential organ failure assessment, IL-6: interleukin-6, CRP: C-reactive protein.

hospital, and the other 12 patients were still in the hospital on the 28th day of admission to ICU, 3 of whom received invasive ventilator therapy, one case using non-invasive ventilator, 2 cases using high-flow nasal cannula for oxygen inhalation, and 6 cases using ordinary nasal cannula to inhale oxygen.

The most important observation is that critically ill patients died within 28 days after entering the ICU, and the median survival time from entering ICU to clinical death was 7 days (IQR 3–7). Compared with survival cases, death cases are more likely to progress to ARDS (40 [86.9%] *vs.* 20 [50.0%]) and are more likely to require mechanical ventilation (44 [95.6%] *vs.* 18 [45.0%]), and there are significant differences between two groups (Table 2). Of the 62 cases receiving mechanical ventilation, 38 patients (61.3%) died within 28 days.

Compared with patients in survival group, patients in death group were older (70.4 ± 11.2 years *vs.* 50.6 ± 12.9 years), and were more common with chronic diseases (40 [86.9%] *vs.* 18 [45.0%]), and the difference between two groups was statistically significant (Table 1). Patients in survival group, compared with death group, were more treated with convalescent plasma (27 [67.5%] *vs.* 10 [21.7%]) and tocilizumab injection (23 [57.5%] *vs.* 7 [15.2%]), and the difference between two groups was statistically significant (Table 2). In death group, the average time from onset of clinical symptoms to imaging manifestations of pneumonia and to ICU admission was 2.9 days and 5.3 days, respectively, which were significantly shorter than 6.5 days and 12.1 days in survival group (Table 3). The oxygenation index (OI, the ratio of PaO_2 to FiO_2) of the death group was significantly reduced to 57.9 mmHg. However, OI of survival group was 105.2 mmHg (Table 3).

DISCUSSION

We reported 86 laboratory-confirmed severe cases of COVID-19 caused by SARS-CoV-2 infection. And 58 patients (67.4%) of them suffered from chronic diseases. The patients were characterized by severe hypoxemia with significantly reduced oxygenation index. There were 46 patients (53.5%) who died within 28 days after entering ICU. Moreover, 60 patients (69.7%) progressed to ARDS, 62 patients (72.1%) required mechanical ventilation, 37 patients (43.0%) received convalescent plasma, and 30 patients (34.9%) were injected with anti-IL-6 receptor monoclonal antibody.

Since there are no specific antiviral drugs for SARS-CoV-2 infection, the most important measure at present is supportive treatment.[13–15] Therefore, critical cases should be transferred to ICU as soon as possible for organ function support. Among the previously published studies, the treatment for severe cases was mainly under extreme epidemic conditions.[16,17] Our study enrolled 86 critically ill cases whose treatment measures have become more perfect due to government's overall arrangement of medical personnel and rescue equipments.

Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 is also a coronavirus that can be transmitted to humans, with a high mortality rate for severely infected patients.[18] Our study found that the mortality rate of severe cases of SARS-CoV-2 infection was 53.5%, which was higher than the previous SARS and lower than MERS. A study of severe SARS cases from Canada showed that the 28-day mortality rate was 43%.[8] In addition, studies from Singapore[19] and Hong Kong, China[20] found that the 28-day mortality rate of severe SARS cases was 38% (17/45 cases) and 26% (14/54 cases), respectively. A study from Saudi Arabia found that the 90-day mortality rate of 12 people infected with MERS was 58%.[21] According to the limited autopsy and puncture histopathological observations, the pathological changes of SARS-CoV-2 infection are mainly lung consolidation. The pathophysiological basis of severe viral pneumonia is ARDS. Therefore, the mortality rate of severe SARS-CoV-2 infection is about 50%, similar to that of severe ARDS.[22]

In SARS and MERS patients, elderly men are more likely to progress to critically ill cases than elderly women and young men.[23] Similar to previous studies, our study observed that 72% of COVID-19 critical cases were male with a median age of 68 years, and the average age of the death group was 19.8-year (70.4–50.6 years) higher than survival group.[24,25] Suffering from chronic diseases is an increased risk factor for death.

In our research, fever is the most common symptom of COVID-19 critically ill patients in the early stage of onset, but not all cases have fever symptoms. We found that 6 patients (6.9%) did not develop fever at the time of onset. The delayed appearance of the obvious clinical symptoms of fever is not conducive to the early recognition of SARS-CoV-2 infection, however, of whom are already infectious at this time. This means that routine SARS-CoV-2 nucleic acid screening for high-risk infectious populations may be identify infected persons early, even in the asymptomatic stage, which is very beneficial for isolating the source of infection and blocking the spread of the virus.

Regarding laboratory tests, in our study, more than 92% of critically ill cases had decreased lymphocyte counts. This is mainly due to the SARS-CoV-2 virus targeting lymphocytes, especially T-lymphocytes.[26] Decrease in lymphocytes in critically ill patients with MERS is also common, nevertheless, the main cause is apoptosis.[27] Therefore, we speculate that cell necrosis or apoptosis is the possible cause of the decrease of lymphocyte counts in severe SARS-CoV-2 cases. Degree of lymphocyte reduction may be an important reason for the deterioration of the patient's condition.[28] In our study, we also observed that the degree and duration of lymphocyte count decrease in the death group were more significant than those in the survival group, and there was no obvious improvement after treatment in dead cases.

In this study, more than 79% of critical cases had abnormally elevated levels of three typical pro-inflammatory cytokines including Interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF), especially IL-6. This indicated that a significant cytokine

storm, cytokine release syndrome (CRS), occurred in critical cases.[29] The damage of lung cells caused by SARS-CoV-2 virus particles does not directly lead to death. The main cause leading to death is excessive activation of non-specific immune cells, which release a number of pro-inflammatory factors resulting in the damage of alveolar capillary epithelial cells. Then a large amount of blood flows out of capillary and fills pulmonary alveoli, which affects respiratory function. In addition, the study found that the inflammatory markers CRP in critically ill patients also increased significantly. With dynamically monitoring the changes of IL-6 and CRP, 27 critical cases were exactly identified whose prognosis significantly improved resulting with being treated in time. These results suggest that IL-6 and CRP can be used as early warning indicators of disease deterioration.

Mechanical ventilation is the most important respiratory support method in critical cases. In our study, the proportion of mechanical ventilation was 72.1%, of which invasive mechanical ventilation was 32.5%, and ECMO was 15.1%. The indication for ECMO is when FiO_2 > 90%, the oxygenation index is less than 80 mmHg for 3–4 hours, and the airway plateau pressure is ≥ 35 cmH_2O. The study found that there is a significant difference of oxygenation index between dead cases and survival ones, suggesting that the oxygenation index is closely related to disease progression and outcome. When entering the ICU, there was no significant difference in APACHEII and SOFA scores between death group and survival group. It indicates that the initial impairment occurred in critical cases is lung injury, and then other organ function impairments will occur one after another with disease progressing. In our study, only 3 patients (3.5%) occurred barotraumas, which was mainly related to 28-day use of ventilator and ECOM. However, approximately 25% of SARS patients suffered barotrauma in 2003.[20] At present, the incidence of barotraumas has been significantly reduced, which is related to the widespread use of protective ventilation when using ventilators,[30] which benefits from standardized training after SARS.

In this study, 37 patients (43%) received convalescent plasma which can provide antibody-secreting cells (ASCs), follicular helper T cells (Tfh), activated $CD4^+$ T and $CD8^+$ T cells.[31] The amount of plasma used to each patient was 1200–2000 mL. Among 37 cases achieving convalescent plasma, 27 patients (72.9%, 27/37) were alive, 30 patients (81.1%, 30/37) produced synthetic antibody whose IgG antibody titer increased by more than 300 times. The convalescent plasma may be an effective immunotherapy for COVID-19, however, indications, timing, dosage, evaluation indicators need to be further studied in larger samples. And 34.9% (30/86) of critically ill patients with significantly elevated level of IL-6 and extensive lesions in both lungs were treated with tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor that can inhibit IL-6 signaling pathway by binding to it, which blocks the excessive pulmonary inflammation driven by IL-6. The dosage was 4–8 mg/kg body weight, and the cumulative administration was up to two times. Among 30 cases injecting tocilizumab, 23 patients (76.7%, 23/30) were alive, 20 patients (66.6%, 20/30) whose IL-6 level decreased more than 30 times. It indicated that IL-6 receptor inhibitors may be an effective therapeutic drug.

In our research, 58.1% (50/86) of patients received antiviral therapy, of which 68.0% (34/50) used Lopinavir/Ritonavir, and 32.0% (16/50) used Remdesivir. Lopinavir/Ritonavir is a protease inhibitor that can inhibit the maturation of virus particles.[32] Its application is based on an ongoing Chinese clinical registration trial study (ChiCTR2000029308). Remdesivir is an adenosine triphosphate analog that inhibits virus-dependent RNA polymerase.[33,34] In Wuhan, recruits for Remdesivir include mild and medium SARS-CoV-2 cases (NCT04252664) and severe cases (NCT04257656). However, Remdesivir was not recommended for use in the guideline on drugs for COVID-19 issued by WHO in November, 2020.[35] More than half of the patients received intravenous glucocorticoids. In these cases, the oxygenation index gradually deteriorated and pneumonia progressed rapidly, accompanied by overactivated inflammatory response. Although intravenous glucocorticoids are commonly used in the treatment of severe SARS and MERS pneumonia, its use in SARS-CoV-2 pneumonia is also controversial.[36] With continuous improvement of the treatment of COVID-19, glucocorticoids was strongly recommended for critically ill patients in the guideline issued by WHO in November, 2020.[35] For 40 patients in survival group, psychological assessment was managed in rehabilitation stage using Posttraumatic Sreess Disorder Check List (PCL), Generalized Anxiexy Disorder-7 (GAD-7) and Insomnia Severity Indexto-7 (ISI-7) to evaluate PTSD symptoms, depression, anxiety and stress. 23 patients (57.5%) displayed different degrees of the aforementioned conditions, which were significantly higher than non-infected population. Until now, there is no report on the psychological treatment of COVID-19. Nevertheless, psychological impact of COVID-19 has been paid much attention, and psychosocial crisis prevention and intervention models should be urgently developed.[37] In Chinese guideline, it has been proposed to evaluate psychological situation of sober patients and do psychological nursing.[11] The relevant implementation details need to be further explored.

RESEARCH LIMITATIONS

First, only 86 cases were included in this study. However, the number of cases is still much larger than the previous studies. We hope that the results of the study can encourage further exploration of the diagnosis and treatment strategies for critical COVID-19 cases. Second, the current treatment measures for critical COVID-19 cases are limited. The methods used in this study, such as convalescent plasma, IL-6 receptor inhibitors, antiviral drugs, and glucocorticoids treatment, still need to explore its safety and effectiveness in depth.

CONCLUSIONS

Critical COVID-19 cases infected with SARS-CoV-2 have a

higher mortality rate. Old age, chronic diseases and ARDS increase the risk of death. The oxygenation index is closely related to disease severity, progression and clinical outcome. Mechanical ventilation is currently the main rescue measure for critical cases. Convalescent plasma and anti-IL-6 receptor monoclonal antibody may be effective immunotherapy methods.

Ethics approval

This study was approved by the Ethics Committee of The Sixth People's Hospital of Shenyang. (No. KY-LW-2021-04-01)

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020;91:157–160.
2. Spinelli A, Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. Br J Surg 2020;107:785–787.
3. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775–1776.
4. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. JAMA 2020;323:1839–1841.
5. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus- (ncov)- infection-is-suspected. Accessed on February 8, 2020.
6. New coronavirus pneumonia prevention and control program (Trial version 7). 2020. Available at: http://www.nhc.gov.cn/jkj/s3577/202001/c67cfe29ecfl470e8c7fc47d3b75le88.shtml. Accessed on March 4, 2020.
7. Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, *et al*. Critically ill patients with 2009 influenza A (H1N1) in Mexico. JAMA 2009;302:1880–1887.
8. Fowler RA, Lapinsky SE, Hallett D, Detsky AS, Sibbald WJ, Slutsky AS, *et al*. Critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:367–373.
9. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). Available at: https://isaric.tghn.org/. Accessed on January 25, 2020.
10. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. 2012. Available at: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf. Accessed on February 8, 2020.
11. New Coronavirus pneumonia diagnosis and treatment plan (Trial version 8). 2020. Available at: http://www.nhc.gov.cn. Accessed on August 18, 2020.
12. Clinical treatment plan for convalescent plasma of recovery patients with COVID-19 (Trial version 2). 2020. Available at: http://www.nhc.gov.cn. Accessed March 4, 2020.
13. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020;14:69–71.
14. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020;20:398–400.
15. Baden LR, Rubin EJ. Covid-19 - the search for effective therapy. N Engl J Med 2020;382:1851–1852.
16. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–481.
17. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al*. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA 2020;323:1582–1589.
18. Parry J. Wuhan: Britons to be evacuated as scientists estimate 44 000 cases of 2019-nCOV in the city. BMJ 2020;368:m351.
19. Lew TW, Kwek TK, Tai D, Earnest A, Loo S, Singh K, *et al*. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:374–380.
20. Gomersall CD, Joynt GM, Lam P, Li T, Yap F, Lam D, *et al*. Short-term outcome of critically ill patientswith severe acute respiratory syndrome. Intensive Care Med 2004;30:381–387.
21. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, *et al*. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160:389–397.
22. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, *et al*. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788–800.
23. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016;14:523–534.
24. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
25. Wang DW, Hu B, Hu C, Zhu FF, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–1069.
26. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, *et al*. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202:415–424.
27. Chu H, Zhou J, Wong BH, Li C, Chan JF, Cheng ZS, *et al*. Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. J Infect Dis 2016;213:904–914.
28. Liu WJ, Zhao M, Liu K, Xu K, Wong G, Tan W, *et al*. T-cell immunity of SARS-CoV: implications for vaccine development against MERS-CoV. Antiviral Res 2017;137:82–92.
29. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–513.
30. Liu L, Yang Y, Gao Z, Li M, Mu X, Ma X, *et al*. Practice of diagnosis and management of acute respiratory distress syndrome in mainland China: a cross-sectional study. J Thorac Dis 2018;10:5394–5404.
31. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, *et al*. Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;21:80–90.
32. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MML, *et al*. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399–406.
33. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, *et al*. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS CoV. Nat Commun 2020;11:222.
34. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al*. Remdesivir and chloroquine effectively inhibit therecently emerged novel coro-

navirus (2019-nCoV) in vitro. Cell Res 2020;30:269–271.
35. Rochwerg B, Siemieniuk RA, Agoritsas T, Lamontagne F, Askie L, Lytvyn L, *et al*. A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379.
36. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473–475.
37. Dubey S, Biswas P, Ghosh R, Chatterjee S, Dubey MJ, Chatterjee S, *et al*. Psychosocial impact of COVID-19. Diabetes Metab Syndr 2020;14:779–788.