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CLINICAL COURSE OF 195 CRITICALLY ILL COVID-19 PATIENTS: A RETROSPECTIVE MULTICENTER STUDY

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ABSTRACT—**Introduction:** Coronavirus disease-2019 (COVID-19) outbreak has spread around the world. However, the dynamic course of critically ill COVID-19 has not been described thoroughly. **Patients and Methods:** We retrospectively analyzed 195 critically ill COVID-19 patients in Hubei province, China, between January 5, 2020 and April 3, 2020. Epidemiologic data, clinical features, treatments, and outcomes were collected and analyzed. **Results:** Most critically ill patients were older with higher Acute Physiology and Chronic Health Evaluation II scores. After critical illness onset, a total of 181 (92.8%) patients received ventilation support, of which 84 (43.1%) received noninvasive and 97 (49.7%) received invasive mechanic ventilation (IMV). Among the 97 patients with IMV, 28 (28.9%) received prone ventilation, 57 (58.8%) received neuromuscular blocked therapy, and 22 (11.3%) received tracheostomy due to prolonged ventilator use. Early hypoxemia, subsequent hypercapnia, pulmonary hypertension, and finally pulmonary fibrosis were notable in the clinical course of acute respiratory distress syndrome (ARDS). Eighty-nine (45.6%) patients presented with shock. Acute kidney injury (29.7%) and secondary infection (28.2%) were also notable. The overall mortality of critically ill patients at day 28 was 42.1%. Intensive care unit (ICU) mortality was around 33%, as 16 patients died prior to ICU admission. A low PaO_2/FiO_2 ratio was an independent risk factor for death. High viral load was observed in most non-survivors. **Conclusion:** ARDS and shock were notable in the critical illness of COVID-19. Ventilation support and hemodynamic support were the cornerstones for critical care. High viral load was associated with death of critically ill COVID-19 patients.

KEYWORDS—Coronavirus, critical illness, infection

ABBREVIATIONS—AKI—acute kidney injury; APACHE II—Acute Physiology and Chronic Health Evaluation II; ARDS—acute respiratory distress syndrome; BMI—body mass index; COVID-19—Corona Virus Disease-2019; CRRT—continuous renal replacement therapy; ECMO—extracorporeal membrane oxygenation; FiO2—fraction of inspired oxygen; IMV—invasive mechanic ventilation; IQR—interquartile range; KIDIGO—Kidney DiseaseImproving Global Outcomes; NA—not available; PaCO2—partial pressure of carbon dioxide; PaO2—partial pressure of oxygen; PEEP—positive end-expiratory pressure; PICCO—pulse indicator continous cardiac output; RT-PCR—Reverse Transcription Polymerase Chain Reaction; SARS-CoV-2—severe acute respiratory syndrome coronavirus 2; SOFA—Sequential Organ Failure Assessment

INTRODUCTION

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia in Wuhan, China (1). In February 2020, the pneumonia was named coronavirus disease-2019 (COVID-19), and the virus that caused COVID-19 was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Worldwide cases of SARS-CoV-2 infection climbed above 3 million and deaths over 200,000. COVID-19 mainly manifests as fever, cough, dyspnea, and bilateral infiltrates on chest imaging (3). Additionally, acute respiratory distress syndrome (ARDS), shock, or multiorgan dysfunction were reported in critically ill patients with COVID-19 (4–6). A single-centered, retrospective, study included 52 critically ill patients who were admitted to the ICU of Wuhan Jin Yin-Tan Hospital (Wuhan, China) and reported that the 28-day mortality of critical illness was up to 61.5% (5). However, the clinical course of critically ill patients with COVID-19 during hospitalization was not entirely described. The in-depth understanding of COVID-19-related critical illness is useful for early identification and triaging patients at risk of death; rational allocation of the health care resources and better management of the critical illness; sharing the therapeutic experience and providing baseline COVID-19-associated complication and mortality data. Herein, we analyzed the clinical course of 195 critically ill COVID-19 patients during hospitalization.

PATIENTS AND METHODS

Study design and participants

We retrospectively studied all critically ill patients with COVID-19 admitted to Zhongnan Hospital of Wuhan University, Leishenshan Hospital, Huanggang Central Hospital, and Xishui People's Hospital between January 5, 2020 and

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April 3, 2020. All patients were consecutive. COVID-19 was diagnosed according to the World Health Organization's interim guidance (7). Critically ill patients were defined as those admitted to the adult ICU or those requiring mechanical ventilation (invasive or noninvasive), those with a fraction of inspired oxygen (FIO_2) concentration greater than or equal to 60%, or those with the need for intravenous infusion of vasopressors (8, 9).

Zhongnan Hospital of Wuhan University and Leishenshan Hospital are located in Wuhan, the center of COVID-19 outbreak. Huanggang Central Hospital and Xishui People's Hospital are located in Huanggang, 100 km to the east of Wuhan. The four medical centers were assigned to accept and treat the COVID-19 patients by the government during the disease outbreak. This case series was approved by the institutional ethics board of the four medical centers. Oral consent was obtained from patients. The time frame overlaps with that of a previously reported case series, and 33 patients in the current report have been included in the previous case series (3).

Real-time reverse transcription polymerase chain reaction assay for SARS-CoV-2

The methodology of real-time quantitative PCR (RT-PCR) has been previously reported (3). Throat swab samples were collected and placed into a collection tube with 150 μL of virus preservation solution, and total RNA was extracted within 2 h using the respiratory sample RNA isolation kit (Zhongzhi, Wuhan, China). In brief, 40 μL of cell lysates were transferred into a collection tube followed by vortex for 10 s. After standing at room temperature for 10 min, the collection tube was centrifugated at 1,000 rpm/min for 5 min. The suspension was used for real-time reverse transcription polymerase chain reaction (RT-PCR) assay of SARS-CoV-2. Two target genes, including open reading frame1a (ORF1ab) and nucleocapsid protein (N), were simultaneously amplified and tested during the real-time RT-PCR assay. Target 1 (ORF1ab): forward primer CCCTGTGGGTTTTACACTTAA; reverse primer ACGATTGTGCATCAGCTGA; and the probe 5′-VIC-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3′. Target 2 (N): forward primer GGGGAACTTCTCCTGCTAGAAT; reverse primer CAGACATTTTGCTCTCAAGCTG; and the probe 5′-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3′. The real-time RT-PCR assay was performed using a SARS-CoV-2 nucleic acid detection kit according to the manufacturer's protocol (Shanghai bio-germ Medical Technology Co Ltd). The reaction mixture contains 12 μL of reaction buffer, 4 μL of enzyme solution, 4 μL of Probe primers solution, 3 μL of diethyl pyrocarbonate-treated water, and 2 μL of RNA template. The RT-PCR assay was performed under the following conditions: incubation at 50°C for 15 min and 95°C for 5 min, 40 cycles of denaturation at 94°C for 15 s and extending and collecting fluorescence signal at 55°C for 45 s. A cycle threshold value (Ct-value) less than 37 was defined as a positive test result, and a Ct-value of 40 or more was defined as a negative test. A medium load, defined as a Ct-value of 37 to less than 40, required confirmation by retesting.

Data collection

The data were extracted from the medical records of patients. The research team of the Department of Critical Care Medicine at Zhongnan Hospital of Wuhan University analyzed and reviewed the data. Data collection included epidemic data, demographic data, comorbidities, symptoms and signs, laboratory findings, radiologic findings, respiratory mechanics variables, complications, treatments, and time course of the illness. The severity of the illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and organ dysfunction was assessed using the Sequential Organ Failure Assessment (SOFA) score. Ventilatory parameters, arterial blood gas values, laboratory values, and SOFA scores were followed on 1, 3, 7, 14, and 21 days after critical illness onset. Living status at 28 days after the onset of critical illness was recorded. ARDS was diagnosed according to the Berlin Definition and acute kidney injury (AKI) was diagnosed according to the Kidney Disease: Improving Global Outcomes clinical practice guidelines (10, 11). Shock was defined according to the definition of sepsis 3.0 (12). Acute cardiac injury was defined as blood levels of hypersensitive troponin I above the upper reference limit (>26.2 pg/mL). The time to SARS-CoV-2 RNA clearance in respiratory secretions by RT-PCR was defined as the time from illness onset until the test was negative on two occasions, without a positive test afterward.

Statistical analysis

Categorical variables were shown as frequency rates and percentages, while continuous variables were described using mean and standard deviations or medians and interquartile range (IQR) values. Independent group *t* tests or the Mann–Whitney test was used for continuous variables as appropriate. Proportions for categorical variables were compared using the chi-square test, although the Fisher exact test was used when the data were limited. The Kaplan–Meier method was used to depict the probability of survival over the duration of follow-up and to generate survival curves. Univariate analyses were performed to evaluate the risk factors associated with death. Multivariable logistic regression analysis was used to identify independent predictors of mortality. For all statistical tests, a two-sided α of less than 0.05 was considered statistically significant. SPSS (Statistical Package for the Social Sciences) version 24 software (SPSS Inc) was used for all analyses.

RESULTS

Epidemic and demographic data

Between January 5, 2020 and April 3, 2020, 3,749 patients with COVID-19 were admitted to the four medical centers; 195 critically ill patients (3.0%) were included and 82 critically ill patients (42.1%) died at 28 days after the onset of critical illness (Fig. 1). Of all 195 critically ill patients, the median age was 66.0 (IQR, 56.0–76.0) years; 130 (66.7%) were male (Table 1). Comorbidities were common in 137 patients (70.3%). The most common comorbidities were hypertension (45.6%) and diabetes (28.2%).

Organ dysfunction on day 1

On day 1 after critical illness onset, the median APACHE II score and SOFA score were 14.0 (IQR, 11.0–17.0) and 6.0 (IQR, 4.0–9.0), respectively (Tables 1 and 2). Arterial blood gas analysis revealed the median PH value as 7.42 (IQR, 7.38–7.48) with a $PaCO_2$ of 36.8 (IQR, 31.8–40.95) mm Hg. The median PaO_2/FiO_2 ratio and lactate level were 101 (IQR, 73–151) mm Hg and 1.8 (IQR, 1.3–2.5) mmol/L, respectively. Increased neutrophil count and lymphopenia were reported. The median lymphocyte count was 0.61 (IQR, 0.39–0.86) $\times 10^9$/L. Sixty-one cases (31.3.0%) showed elevated levels of hypersensitive troponin I. Additionally, prolonged prothrombin time and increased aspartate aminotransferase levels were observed. Median aspartate aminotransferase was 43 (IQR, 28–69) U/L.

Organ dysfunction from week 1 to week 3

Organ dysfunction from week 1 to week 3 is shown in Table 2 and Figure 2. For the survivors, the PaO_2 and PaO_2/FiO_2 ratios began to improve during week 2. For the non-survivors, $PaCO_2$ gradually increased and severe hypoxemia was persistent from week 1 to week 3. During week 3, notable high $PaCO_2$ levels were shown in non-survivors. For patients who received mechanical ventilation, tidal volume was set as 5 mL to 7 mL per kg of predicted body weight, plateau pressure ranged from 20 cmH_2O to 25 cmH_2O and positive end-expiratory pressure (PEEP) was 8 cmH_2O to 10 cmH_2O. For the patients with ventilator dependence, the set PEEP level was down to 5 (IQR, 5.0–6.0) cmH_2O due to the improved pulmonary edema associated with ARDS in week 3. However, low pulmonary compliance (about 27–30 mL/cmH_2O) was still present in week 3. The patients with ventilator dependence after week 3 showed a reticular pattern of lung infiltration, and representative images of CT scan are shown in Figure 3.

Over the course of critical illness, 89 patients presented with hypotension requiring vasopressors. Etiologies of shock included septic shock (78 cases), hypovolemic shock (seven cases), cardiogenic shock (six cases), and unknown causes (three cases). Among of the 89 patients, four presented with

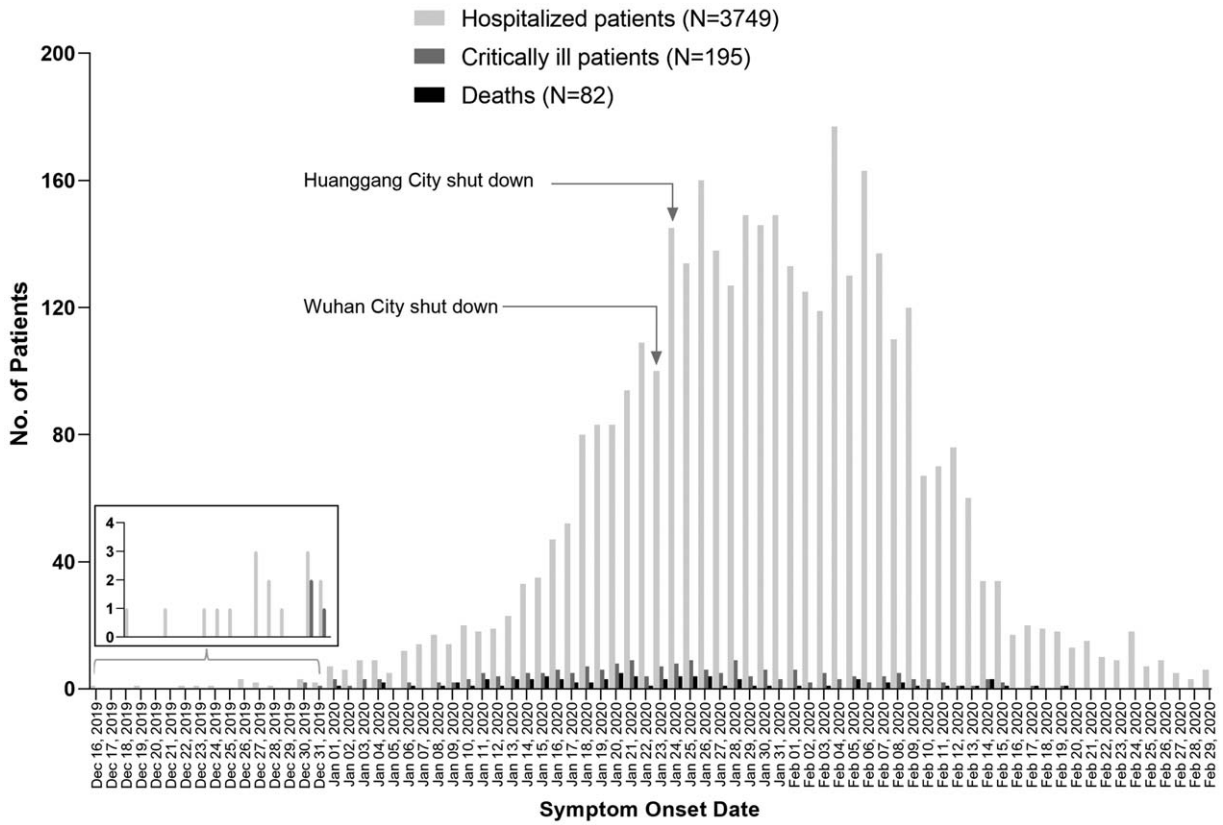

Fig. 1. **Hospitalized patients, critically ill patients and deaths with COVID in four medical centers located in Wuhan City and Huanggang City between December 30, 2019 and February 19, 2020.** Four medical centers included Zhongnan Hospital, Wuhan University; Leishenshan Hospital, Wuhan; Huanggang Central Hospital, Huanggang; and Xishui People's Hospital, Huanggang. COVID indicates coronavirus disease.

Table 1. **Baseline characteristics and laboratory data in 195 critically ill patients with COVID-19**

	Normal range	Total (n = 195)
Age, years	NA	66.0 (56.0–76.0)
Sex	NA	
Male	NA	130 (66.7)
Female	NA	65 (33.3)
Any comorbidity	NA	137 (70.3)
APACHE II score	NA	14.0 (11.0–17.0)
Arterial blood gas		
PH	7.35–7.45	7.42 (7.38–7.48)
PaO_2, mm Hg	83–108	64.10 (48.75–74.00)
PaO_2/FiO_2	400–500	101 (73–151)
$PaCO_2$, mm Hg	35–48	36.80 (31.80–40.95)
Bicarbonate, mmol/L	22–27	23.40 (21.55–25.50)
Lactate, mmol/L	0.5–1.6	1.80 (1.30–2.50)
White blood cell count, $\times 10^9$/L	3.5–9.5	8.89 (5.94–12.74)
Neutrophil count, $\times 10^9$/L	1.8–6.3	7.50 (5.05–11.16)
Lymphocyte count, $\times 10^9$/L	1.1–3.2	0.61 (0.39–0.86)
Platelet count, $\times 10^9$/L	125–350	161 (114–208)
Prothrombin time, s	9.4–12.5	13.0 (11.9–14.5)
Hypersensitive troponin I, >26.2 pg/mL	0–26.2	61 (31.3)
Aspartate aminotransferase, U/L	15–40	43.0 (28.0–69.0)
Urea, mmol/L	2.8–7.6	6.50 (4.56–9.50)
Creatinine, μmol/L	64–104	74.0 (62.9–100.6)

APACHE II score and laboratory values were obtained on day 1 after critical illness onset. Data are median (IQR) or n (%).
APACHE II indicates Acute Physiology and Chronic Health Evaluation II; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.

both septic shock and hypovolemic shock, and one presented with septic shock as well as cardiogenic shock. Furthermore, 35 of 78 cases with septic shock had no evidence of secondary infection. In week 1, 63 (70.7%) patients developed shock. Among of them, 57 were septic shock, five were cardiogenic shock, and one was hypovolemic shock. In week 2, 16 (18.0%) patients developed shock. Among of them, 13 were septic shock, two were hypovolemic shock, and one was due to unknown causes. In week 3, 10 (11.2%) patients developed shock. Among them, eight were septic shock and two were due to unknown causes. Additionally, lymphopenia, thrombocytopenia, and elevated creatinine levels were remarkable in nonsurvivors. AKI occurred and half of them received continuous renal replacement therapy (CRRT).

Complication and nosocomial infection

Over the course of days 1 to 28, 184 (94.4%) patients presented lymphopenia, 162 (83.1%) presented with ARDS, and 89 (45.6%) presented with shock. Acute kidney injury occurred in 58 cases (29.7%). ARDS-induced pulmonary hypertension was identified in 10 cases and representative echocardiogram was shown in movie 1 (supplemental digital content 1, video 1, http://links.lww.com/SHK/B111). Less common complications were cerebral infarction (six cases, 3.1%), deep vein thrombosis (four cases, 2%), cerebral hemorrhage (two cases, 1%), myocardial infarction (two cases, 1.0%), and suspected pulmonary embolism (one case, 0.5%).

TABLE 2. **Organ dysfunction of 195 critically ill patients on days 1, 3, 7, 14, and 21 after critical illness onset**

	Normal range	Day 1 (n = 195)	Day 3 (n = 178)	Day 7 (n = 159)	Day 14 (n = 124)	Day 21 (n = 98)
SOFA	NA	6.0 (4.0–9.0)	4.0 (3.0–6.0)	4.0 (3.0–7.2)	4.0 (2.0–7.0)	4.0 (1.3–8.5)
PaO_2, mm Hg	83–108	64.10 (48.75–74.00)	64.20 (53.30–78.50)	68.00 (57.00–84.00)	71.40 (59.70–85.15)	80.80 (63.90–92.10)
$PaCO_2$, mm Hg	35–48	36.80 (31.80–40.95)	39.50 (34.40–45.30)	40.75 (35.00–48.80)	46.00 (39.00–51.80)	49.00 (34.80–57.45)
PaO_2/FiO_2 ratio	400–500	101 (73–151)	109 (77–154)	109 (74–186)	151 (86–223)	167 (122–258)
Tidal volume per kg of predicted body weight, mL/kg	NA	6.05 (5.78–6.75)	6.43 (5.97–6.95)	6.03 (5.73–6.81)	5.99 (4.82–7.39)	6.58 (5.66–7.02)
Plateau pressure, cmH_2O	NA	24.00 (20.00–26.00)	20.00 (20.00–25.00)	21.00 (20.00–30.00)	25.00 (20.00–28.00)	22.00 (20.00–28.00)
PEEP, cmH_2O	NA	8.00 (6.00–10.00)	10.00 (8.00–12.00)	10.00 (7.00–10.00)	8.00 (6.00–10.00)	5.00 (5.00–8.00)
Lung compliance, mL/cmH_2O	60–100	30.00 (20.50–34.25)	30.00 (22.00–34.00)	27.00 (17.00–35.00)	30.00 (17.25–34.25)	30.00 (18.75–37.50)
Vasopressors	NA	30 (15.4%)	31 (17.4%)	31 (19.5%)	31 (25.0%)	21 (21.4%)
Lymphocyte count, $\times 10^9/L$	1.1–3.2	0.61 (0.39–0.86)	0.51 (0.32–0.77)	0.47 (0.33–0.78)	0.72 (0.38–1.07)	0.60 (0.23–1.07)
Platelet count, $\times 10^9/L$	125–350	161 (114–208)	160 (113–247)	141 (101–261)	161 (87–239)	141 (63–225)
Creatinine, μmol/L	64–104	74.0 (62.9–100.6)	76.6 (55.0–127.7)	67.6 (51.1–106.7)	60.4 (48.0–117.5)	75.7 (38.2–121.1)

Data are median (IQR) or n (%).
FiO_2 indicates fraction of inspired oxygen; NA, not available; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PEEP, positive end expiratory pressure; SOFA, Sequential Organ Failure Assessment.

Most nosocomial infections occurred in weeks 2 and 3. Nosocomial infection was noted in 55 cases (28.2%). The sites of infection include lungs (52 cases), blood stream (10 cases), and urinary tract (four cases). Among of the 55 cases, two patients presented both respiratory infection and urinary infection; eight patients presented with both respiratory infection and blood stream infection; and one developed respiratory infection, urinary infection and blood stream infection. For the isolated pathogen, acinetobacter baumannii was the most common pathogen (19 cases). Other microorganisms identified included

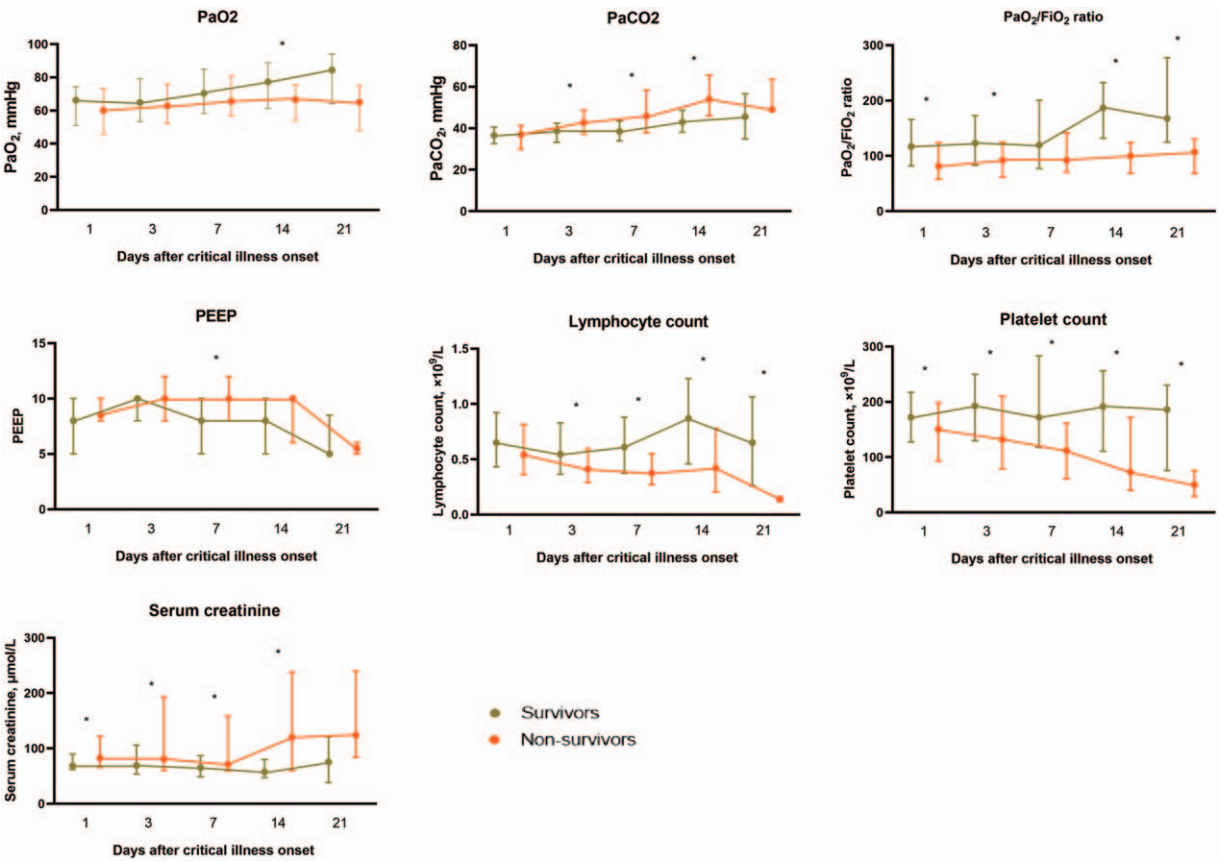

FIG. 2. **Organ dysfunction of 195 critically ill COVID-19 patients during the first 3 weeks after critical illness onset.** PaO_2 indicates partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; FiO_2, fraction of inspired oxygen; PEEP, positive end expiratory pressure. $^*P < 0.05$ for survivors versus non-survivors. COVID-19 indicates coronavirus disease 2019.

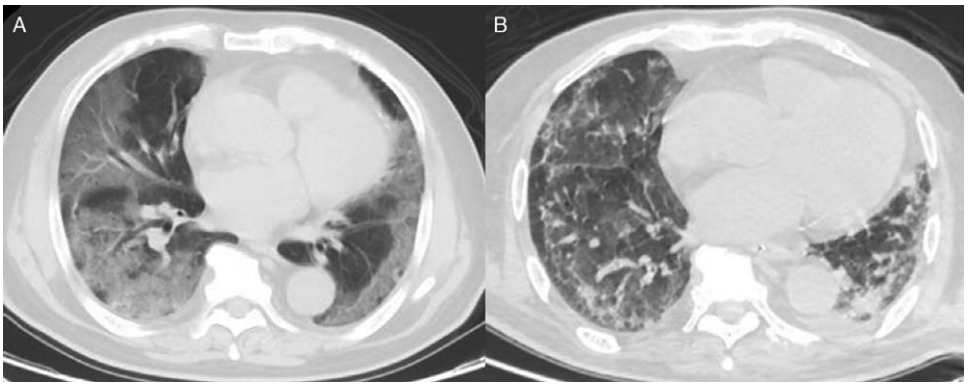

Fig. 3. **Chest computed tomographic images of post-ARDS pulmonary fibrosis in a 66-year-old COVID-19 patient.** The patient was admitted to the ICU on January 8, 2020. Transverse chest CT images showed ground-glass opacity and condensation shadows upon ICU admission (A) and pulmonary fibrosis on February 25, 2020 (B). The patient underwent tracheostomy due to ventilator dependence and died on March 16, 2020 due to secondary infection. ICU indicates intensive care unit; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome; CT, computed tomography.

candida albicans (six cases), enterococcus faecalis (four cases), klebsiella pneumoniae (two cases), coagulase-negative staphylococcus (one case), *Escherichia coli* (one case), *Hemophilus influenza* (one case), and *Corynebacterium striatum* (one case).

Treatment and outcome

Among the 195 critically ill patients, 181 (92.8%) were mechanically ventilated, which included 84 (43.1%) noninvasively and 97 (49.7%) invasively. Among the 97 invasively mechanical ventilated patients, 28 (28.9%) received prone ventilation, 57 (58.8%) received neuromuscular blocked therapy, and 22 (11.3%) received tracheostomy because of prolonged mechanical ventilation. On day 28, 41 (42.3%) of 97 intubated patients survived. Among the 41 survived patients, 36 were successfully extubated and five were still on ventilators on day 28. Among the 98 noninvasively mechanical ventilated patients, 72 survived and 26 died. For the 26 deaths, 16 died in the general ward because of a shortage of ICU beds. Additionally, 16 patients with severe hypoxemia received extracorporeal membrane oxygenation (ECMO) including five who died, four who recovered and were discharged, three who were on ECMO, three who were on mechanical ventilation, and one who was transferred to the ward. Among the 58 patients with AKI, 26 patients (44.8%) received CRRT. For the 26 patients who received CRRT, 13 patients died within 28 days. Most patients received antivirus therapy (76.9%) and glucocorticoids (71.3%).

The survival curve of the 195 critically ill patients is shown in Figure 4. Eighty-two (42.1%) patients died within 28 days and

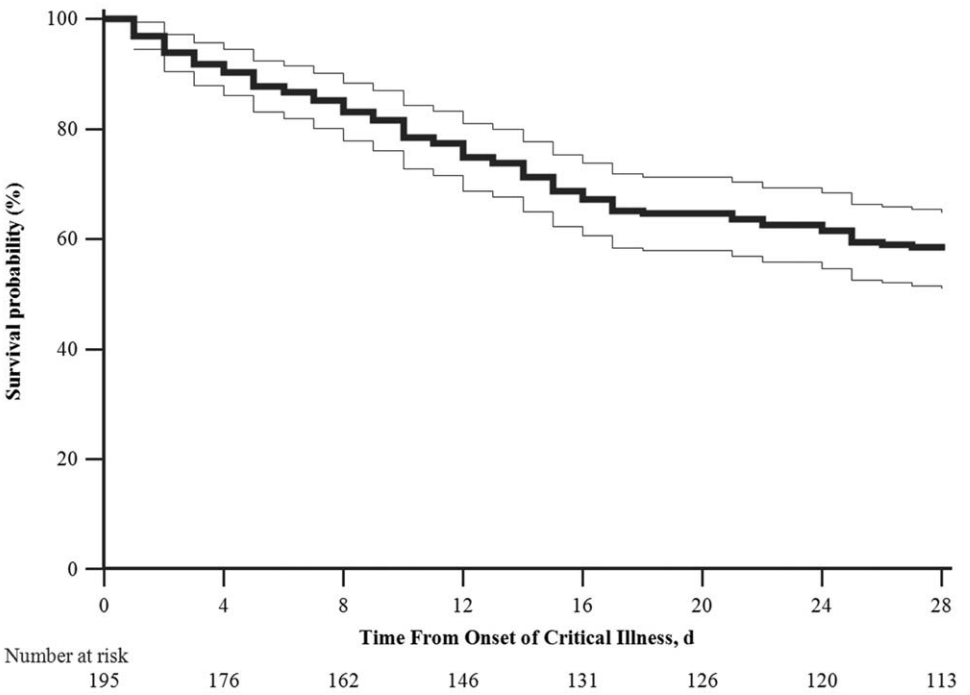

Fig. 4. **Survival curves of 195 critically ill patients with COVID-19.** Gray lines represent 95% confidence intervals. COVID-19 indicates coronavirus disease 2019.

TABLE 3. **Clinical course and outcomes for 195 critically ill patients with COVID-19**

	All patients (n = 195)
28-day mortality	82 (42.1)
Location of patients at 28 days	
Intensive care unit	19 (9.7)
Hospital ward	46 (23.6)
Home	48 (24.6)
Time course of illness, day	
Symptom onset to hospital admission	7.00 (5.00–10.00)
Symptom onset to ICU admission	10.00 (7.00–15.00)
Symptom onset to discharge	24.00 (16.00–31.00)
Symptom onset to death	19.00 (14.00–27.75)
ICU length of stay	
Discharged patients	11.00 (6.50–19.50)
Non-survivors	10.00 (6.25–15.00)
Duration of ventilation	
Discharged patients	10.00 (5.00–20.75)
Non-survivors	8.00 (5.00–15.00)

Data are median (IQR) or n (%).
COVID-19 indicates Corona Virus Disease-2019.

most deaths occurred in first 2 weeks. The overall ICU mortality was around 33%, as 16 of them died prior to ICU admission. The documented cause for death was multi-organ failure induced by ARDS (71 cases), followed by sudden cardiac arrest due to severe hypoxia (five cases). Deaths induced by septic shock and myocardial infarction occurred in three and two patients, respectively. One died from brain death due to hypoxic-ischemic encephalopathy. As shown in Table 3, 28-day mortality was 42.1%. On day 28, 48 (24.6%) were discharged, 46 (23.6%) were transferred to the ward, while 19 (9.7%) were still in the ICU. For discharged patients and non-survivors, the ICU length of stay was 11 (IQR 6.5–19.5) days and 10 (IQR 6.25–15) days, respectively; the duration of ventilation was 10 (5.00–20.75) days and 8.00 (5.00–15.00) days, respectively. A low PaO_2/FiO_2 ratio was the independent risk factor for death in multivariable analysis (Table 4).

Viral load and death

We tracked the PCR results of 195 critically ill patients. For the 113 survivors, the time to SARS-CoV-2 RNA clearance was 22.00 (IQR 14.00–29.00) days. Among the 82 non-survivors, 59 (72.0%) died with positive PCR results. In Zhongnan Hospital and Xishui People's Hospital, PCR tests of 16 discharged patients and 23 deaths as of January 14, 2020 are shown in Figure 5. PCR results turned negative from day 1 to day 20 after illness onset in most survivors. Most non-survivors died with positive PCR results. However, death still occurred in a few patients with sustained negative PCR tests. Among survivors, patients 1, 4, 6, 11, and 15 had negative PCR results and then turned positive later. Patients 21 and 22 in non-survivors had negative results in their clinical course.

DISCUSSION

This study demonstrated that the 28-day mortality of critically ill patients with COVID-19 was 42.1%. In week 1, critically ill COVID-19 was characterized with shock and hypoxemia requiring vasopressors and a high concentration of inspired oxygen, intubation or even ECMO. As the disease progressed, low lung compliance, high dead space, pulmonary fibrosis, and pulmonary hypertension were notable. Viral infection-induced septic shock was notable in week 1. Acute kidney injury and secondary infection were notable in week 3. A high viral load was observed in most non-survivors. A high APACHE II score and low PaO_2/FiO_2 were the independent risk factors for death.

In this study, the epidemiological curves showed the number of new-onset patients did not continue to grow after Wuhan City and Huanggang City shut down. This suggests that controlling the source of infection and cutting the chains of transmission were effective for controlling the epidemic in China (13). In the early outbreak, capacity for the care of ICU patients was challenged compared with the rapidly growing number of patients. Among the 195 critically ill patients, 17 were stranded in general wards, did not receive high-quality intensive care, and died before day 28. As shown in the survival curve, most deaths occurred within the first 2 weeks. Then main death cause was multi-organ failure induced by ARDS. For the survived ICU patients on day 14, their vital signs were relatively stable with critical care therapy and most of them survived on day 28.

ARDS was the most notable complication of the critical illness of COVID-19. Herein, ARDS induced by SARS-CoV-2 infection manifested as severe hypoxia, hyperventilation in the early phase (presumed exudation phase), which progressed to dead space ventilation, hypercapnia, pulmonary hypertension, and post-ARDS pulmonary fibrosis (presumed fibroproliferative phase). Pulmonary hypertension and dilated right heart, a hallmark of acute cor pulmonale, were identified in some enrolled cases. The incidence of acute cor pulmonale in our patients was probably underestimated because no right heart catheterization or transesophageal echocardiography was available in the isolation wards (14). For the survivors, PaO_2/FiO_2

TABLE 4. **Univariate and multivariate analysis of risk factors associated with death of 195 critically ill patients with COVID-19**

	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PaO_2/FiO_2 ratio	0.989 (0.983–0.996)	0.002	0.992 (0.985–0.999)	0.027
Lactate, mmol/L	1.341 (1.014–1.773)	0.040	1.245 (0.893–1.736)	0.196
Platelet count, $\times 10^9$/L	0.996 (0.992–1.000)	0.063	1.000 (0.994–1.006)	0.932
Urea, mmol/L	1.086 (1.034–1.141)	0.001	1.046 (0.980–1.116)	0.180

FiO_2 indicates fraction of inspired oxygen; PaO_2, partial pressure of oxygen.

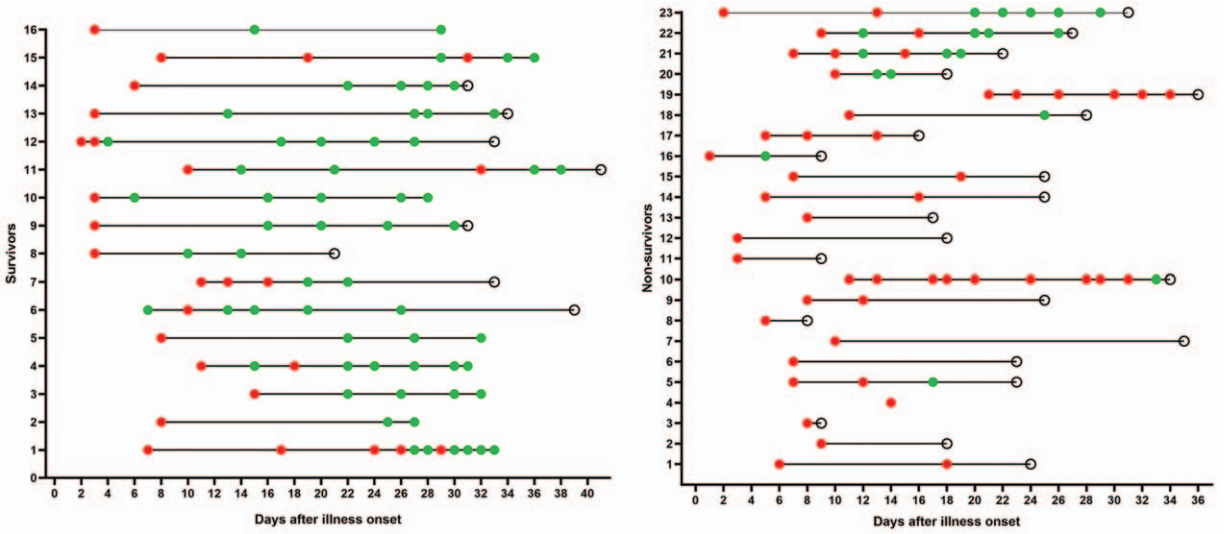

Fig. 5. **Results of sequential RT-PCR in 39 critically ill patients, including 16 discharged patients and 23 deaths between December 30, 2019 and February 19, 2020 in Zhongnan Hospital and Xishui People's Hospital.** Each line represented one patient. The starting point was the time point of the first positive PCR result for SARS-CoV-2. The terminal point was the time point of discharge or death. Red circles indicate positive PCR results for SARS-CoV-2, while green circles represent negative results. RT-PCR indicates reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

was low in week 1 and improved in week 2; even the set PEEP level was not changed. So we conducted the pulmonary edema and ARDS improved in week 2 for the survivors. For the non-survivors, the PaO_2/FiO_2 was stable and set PEEP level was down in week 3. This also implies that permeability pulmonary edema improved in week 3.

Notably, in the presumed exudative stage of ARDS (first 2 weeks) induced by SARS-CoV-2 infection, hypoxemia was severe and nearly all critically ill patients were on mechanical ventilation. Usually, ventilated patients required sedation and paralysis to reduce oxygen consumption. Low tidal volume ventilation (4 mL/kg to 8 mL/kg predicted body weight) and targeted plateau pressure $\leq$30 cmH_2O was followed. Low compliance was seen at all times. Prone positioning was used to improve oxygenation efficiency. ECMO was used as a rescue therapy for patients whose gas exchange could not be satisfied by mechanical ventilation (15). Some patients who survived this initial course began to exhibit better oxygenation and weaning was successful. However, some patients progressed to the presumed fibroproliferative phase, probably in week 4. Due to low lung compliance and high dead space, weaning was not successful and persistent ventilator dependence was notable in these patients. These patients had to receive tracheostomy.

Except for ARDS, shock was notable in critically ill patients. Septic shock was the main cause and half of them presented without evidence of secondary infection. COVID-19 patients with septic shock have evidence of cytokine storm, which has been reported previously. For example, a cytokine profile is associated with COVID-19 disease severity and is characterized by increased plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα (16). Additionally, most shock cases occurred in week 1, probably due to virus-induced sepsis, sedation, paralysis, and adverse cardiac events. After week 2, especially in week 3, shock induced by secondary infection was notable. During the clinical course of critical illness, liver injury and coagulation dysfunction were present but not remarkable (17).

Due to the prolonged ICU stay, many patients suffered AKI, which probably was induced by hypoxemia, shock, or viral invasion. Some AKI patients needed CRRT. Most secondary infections occurred in weeks 2 and 3 after ICU admission and the infections were probably due to impaired cellular immunity caused by lymphopenia. Furthermore, glucocorticoids were used in most cases, which probably posed threats to immune dysfunction and led to aggravated infections.

Herein, the relation between viral load and poor outcome in critically ill patients was first reported. Most non-survivors died with positive RT-PCR results, which indicated that most deaths in critical illness were directly related to virus replication *in vivo*. Interestingly, the RT-PCR tests turned negative before death in several non-survivors. This means that deaths were not related to high viral loads in these cases but may be associated with multi-organ dysfunction induced by initial viral insult. Notably, two consecutively negative RT-PCR tests followed by a positive RT-PCR test were reported in our patients, which was similar to a previous report (18). As a result, we recommend three or more consecutively negative RT-PCR tests as an essential condition of SARS-CoV-2 RNA clearance in respiratory secretions. Moreover, specimens collected from the lower respiratory tract may be a better choice, if possible (19, 20). We identified a low PaO_2/FiO_2 ratio as the independent risk factor of poor outcomes in COVID-19. Similar to this finding, patients with poor gas exchange had an increased likelihood of death in ARDS patients (10).

This study has limitations. First, patients were isolated in the ICU ward, where pulse contour cardiac output analysis (PICCO), ultrasonic instruments, and computed tomography scans were in shortage or not available. A lot of data about the

hemodynamic values and radiologic findings were absent. The exudation phase and fibroproliferative phase of ARDS induced by the SARS-CoV-2 infection were presumed. Second, data was collected up to day 28 after critical illness onset. Future studies should focus on 90-day mortality or morbidity among survivors. Third, SARS-CoV-2 RNA in the upper airway was not detected regularly in our cases. To further identify the association between viral load and outcome, RT-PCR tests should be continuously followed.

CONCLUSIONS

The mortality of critically ill patients with COVID-19 was high. ARDS and shock were notable in the clinical course of the critical illness. Ventilation support and hemodynamic support were the cornerstones for critical care. A high viral load was associated with the death of critically ill COVID-19 patients.

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