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Critically ill patients with COVID-19 with ECMO and artificial liver plasma exchange

A retrospective study

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Abstract

COVID-19 is an emerging infectious disease capable of causing severe pneumonia. We aimed to characterize a group of critically ill patients in a single-center study.

This was a retrospective case series of 23 patients with confirmed COVID-19-related critical illness in the intensive care unit (ICU) of a hospital in Hangzhou Zhejiang Province between January 22 and March 20, 2020.

Of the 23 critically ill patients, the median age was 66 years (interquartile range [IQR] 59–80 years). The median time from disease onset to ICU admission was 10 days (IQR 6–11 days), to mechanical ventilation (MV) was 11 days (IQR 7.75–13 days), to artificial liver plasma exchange was 12 days (IQR 9.75–14.75 days), and to extracorporeal membrane oxygenation (ECMO) was 22 days (IQR 17.5–30 days). Nine patients required high flow oxygen. Fourteen patients received MV. Six required ECMO. Nine received artificial liver plasma exchange. Mortality was 0 at day 28.

Mortality was 0 at day 28 in our single-center study. Extracorporeal membrane oxygenation reduced the requirements for ventilator support. Artificial liver plasma exchange significantly reduced inflammatory cytokine levels. These supportive therapies helped to extend the patients' survival times and increase the chance of follow-up treatments.

Abbreviations: APACH II = Acute Physiology and Chronic Health Evaluation, COPD = chronic obstructive pulmonary disease, COVID-19 = 2019 coronavirus disease, CRP = C-reactive protein, DIC = disseminated intravascular coagulation, ECMO = extracorporeal membrane oxygenation, ELISA = enzyme-linked immunosorbent assay, ESR = erythrocyte sedimentation rate, ICU = intensive care unit, IL = interleukin, IQR = interquartile range, LDH = lactate dehydrogenase, MERS-CoV = Middle East respiratory syndrome coronavirus, MV = mechanical ventilation, pH = potential of hydrogen, SARS-CoV = severe acute respiratory syndrome coronavirus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SD = standard deviations, SOFA = Sequential Organ Failure Assessment, TBil = total bilirubin.

Keywords: artificial liver plasma exchange, COVID-19, critically, ECMO, ill

1. Introduction

In December 2019, an outbreak of acute pneumonia, now named coronavirus disease 2019 (COVID-19), was detected in Wuhan, China. Coronaviruses are RNA viruses belonging to the Coronaviridae family and are widely distributed.[1] In just 5 months, the disease was confirmed in >205 different countries; among them, the United States of America has the most laboratory-confirmed cases, reaching >278,458 cases on April 5. The mortality in Italy, with the second largest number of patients, may be as high as 7% according to the statistics provided by the Italian government. The mortality rate was 2.01% in China according to national official statistics.[2] The

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epidemics of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) led to >10,000 cumulative cases during the past 2 decades and, compared with COVID-19, had a higher mortality rate of 10% for SARS and 37% for MERS.

A few studies have made progress in the discovery of the epidemiological, clinical, and molecular characteristics of COVID-19.[3] Guan et al[4] collected the largest number of samples in China from 1099 patients with laboratory-confirmed COVID-19, and concluded that the COVID-19 epidemic spreads rapidly through human-to-human transmission. Factors including respiratory rate, oxygen saturation, chest x-ray/CT manifestations, and blood leukocyte/lymphocyte count predict clinical outcomes. Wang et al[5] found that patients with complications or with dyspnea and anorexia were more likely to require care in the ICU. A study researched 52 severely ill patients with COVID-19 in the ICU and reported that most patients had multiple organ function damage.[6] In addition, nonsurvivors were older, more likely to develop ARDS, and more likely to receive mechanical ventilation (MV), either invasive or noninvasive.[6] The mortality of critically ill patients was high, and 61.5% patients died within 28 days.[6] To date, no single center has reported the clinical spectrum, laboratory indexes, ventilator parameters, ECMO, and artificial liver plasma exchange conditions of COVID-19-related critically ill patients in detail. The objectives of this study were to describe the epidemiology, clinical features, and predictors of 28-day outcomes of 23 critically ill patients with COVID-19 requiring invasive ventilation, ECMO, and artificial liver plasma exchange.

2. Methods

2.1. Study design and participants

This retrospective, single-center, observational study was performed at The First Affiliated Hospital of Medical College of Zhejiang University (Hangzhou, China), which is a designated hospital to treat patients with COVID-19. The patients with COVID-19 were diagnosed from January 22 to March 20 according to the interim World Health Organization guidelines.[7,8] Patients were enrolled in our study if they required high concentration oxygen supplementation (oxygen therapy with $FiO_2 \geq 50\%$), if they presented signs and symptoms of shock or if they had any other conditions that required advanced life support. The ethics commission of the First Affiliated Hospital of Medical College of Zhejiang University approved this study. Oral consent was obtained from participants or their families when data were collected retrospectively.

2.2. Data collection

Data on the hospitalized patients were collected from electronic medical records and nursing records by 2 experienced physicians from the ICU. A second team of 2 experienced physicians verified and updated information in a standardized format. Any ambiguous or missing records were clarified through direct communication with the attending clinicians, patients, or their family members.

The data collected included age, sex, occupation, medical history (initial symptoms, exposure history), chronic complications, and basic information at ICU admission including Acute Physiology and Chronic Health Evaluation (APACHE) II scores,[9] Sequential Organ Failure Assessment (SOFA) scores,[10] laboratory findings, ventilator parameters the first day of MV (before and after ECMO), cytokine changes before and after artificial liver plasma exchange.

2.3. Laboratory confirmation strategy for nucleic acid tests

Throat swabs, nose swabs, and sputum samples were obtained from each suspected patient and sent simultaneously to our clinical laboratory department and Centers for Disease Control and Prevention in Hangzhou to detect COVID-19 by real-time quantitative polymerase chain reaction analysis. We will recollect and retest the samples the next day if the first result was negative.

2.4. Cytokine measurement

Plasma cytokines interleukin (IL)-6 and IL-10 were measured using enzyme-linked immunosorbent assay. The samples were sent to the clinical laboratory department in the First Affiliated Hospital, College of Medicine, Zhejiang University for testing.

2.5. Management of ventilated patients

Management of MV was performed in accordance with the protocol proposed by the ARDS Network as much as possible.[11,12] When patients could not maintain adequate oxygenation with MV, adjunctive therapies such as glucocorticosteroid therapy and prone positioning were also used at the discretion of the physician.

2.6. Drug and supportive treatment

Lopinavir/ritonavir (2 tablets every 12 hours) combined with Arbidol (200 mg 3 times a day) were used as for the basic treatment scheme. Chloroquine phosphate was used if the basic scheme did not work. Glucocorticoids (40 mg every 12 hours) combined with intravenous immunoglobulin (0.4 g/kg of body weight) were administered once daily for at least 3 consecutive days for those who needed high-level ventilator support. Microecologics such as prebiotics or probiotics were given to patients who showed intestinal microbial dysbiosis. Human serum albumin was used for those suffering hypoproteinemia. Traditional Chinese Medicine was used as supportive therapy (supplementary Table 1, http://links.lww.com/MD/E478).

2.7. Laboratory safety

Specimens were transported in special tanks and boxes that met biosafety requirements. Personal protective equipment was in accordance with the BSL-3 laboratory protection requirements in doing respiratory tract specimen collection, nucleic acid testing, and viral culture. Personal protective equipment was in accordance with BSL-2 laboratory protection requirements for biochemical and immunological tests and other routine laboratory tests.

2.8. Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY). Continuous variables were expressed as the medians and IQR or means and standard deviations (SD) as appropriate. The data between groups were compared by

2-sample *t* test or Wilcoxon rank-sum test depending on parametric or nonparametric data for continuous variables and Fisher exact test for categorical variables. *P* values <.05 were regarded as statistically significant.

3. Results

3.1. Patient characteristics and spectrum of clinical course

From January 22 to March 20, 28 confirmed patients were admitted to the COVID-19 ICU. Among these patients, 5 did not meet our definition for critical illness: 1 patient was admitted because of pregnancy and the other 4 patients were admitted due to their advanced age; hence, they were excluded. Twenty-three patients were ultimately investigated in our study.

Baseline characteristics are presented in Table 1. One patient was a health care worker transferred from another hospital. The median age was 66 years (IQR 59—80), and 18 (78%) were men. The most common symptoms were fever (70%) and cough (43%), which was in agreement with previous reports.[6,13] In those 23 patients, 30% had ≥1 previous medical conditions. Hypertension (15 [65%]) and diabetes (5 [22%]) were the most common coexisting comorbidities. The median APACHE II score of all patients at ICU admission was 7 (IQR 5–13), and the SOFA score was 3 (IQR 3–6). In total, 14 (61%) patients required MV, 10 (43%) received artificial liver plasma exchange, and 6 (26%) required ECMO. All patients received lopinavir/ritonavir, and other supportive treatments are listed in Table 1.

Of the 23 patients, all had abnormal chest CT images showing bilateral pneumonia. Typical image findings of infected patients were multiple subsegmental or lobular areas of ground glass opacities or consolidation (Fig. 1).

From disease onset, the median time to hospital admission was 4 days (IQR 1–5 days), to ICU admission was 10 days (IQR 6–11 days), to MV was 11 days (IQR 7.75–13 days), to artificial liver plasma exchange was 12 days (IQR 9.75–14.75 days) and to ECMO was 22 days (IQR 17.5–30 days). Of the patients who discharged from the ICU by March 20, 2020: the median ICU length of stay was 11 days (IQR 6–14 days) (Fig. 2).

Mortality, MV support and location of patients at 28 days from disease onset are shown in Table 2.

Table 1

Characteristics of patients on admission to the intensive care unit.

Characteristics	Patient (n = 23)
Age, y	66 (59–80)
Man	18 (78%)
Health care workers	1 (4%)
Selected presenting signs and symptoms	
Fever	16 (70%)
Cough	10 (43%)
Diarrhea	4 (17%)
Myalgia	4 (17%)
Shortness of breath	3 (13%)
No obvious disease symptoms	1 (4%)
Comorbidities	
Valvular heart disease	1 (4%)
Hypertension	8 (35%)
Liver transplantation	1 (4%)
Diabetes mellitus	1 (4%)
Renal failure	
≥ Complications	7 (30%)
APACHE II score	7 (5–13)
SOFA score	3 (3–6)
Requiring MV	14 (61%)
Requiring artificial liver plasma exchange	10 (43%)
Requiring ECMO	6 (26%)
Drug treatment	
Lopinavir/ritonavir and abidor	23 (100%)
Traditional Chinese Medication	19 (82.61%)
Microecologics	18 (78.26%)
Immunoglobulin and glucocorticoids	12 (40%)
Human serum albumin	9 (30%)

APACHE = Acute Physiology and Chronic Health Evaluation, ECMO = extracorporeal membrane oxygenation, MV = mechanical ventilation, SOFA = Sequential Organ Failure Assessment.
Values are numbers (percentages) except for the following: age, APACHE II score, SOFA score, which are presented as median (interquartile range).

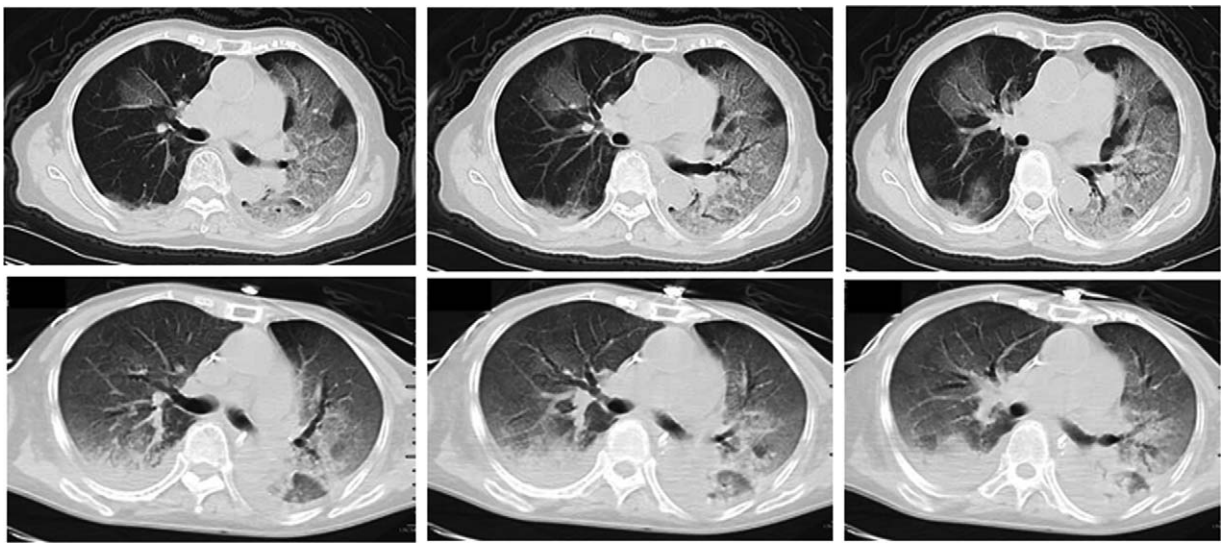

Figure 1. Transverse chest computed tomograms from an 81-year-old woman, showing bilateral ground glass opacity on ICU admission (top row). Twelve days later, she developed bilateral consolidation and ground glass opacity (bottom row).

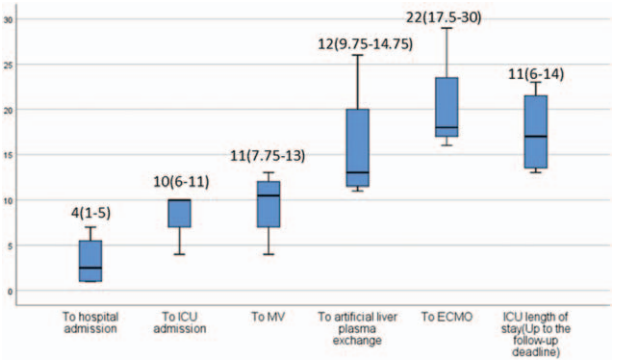

Figure 2. Time course (median [IQR], days) of clinical progression for patients becoming critically ill with COVID-19. ICU = intensive care unit, IQR = interquartile range, ECMO = extracorporeal membrane oxygenation, MV = mechanical ventilation.

3.2. Laboratory parameters of ICU patients

Nine (39%) patients were treated with high-flow nasal cannula, and 14 (61%) required MV. We compared laboratory indicators on the first day of ICU admission of patients with and without invasive MV (some patients did not require invasive MV on admission, and as the disease worsened, they had to be put on invasive ventilators). The white blood cell counts for each group, respectively, were 12.3×10^9cells/L (IQR 4.7×10^9–14.9×10^9 cells/L) and 10.1×10^9 cells/L (IQR 7.8×10^9–18.2×10^9 cells/L) ($P \geq .05$). Both groups showed lymphopenia: 10.1% (IQR 7.8%–18.2%) ($P \geq .05$). Higher serum creatinine levels were found in who required invasive ventilaton: 64 μmol/L (60.5–81.5 μmol/L) versus 93 mol/L (68–126.75 μmol/L), but the difference was not statistically significant. The median levels of D-dimer, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), interleukin (IL)-6, and IL-8 were higher than the normal range in both groups (Table 3).

Table 2

Clinical outcomes for critical illness with COVID-19.

Outcomes	Patients (N = 23)
28-Day mortality	0
MV dependency at 28 days	12 (52%)
Location of patients at 28 days after initial symptoms	
ICU	13 (56%)
Hospital ward	5 (22%)
Home	5 (22%)

ICU = intensive care unit.

Table 3

Characteristic of patients with COVID-19 not requiring versus requiring invasive MV.

Characteristics		Not requiring invasive MV	Requiring invasive MV	*P*
Age, y, median (IQR)		72 (59.75–83)	61 (49.5–71)	.08
Sex				
Men		8	10	.3
Women		1	4	.3
Comorbidities				
Valvular heart disease		1	0	.9
Hypertension		3	5	.9
Liver transplantation		0	1	.9
Diabetes mellitus		1	0	.9
≥2 Complications		2	5	.9
First day in ICU				
Laboratory findings,median (IQR)	**Range**			
WBC (10×10^9 cells/L)	4–10	10.1 (7.8–18.2)	12.3 (4.7–14.9)	.8
NE	50%–70%	92.7% (85.65%–93.55%)	92.1% (83.83%–94.7%)	.9
LY	20%–40%	2.8% (2.55%–8.35%)	3.95% (2.2%–11.95%)	.9
D-dimer, μg/L	0–700	793.5 (602.5–862)	916.5 (454.75–1708.75)	.3
LDH, U/L	120–250	329 (290.5–419)	354.5 (326.25–437.25)	.9
Cr, μmol/L	41–73	64 (60.5–81.5)	93 (68–126.75)	.6
CTnI, ng/mL	0–0.034	0.008 (0.003–0.02)	0.0085 (0.0033–0.0435)	.2
LAC, mmol/L	0.5–1.6	1.7 (1–2.5)	1.4 (1–1.93)	.3
TBil, μmol/L	0–21	15.9 (6.85–27.9)	14.4 (8.58–21.95)	.6
ESR, mm/h	0–15	54 (33.75–82)	63.5 (33–82.75)	.8
PCT, ng/mL	0–0.05	0.06 (0.045–0.85)	0.15 (0.05–0.6)	.4
IL-6, pg/mL	0–6.61	41.36 (15.69–180.92)	64.62 (40.35–141.6)	.4
IL-10, pg/mL	0–2.31	5.45 (3.25–9.72)	6.7 (3.94–11.32)	.8
First day of ventilator parameters of Invasive MV				
Tidal volume, median (IQR), mL			414.3 (267.5–625)	
Minute volume, L			6.9 (5.9–8.3)	
Peak pressure, median (IQR), cmH2O			28 (26.8–30)	
PEEP, median (IQR), cmH_2O				
Mean			12.6 (12–14)	
Maximum			15	

Cr = creatinine, CTnI = cardiac troponin I, ESR = erythrocyte sedimentation rate, IL = interleukin, IQR = interquartile range, LAC = lactic acid, LDH = lactic dehydrogenase, LY = leukomonocyte, MV = mechanical ventilation, NE = neutrophile, PCT = procalcitonin, TBil = total bilirubin, WBC = white blood cell, y = year.

Table 4

Medical management before venovenous extracorporeal membrane oxygenation.

Medical management	Patients (N = 6)
Duration of MV before ECMO, days	12.5 (6.8–19.8)
Pre-ECMO treatment	
NMBA	1
Prone position	2
Steroid	6

ECMO = extracorporeal membrane oxygenation, MV = mechanical ventilation, NMBA = neuromuscular blocking agent.

3.3. Ventilator management

We summarized ventilator parameters on the first day of MV. Pressure-controlled ventilation mode was applied in all patients. The median tidal volume was low and approximately 6.5 mL/kg (IQR 4.4–8.4 mL/kg). Tidal volume exceeded 9 mL/kg in 1 patient with chronic obstructive pulmonary disease (COPD). The median peak airway pressure was 28 cmH_2O (IQR 26.8–30 cmH_2O). We usually employed high PEEP on the first day (median PEEP was 12.6 cmH2O [IQR 12–14 cmH_2O]) to maintain oxygen saturation 88% to 92% and as patients recovered, the value was gradually reduced (Table 3).

3.4. Medical management before ECMO

Treatment modalities for patients before ECMO initiation are shown in Table 4. Two patients received ventilation in the prone position for 12 to 16 h/day. One patient received neuromuscular blocking agents for strong spontaneous breathing. All 6 patients received methylprednisolone at least 40 mg every 12 hours. The duration of MV before initiation of ECMO was 12.5 days (IQR 6.8–19.8 days).

3.5. Laboratory and ventilation characteristics pre and post ECMO

As shown in Table 5, the serum C-reactive protein (CRP), total bilirubin (TBil), and potential of hydrogen (pH) values were higher after ECMO initiation in the first 72 hours, whereas serum $PaCO_2$ was lower ($P < .01$). Other laboratory findings were not different between the 2 groups.

Table 6

Ventilator parameters and blood gas changes pre and during the first 72 hours after initiation of venovenous extracorporeal membrane oxygenation.

Ventilator parameters	Pre-ECMO MV setting	Post-ECMO MV setting	P
PaO_2/FiO_2	96 (55.4–103.8)	329.4 (269.8–398.4)*	<.01
PEEP, cmH_2O	11.5 (9.2–12)	5.2 (4.6–5.8)*	<.01
Minute volume, L/min	6.8 (5.6–8.9)	9.3 (8–11.1)*	<.05
Tidal volume, mL	525 (287.5–625)	650 (500–800)*	<.05
Peak inspiratory pressure, cmH_2O	28.5 (25–30.5)	20 (18.8–21)*	<.05
Respiratory rate, breaths/min	18 (14.3–25.5)	15 (13.5–22.8)	.4

ECMO = extracorporeal membrane oxygenation, MV = mechanical ventilation.
* $p < 0.05$.

The differences in the PaO_2/FiO_2 ratio and ventilation parameters before and after ECMO are shown in Table 6. The PaO_2/FiO_2 ratio was greatly improved after ECMO: 329.4 (IQR 269.8–398.4) after ECMO versus 96 (IQR 55.4–103.8) before ECMO, $P < .01$. Ventilator parameters were greatly decreased, including PEEP and peak inspiratory pressure ($P < .01$). At the same time, minute volume and tidal volume were greatly improved ($P < 0.05$).

3.6. Artificial liver plasma exchange

Nine patients underwent artificial liver plasma exchange. Each patient received 3 times on average. Among these patients, 2 received 1 treatment because of septic shock and hemodynamic instability and later received renal replacement therapy. Laboratory changes pre and post artificial liver plasma exchange are displayed in Table 7. The PaO_2/FiO_2 ratios were significantly improved. There was a declining trend in the levels of cytokines and inflammatory factors after a course of treatment. In particular, serum IL-6 and CRP levels were greatly reduced and, which achieved statistical significance ($P < 0.01$).

4. Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected >1.2 million people and caused 64,703 deaths as of April 5, 2020. There were 81,708 confirmed cases, 1047 asymptomatic cases and 3331 deaths in China as of April 5,

Table 5

Laboratory characteristics in the patients receiving venovenous extracorporeal membrane oxygenation.

Characteristics	Pre-ECMO	Post-ECMO 72 h	Range	P
LAC, mmol/L	3.4 (1.9–4.7)	1.7 (1.4–2.2)	0.5–1.6	.5
WBC (10×10^9 cells/L	12.2 (8.1–16.2)	7.2 (3.7–10.9)	4–10	.8
Platelet 10×10^9 cells/L	114 (60–172.5)	72.8 (33–97.8)	83–303	.3
TBil, μmol/L	39.6 (9.3–76.4)	78.4 (21.3–114.2)*	0–21	<.01
Cr, μmol/L	67.7 (41.2–88.3)	56.8 (42.8–74)	41–73	.6
CRP, mg/L	55.6 (9.2–92.7)	56.3 (12.1–94.2)*	0–8	<.01
PCT, ng/mL	3.4 (0.1–5.2)	1.4 (0.1–2.1)	0–0.05	.3
pH	7.4 (7.3–7.5)	7.53 (7.46–7.55)*	7.35–7.45	<.01
$PaCO_2$, mmHg	47.1 (42.1–47.8)	36.2 (33.2–40.5)*	35–45	<.01
PaO2, mmHg	69.6 (60.4–79.5)	88.6 (71.6–104.7)	80–110	.15
$HCO3^-$, mmol/L	26.2 (23.2–32.4)	30.5 (25.9–32.3)	22–27	.2

Cr = creatinine, CRP = C-reactive protein, ECMO = extracorporeal membrane oxygenation, IL = interleukin, LAC = Lactic acid, PCT = procalcitonin, PH = potential of hydrogen, TBil = Total bilirubin, WBC = white blood cell.
* $p < 0.05$.

Table 7

Cytokine changes pre- and post-artificial liver plasma exchange.

	PaO_2/FiO_2	IL-6, pg/mL	IL-10, pg/mL	TNFα, pg/mL	IFNγ, pg/mL	WBC (10E9/L)	CRP, mg/L	PCT, ng/mL
Pre-treatmen	143 (93.5–197.6)	438.9 (30.8–1132.5)	6.8 (4.8–16.1)	18.7 (12.7–30.8)	11.3 (4.7–19)	11.5 (8.8–13.5)	72.3 (29.5–159.6)	0.4 (0.04–1.2)
Post-treatment	217.8 (129.4–327.2)*	10.2 (6.5–141.7)*	4.9 (3.2–10.2)	17.4 (12.6–27.8)	5.3 (3.2–8.4)	6.9 (4.1–9.7)	14.3 (1.9–106.1)*	0.2 (0.03–1.3)
P	.02	.008	.139	.4	.075	.15	.008	.108

CRP = C-reactive protein, IFN = interferon, IL = interleukin, PCT = procalcitonin, TNF = tumor necrosis factor, WBC = white blood cell.
* $p < 0.05$.

2020. Once the illness develops from mild disease to critical disease, the clinical outcome is not optimistic. Appropriate treatment of critically ill patients is important to reduce mortality. We studied 23 critically ill patients in the ICU with confirmed COVID-19. Most patients were male, were older, and had more previous complications than those of patients not admitted to the ICU, in accordance with other published reports.[6,14] Unlike a previous report,[6] the mortality rate in this study was 0 at day 28.

In this cohort, common symptoms at onset were fever and cough, and few patients had signs and symptoms of upper respiratory tract infection (eg, sneezing, rhinorrhea or sore throat), suggesting that the target cells that the virus attacks are in the lower respiratory tract.[14] One patient was asymptomatic while having typical imaging changes in CT and infection was later confirmed by nucleic acid test. All patients had a contact history in the epidemic area or had contact with confirmed patients. Isolation is necessary for people coming from epidemic areas or interacting with confirmed patients to prevent further spread of the disease. Patients with ≥2 comorbidities are more vulnerable and show more severe disease outcomes. This finding may be because of damage caused by COVID-19 to other organs, such as the heart, the liver, and the kidneys, as well as to organ systems, such as the blood and the immune system.[5,14,15] This damage may ultimately lead to multiple organ failure.

Regarding laboratory abnormalities, lymphocytopenia occurred in all critically ill patients in our cohort, and previous reports found lymphocytopenia in 80% of patients.[6] Lymphopenic CAP is a particular immunological phenotype that is related to an increased risk of mortality.[16] Lymphopenia may be a cause or a consequence of COVID-19. Increased apoptosis or impaired production of lymphocytes caused by the presence of critical illness,[17] massive lymphocytic migration to the lungs, or enhanced adhesion of lymphocytes to the vascular endothelium could explain the presence of lymphopenia in patients with this disease.[16] Serum LDH, D-dimer, ESR, IL-6, and IL-10 levels were high on admission to the ICU. Although these findings did not reach statistical significance between patients receiving MV or not, the observation that higher levels of serum LDH correlated with mortality of COVID-19 is similar to patients with SARS.[18] Shorr et al[19] showed that D-dimer levels identify patients at increased risk for both multiple systemic organ failure and death. There is increasing clinical evidence that multiorgan failure caused by cytokine storms is an important factor in the death of severe patients with COVID-19.[14] IL-6 is importantly involved in cytokine storms and can lead to vascular leakage, complement activation, and even disseminated intravascular coagulation (DIC).[20,21] Notably, IL-6 is likely to cause cardiomyopathy by promoting cardiac dysfunction,[22] which has already been observed in patients with COVID-19.[14] According to these clinical findings, artificial liver plasma exchange was used to remove the activated cytokines and other toxic substances in the body, supplement the bioactive substances, such as coagulation factors, plasma proteins, and immune regulatory factors, and finally maintain the physiological balance in the body.

We managed our ventilator settings with the purpose of low tidal volumes, plateau pressures $<30\,cmH_2O$ and titrating PEEP in regard to FiO_2 to implement lung protection strategies. The mechanically controlled breathing rate is artificially increased to ensure adequate minute ventilation volume. One patient with COPD who had strong autonomous respiration suffered barotrauma. We found it difficult to achieve tidal volumes of 6 mL/kg (predicted body weight). The neuromuscular blocking agent has a negative effect on sputum excretion, and was therefore only used for a relatively short time. As patients' conditions deteriorated, ECMO was used to prevent the potentially injurious aspects of MV and to further support respiration.[23] The strength of the ventilator support settings was greatly reduced after ECMO initiation. ECMO helps patients overcome the inflammatory cascade and saves time for further clinical treatment.

In spite of a lack of solid evidence, all patients in this study received antiviral therapy. For severe inflammation caused by COVID-19, steroids are used for their anti-inflammatory properties and attenuation of lung injury. Current evidence on the use of steroids in SARS and COVID-19 is controversial. Some authors reported a positive role of steroids on survival,[24,25] whereas some revealed inconclusive or even possible harmful impacts on survival.[26,27] The most severe illness in our case series received short-term glucocorticoid therapy. Routine fecal examination and bacterial culture of some patients showed intestinal microbial dysbiosis with decreased probiotic strains, such as *Lactobacillus* and *Bifidobacterium*. Prebiotics or probiotics were given to such patients to regulate the balance of intestinal microbiota and reduce the risk of secondary infection due to bacterial translocation.[28] Traditional Chinese medicine aimed at enhancing immunity and inhibiting inflammation was used in some patients to help achieve therapeutic results. Intravenous immunoglobulin and human serum albumin were also used as supportive therapies. Tracheobronchoscopy was used to clear the airway of patients with excessive sputum.

Our study has limitations. First, a limited number of patients were included. Multicenter and large sample data are needed to obtain a multifaceted understanding of the characteristics of the critical illness. Second, at the time of study submission, most severe patients were not discharged, and the final prognosis was unavailable.

In summary, the treatment of patients who progressed to severe critical illness was challenging. Up to now, no specific medicine was available for this epidemic disease. This infectious disease is highly contagious. If a lot of people get sick at one time with insufficient medical resources, the mortality can be very high. Effective vaccines for the virus are urgently needed.

Author contributions

Jian Liu, Yongquan Dong, and Jie Yin contributed equally to this article. Jianping Li and Jian Liu designed the study, and had full access to all data. Jianping Li and Jian Liu collected the data. Jian Liu wrote the initial draft. Yongquan Dong contributed to all table drawing. Jie Yin conducted statistical analysis. Guojun He and Xiaoxin Wu contributed to critical revision of the report. Yunqing Qiu and Xuelin He contributed to second revision of the article. All authors contributed to reviewing and approving the final version.

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