Clinical features of critically ill patients with COVID-19 infection in China

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Research Article

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Abstract

Importance: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections outbreak in China is now a global issue. There is only a limited understanding of the clinical characteristics of patients with SARS-CoV-2 infections is available.

Objective: To describe the characteristics, management strategies, and outcomes of critically ill patients with SARS-CoV-2 infection.

Design, Setting, and Patients: This is aretrospective, multi-center case series of 50 critically ill patients with confirmed SARS-CoV-2 infection who were admitted at Zhongnan Hospital of Wuhan University and Wuhan Pulmonary Hospital in Wuhan, China, from January 8 to February 9, 2020.

Exposures: Documented Corona Virus Disease, 2019 (COVID-19).

Main Outcome Measures: Demographic, clinical, laboratory, imaging data were collected along with management strategies, complications and outcomes of enrolled individuals.

Results Fifty critically ill patients with SARS-CoV-2 infections were enrolled. Their median age was 62 (range, 29-92) [IQR,49.5-69.0] years, 68% were male, and 28 (56%) patients had comorbidities, the most common being hypertension. In this cohort, 20(40%) patients survived ,16(32%) patients died, and the rest remained hospitalized. The invasive mechanical ventilator was used in 36(72%) patients with 15(30%) of them requiring prone positioning, and 17(34%) switched to ECMO. The compliance scores of lungs (Cstat)on the day of ICU admission among survivors were higher than those in non-survivors [42.0(18.0-47.0), vs. 19.5(14.0-24.2), p=0.038].The blood IL-6 levels and neutrophils counts at the first day of ICU admission were significantly higher in non-survivors compared to survivors [123.7(85.3-228.8), vs. 20.2(6.8-67.2) ng/ml, p=0.025 for IL-6, and 20.2(6.8-67.2) vs. 4.01(1.99-7.05) × 10⁹/L, p=0.02 for neutrophils counts].The heart rates, PaCO2, lung injury scale (LIS), and positive end-expiratory pressure levels were constantly higher for 10 days in non-survivors than those who survived (p<0.05). The frequency of vasopressor uses and neuromuscular blockers was higher in non-survivors from day 1 to day 10 compared to survivors (p<0.05). In the whole cohort, the most common complications were ARDS (97%), shock (44%), arrhythmia (38%), acute cardiac injury (26%), and acute kidney injury (22%). A secondary bacterial infection was noted in 17(34%) patients. Univariate analysis indicated that lower lung complianceand higher neutrophil counts at the day of ICU admission were related to higher mortality (p-0.03, and 0.04, respectively)

ConclusionWe demonstrated that SARS-CoV-2 infection-related critical illness predominantly affected old individuals with comorbidities and characterized by severe hypoxemic respiratory failure, often requiring prolonged mechanical ventilation and rescue therapies. Low lung compliance and persistently elevated PaCO2 indicated poor outcomes.

Introduction

In February 2019, a new coronavirus was isolated for the first time from a patient in Wuhan, China, who presented with acute pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ dysfunction syndrome (MODS) [1–3]. The virus was identified as a family member of severe acute respiratory syndrome coronaviruses (SARS-CoVs), and it was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) [4]. The clinical disease caused by SARS-CoV–2 was named Corona Virus Disease, 2019, or COVID–19. The main route of human-to-human transmission of SARS-CoV–2 is probably airborne [5–8]. As of Feb 14, 2020, statistical data show that the outbreak constitutes an epidemic threat in China, where the exponential increase in the number of individuals acquired SARS-CoV–2 has reached 52,526 confirmed cases, with 8,083 (15%) of them being in critical conditions and 1,367 (26%) died. The disease has a high fatality rate and has several clinical features that resemble the infection caused by SARS-CoV and MERS-CoV [9–13]. This viral infection has resulted in a significant concern regarding the global pandemic. While the knowledge about this virus is accumulating, the information regarding critical illness among infected individuals with SARS-CoV–2 remains limited. Therefore, we describe the clinical course and outcomes of 50 critically ill patients with SARS-CoV–2 admitted to 2 intensive care units (ICUs) in tertiary hospitals in Wuhan, China, which is considered the epicenter of this viral outbreak.

Methods

Study Design and Participants

This case series was approved by the institutional ethics board of ZhongnanHospital of Wuhan University (No. 2020020) and Wuhan Pulmonary Hospital (No. 2020020). Oral consent was obtained from patients or patients' relatives. All consecutive patients with COVID–19 admitted to ICU of the two hospitals from January 8 to February 9, 2020, were screened. Included patients with COVID–19 had virology confirmation with RT-PCR methods. Patients were admitted to ICU if respiratory or other organ supports were needed. Zhongnan Hospital and Wuhan Pulmonary Hospital located in Wuhan, Hubei Province, the endemic areas of COVID–19, are responsible for the treatments for COVID–19 assigned by the government. All patients with COVID–19 enrolled in this study were diagnosed according to World Health Organization interim guidance [14].

Data Collection

The medical records of patients were analyzed by the research team of the Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University. The electronic medical records was used to abstract the information regarding demographics, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings, chest CT scans, and management or treatment strategies (i.e., antiviral therapy, antibiotics, vasopressor, sedative-analgesic agents, corticosteroid therapy, respiratory support, extracorporeal membrane oxygenation (ECMO), kidney replacement therapy) and patient

outcomes. The data were reviewed by a trained team of physicians. Heart rate, mean arterial pressure, arterial blood gas, and ventilation parameters were obtained at 8 a.m. of every day during ICU stay. All patients were followed for the assessment of complications and outcomes until hospital discharge or death. ARDS was defined according to the Berlin definition [15]. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes criteria [16]. The cardiac injury was defined when the serum levels of cardiac biomarkers (e.g., troponin I) were above the 99th percentile upper reference limit or new abnormalities were shown in electrocardiography and echocardiography [13]. The Acute Physiology and Chronic Health Evaluation (APACHE II), Glasgow Coma Score (GCS), Sequential Organ Failure Assessment (SOFA), and Murray scores were followed every 2 days during ICU stay. Also, the information regarding dyspnea, ARDS, use of high-flow nasal cannula oxygen therapy (HFNC), invasive or non-invasive mechanical ventilator,intubation, and ECMO were abstracted.

Statistical Analysis

Categorical variables were described as frequencies and percentages, and continuous variables were summarized using mean and standard deviations or median and interquartile range (IQR) values, as appropriate based on the variable normal distribution. Means for continuous variables were compared using independent group t-tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Data (nonnormal distribution) from repeated measures were compared using the generalized linear mixed model. Proportions for categorical variables were compared using the X^2 test, although the Fisher exact test was used when the data were limited. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 13.0 software (SPSS Inc). For unadjusted comparisons, a 2-sided α of <.05 was considered statistically significant. We did not adjust for multiple comparisons and, given the potential for type I error, the findings should be interpreted as exploratory and descriptive.

Results

Characteristics of Study Patients

Table 1 shows the basic characteristics of the 50 enrolled patients (36 from Zhongnan Hospital and 14 from Wuhan pulmonary Hospital). While 14(28%) patients were still in the hospital, 20(40%) patients were discharged, and 16(32%) patients died by February 13, 2020. The median age of the enrolled patients was 62 (range, 29–92) years, 34(68%) of them were male, and 28 (56%) patients have other comorbidities. The most common comorbidities were hypertension (36%), diabetes mellitus (24%), cardiovascular disease (16%), and cerebrovascular disease (12%). The median of APACHE II score, SOFA, and LIS scores at the ICU admission were 13, 5, and 3.33, respectively. Meanwhile, the median of static lung compliance (Cstat), arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2), partial pressure of carbon dioxide (PaCO2) and positive end-expiratory pressure (PEEP) were 22.5

ml/cmH2O (IQR, 6–10), 115 mmHg (IQR, 87–190), 33.8mmHg (IQR, 31.7–38.6), and 10.0 cmH2O (IQR, 6.8–10.0). The median of ICU length of stay was 12 days (IQR, 8.3–16.8).

As shown in Table 2, there were abnormal laboratory values in the 50 enrolled patients, which included elevated level of neutrophil counts (7.15× 10⁹/L [3.72–10.84]), interlukin–6 (IL–6) (62.2 pg/ml [IQR, 18.2–67.2]), lactate dehydrogenase (512 U/L [IQR, 318–622]), aspartate aminotransferase (51 U/L [IQR, 31–69]) and prothrombin time (13.6 s [IQR, 12.9–16.0]) and lymphopenia (0.59× 10⁹/L [IQR, 0.32–0.85]).

Comparisons of survivors and non-survivors

The non-survivors were older than survivors (66.5 years [IQR, 61.3–75.0] vs. 56 years [IQR, 48.5–67.5], P =.043). The C_{stat} on the first day of ICU admission was lower in non-survivors than that in survivors (19.5 ml/cmH2O [IQR, 14–24.2] vs. 42 ml/cmH2O [IQR, 18–47], P =.038) (Table 1). Meanwhile, the level of white blood cells and neutrophils counts were higher in non-survivors than those in survivors (8.77×10⁹/L [IQR, 6.39–11.69] vs. 3.65×10⁹/L [IQR, 3–8.14], and 8.03×10⁹/L [IQR, 5.35–9.73] vs. 4.01×10⁹/L [IQR,1.99–7.05], respectively). IL–6 concentration in non-survivors was also higher than that in survivors (123.7pg/ml [IQR, 85.3–228.8] vs. 20.2 pg/ml [6.8–67.2], P =.025) (table 2). There were continuously elevated heart rates, PaCO2, LIS, and PEEP in non-survivors compared to survivors ($p<0.05$, respectively, Figure 1). Non-survivors received significantly more vasopressors than survivors ($p<0.05$; Figure1).

Dynamic clinical course of Illness

Table 3 and Figure 1 show the dynamic changes of vital signs, mechanical ventilation parameters, treatment measures, and scores from day 1 to day 10. During this period, the vital signs were roughly kept within normal range by using various organ support therapy modalities, although non-survivors had higher heart rates. From day 5, the level of PaCO2 in non-survivors began to increase and was continuously higher than that in ICU-survivors. At the same time, the LIS was higher in non-survivors than in the survivors. The median of PEEP was 10mmHg from day 1 to day 10. Vasopressors and neuromuscular blockers were used more frequently in non-survivors from day 5 than those in survivors ($p<0.05$).

Treatments, complications, and outcomes

As shown in Table 4, among the enrolled 50 patients, 14(28%) patients received NIMV, and 36 (72%) patients were on IMV. Of the 36 patients on the mechanical ventilator, 17(47%) switched to ECMO, and 15(42%) patients underwent prone position ventilation. The antiviral therapy, glucocorticoid therapy, and antibiotic use were used in 74, 76, and 90 percent of patients, respectively. The most common complications were ARDS (94%), shock (44%), arrhythmia (38%), acute cardiac injury (26%), and acute kidney injury (22%). Less common complications included cerebral infarction, cerebral hemorrhage, and hypoxic-ischemic encephalopathy. Among those with AKI, 50% required continuous renal replacement

therapy (CRRT). In the 36 enrolled discharged patients, 7(19.4%) patients suffered a secondary bacterial infection. These infections included nosocomial pneumonia (6 patients, 12%) and bacteremia (4 patients, 8%). The nosocomial pneumonia cases were associated with included Klebsiella pneumoniae (4 patients, 8%), Escherichia coli (1 patient, 2%), Elizabethkingia meningosepticum (1 patient, 2%) and Aspergillus fumigatus (1 patient, 2%). The bacteremia pathogen included Klebsiella pneumoniae (4 patients, 8%) and Enterococcus faecium (1 patient, 2%). Among the causes of death, one patient died from sudden cardiac arrest with unknown reason, and the other 15 patients died from multiorgan failure associated with ARDS.

Univariate analysis and multivariate analysis for mortality-related risk factors

Table 5 shows the risk factors associated with death for COVID–19. On univariate analysis, the risk factors associated with death were low Cstat (0.907[0.831–0.990], p = 0.03), raised white blood cells counts (1.244[1.014–1.526], p = 0.037), and elevated level of neutrophil counts (1.250[1.013–1.542], p = 0.037). However, the multivariate analysis only demonstrated the Cstat trends (0.866(0.734–1.021), p = 0.08) to be significantly associated with death.

Discussion

Our analysis of critically ill patients with COVID–19 revealed that this disease affected older patients with comorbidities. These patients had severe hypoxia/ ARDS, and the majority of them required mechanical ventilation. Some of these patients needed prone ventilation and ECMO to maintain their gas exchange.The survivors had lower IL–6 and higher Cstat than non-survivors on the first day of ICU admission. The dynamic assessment of variables indicated that the persistent elevation in PaCO2, LIS, HR, and neutrophil counts occurred more often in non-survivors. Also, non-survivors persistently required higher PEEP, more neuromuscular blockers and vasopressor support. Lower Cstat and higher neutrophil counts were risk factors for mortality.

To our knowledge, this is the first report to summarize the clinical features and dynamic pulmonary parameters among critically ill patients with COVID–19.

The high median age and high rate of comorbidities between this cohort of critically ill patients were similar to SARS and MERS [17,18]. The high prevalence of comorbid conditions may be explained in part by the rising prevalence of hypertension and diabetes in the Chinese population. However, it also strongly suggests that patients with such comorbid conditions are susceptible hosts for more severe complications of infection with SARS-CoV–2. Notably, cardiovascular disease was more common in non-survivors than in survivors. Future studies should validate the relationship between cardiovascular diseases and other comorbidities with the poor outcomes in critically ill patients with COVID–19. The timeline between the illness onset to ICU admission was about 10 days, which was similar to previous reports [11,13]. This time point may represent the peak viral shedding period.

At ICU admission, we noted some abnormal laboratory findings in critically ill patients with COVID–19, which included neutrophilia, lymphopenia, prolonged prothrombin time, and hypoxemia. An elevated level of lactate dehydrogenase and aspartate aminotransferase was also common. The above abnormal values indicated the presence of MODS in this systemic viral infection. In the early stage of MODS induced by SARS-CoV–2 infection, the common manifestations included ARDS, coagulation dysfunction, and acute liver injury. Furthermore, the level of white blood cell count, neutrophil count, and IL–6 were higher in non-survivors than those in survivors. Neutrophilia was also a risk factor for death in our cohort. It indicated that systemic inflammatory response syndrome (SIRS) was more obvious in non-survivors. systemic inflammation may be one of the mechanisms of MODS and death related to COVID–19 infection.

During ICU stay, ARDS and refractory hypoxemia were found to be the main presentation of the enrolled patients in our study. The Cstat and PaO2 were lower, particularly in non-survivors. In non-survivors, the PaO2/FiO2 ratio ranged 100–150 mmHg, despite being on average PEEP level of 10cmH2O. To facilitate mechanical ventilation in patients with severe hypoxemia, neuromuscular blockade, and prone ventilation were used frequently in our study, especially for the non-survivors. Low tidal volume ventilation was used in these patients, and as a result of permissive hypercapnia, hypercapnic respiratory acidosis was observed. This was even more obvious among non-survivors from day 3 to day 10. Severe and persistent hypercapnia was probably related to decreased Cstat. Thus, ECMO had to be used for improving gas exchange [19,20]. In the 50 enrolled patients, 15 underwent prone positioning, and 17 were initiated on ECMO. Up to February 15, 6 patients were weaned off ECMO successfully, and the other 7 were still on ECMO, excluding 4 patients who died on ECMO. ECMO was used during the SARS and H1N1 influenza epidemics and has been considered as a useful management measure to salvage the severe ARDS patients.

There is currently no treatment recommended for coronavirus infections except for supportive care as needed [21]. Several antivirals and other agents have been used during the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak. Herein, most patients were given antiviral and glucocorticoid therapy prior to ICU admission, but the efficacy of these drugs should be assessed in the future. Secondary infection was common in the late stages of the illness and at least partly due to the prolonged ICU length of stay. Thus, controlling the secondary infection is also critical to reduce hospital mortality.

Diffuse alveolar damage with varying degrees of the organization is seen on pathologic examination in patients with SARS who have acute lung injury [22]. For our patents, severe disease with lung injury is believed to reflect an excessive host response with the production of large quantities of proinflammatory cytokines (“cytokine storm”). Angiotensin-converting enzyme 2 (ACE2) and lymphopenia may also be associated with organ injury in SARS-CoV–2 infection, as they were found in other similar viral infection outbreaks [23,24]. Other possible mechanisms include direct viral invasion; the virus was recovered from lung and stool in one report [25]. Additionally, the post-mortem examination may be needed to discover the pathogenesis of the COVID–19. We also identified the Cstat of ICU admission as a clinical risk factor

for death by univariate logistic regression analysis. Additionally, increased dead space has been shown in the previous reports. Furthermore, positive pressure ventilation tends to increase alveolar dead space by increasing ventilation in alveoli that do not have a corresponding increase in perfusion, thereby worsening V/Q mismatch and hypercapnia. In fact, hypercapnia was obvious in ICU-non-survivors of our patients.

This study has several limitations. Only 36 patients were discharged (including alive and dead) were used to compare between survivors and non-survivors in this study. Due to the limited number of patients, the differences between survivors and non- survivors should be interpreted carefully. The median of ICU length of stay was 10 days, and we tracked some important data during this timeline. Future studies are needed to track temporal changes for longer periods of time to describe the whole clinical progress among critically ill patients with COVID–19. Although we collected cases from two ICU located in Wuhan, multicenter studies are needed to thoroughly describe the comorbidities and clinical features of this illness.

In conclusion, we have demonstrated that SARS-CoV–2 infection-related critical illness predominantly affects older patients with comorbidities and is associated with severe hypoxemic respiratory failure, often requiring prolonged mechanical ventilation. The low Cstat at ICU admission and continuous elevated PaCO2 indicated poor outcomes.

Take Home Message

1. Almost all these patients (94%) developed severe ARDS, and the majority of them (72%) required invasive mechanical ventilation. Some of these patients needed prone ventilation (30%) and ECMO (34%).
2. 64% of these patients were complicated with heart problems, including arrhythmia and acute cardiac injury. 44% of the patients progressed to shock, and 22% to acute kidney injury.
3. The survivors had lower IL-6 and higher Cstat than non-survivors at the day of ICU admission.
4. Persistent elevation in PaCO2, lung injury scores, heart rates, and neutrophil counts occurred more often in non-survivors. Also, non-survivors persistently required higher PEEP, more neuromuscular blockers and vasopressor support.
5. Lower Cstat and higher neutrophil counts were risk factors for mortality.

Declarations

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Conflicts of interest: The authors have no conflicts of interest to declare relevant to this publication.

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Tables

Table 1: **Baseline characteristics of clinically ill patients infected with COVID-19 on the day admitted in ICU**

Characteristics	All patients (n=50)	Survivors (n=20)	non-survivors (n=16)	P value
Age, years	62.0(49.5-69.0)	56.0(48.5-67.5)	66.5(61.3-75.0)	0.043
Male	34(68.0)	13(65.0)	11(68.8)	0.813
Comorbidity				
Hypertension	18(36.0)	8(40.0)	8(50.0)	0.549
Diabetes	12(24.0)	4(20.0)	5(31.3)	0.470
Cardiovascular disease	8(16.0)	0(0.0)	7(43.8)	0.001
Cerebrovascular disease	6(12.0)	3(15.0)	3(18.8)	1.000
COPD	2(4.0)	2(10.0)	0(0.0)	0.492
Chronic liver disease	3(6.0)	1(5.0)	0(0.0)	1.000
Malignancy	2(4.0)	0(0.0)	1(6.3)	0.444
Scoring system				
APACHE II	13(11-19)	12.5(10.5-18.5)	16.5(12.0-24.3)	0.194
SOFA	5(4-8)	4.0(3.3-6.0)	4.5(3.0-8.0)	0.784
LIS	3.33(3.00-3.50)	3.0(3.0-3.42)	3.42(2.63-3.50)	0.585
Cstat (ml/cmH_2O)	22.5(17.0-40.5)	42.0(18.0-47.0)	19.5(14.0-24.2)	0.038
PaO2/FiO2	115(87-190)	114(80-170)	117(91-204)	0.633
PaCO2 (mmHg)	33.8(31.7-38.6)	32.7(30.2-36.1)	35.4(32.7-40.9)	0.115
PEEP	10.0(6.8-10.0)	8.0(6.5-10.0)	10.0(6.5-12.5)	0.386
Length of ICU stay (d)	12.0(8.3-16.8)	10.0(8.3-14.0)	12.5(8.3-22.0)	0.285
Length of mechanical ventilation (d)	8.5(5.5-15.3)	6.0(4.0-9.0)	10.5(6.9-21.3)	0.061

Data expressed as median (IQR) or number (percentage).

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; COVID-19, Corona Virus Disease 2019; COPD, chronic obstructive pulmonary disease; FiO2, fraction of inspiration O; ICU, intensive care unit; IQR, interquartile range; LIS, Lung Injury Score; Cstat:Compliance score of lung; PaCO2,

partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

P values indicate differences between survivors and non-survivors. $P < .05$ was considered statistically significant.

Table 2: **Laboratory findings of patients infected with COVID-19 on the day admitted in ICU**

	Normal range	All patients (n=50)	ICU-survivors (n=20)	ICU-non-survivors (n=16)	P value
White blood cell count, × 10⁹/L	3.5-9.5	7.99(4.71-11.95)	4.96(3.00-8.14)	8.77(6.39-11.69)	0.020
Neutrophil count, × 10⁹/L	1.8-6.3	7.15(3.72-10.84)	4.01(1.99-7.05)	8.03(5.35-9.73)	0.026
Lymphocyte count, × 10⁹/L	1.1-3.2	0.59(0.32-0.85)	0.63(0.32-0.80)	0.67(0.35-1.04)	0.373
Platelet count, × 10⁹/L	125-350	180(123-210)	185(116-225)	169(122-213)	0.656
Prothrombin time, s	9.4-12.5	13.6(12.9-16.0)	13.3(12.6-14.7)	13.3(12.4-15.9)	0.774
Activated partial thromboplastin time, s	25.1-36.5	31.1(28.6-35.2)	31.3(28.4-34.7)	31.5(28.1-37.6)	0.408
D-dimer, mg/L	0-500	435(209-1401)	318(172-902)	480(183-1885)	0.265
Hypersensitive troponin I, pg/mL	<26.2	22.5(7.9-36.8)	11.9(7.0-28.3)	30.0(5.4-60.0)	0.324
Creatine kinase, U/L	<171	96(58-171)	96(61-231)	87(43-232)	0.563
Lactate dehydrogenase, U/L	125-243	512(318-622)	564(235-641)	452(353-600)	1.000
Alanine aminotransferase, U/L	9-50	36(24-57)	30.5(20.3-41.5)	42.5(23.3-68.0)	0.220
Aspartate aminotransferase, U/L	15-40	51(31-69)	45.0(30.3-69.5)	61.0(29.5-68.0)	0.911
Total bilirubin, mmol/L	5-21	13.2(10.2-18.2)	11.7(8.7-16.5)	11.5(9.7-16.7)	1.000
Blood urea nitrogen, mmol/l	2.8-7.6	6.1(4.4-8.4)	4.64(4.21-6.22)	6.39(4.68-8.48)	0.126
Creatinine, μmol/L	64-104	69(58-91)	67.7(62.1-85.4)	72.5(56.3-102.0)	0.824
IL-6, pg/ml	0-7	62.2(18.2-129.5)	20.2(6.8-67.2)	123.7(85.3-228.8)	0.025

Data expressed as median (IQR).

Abbreviations: COVID-19, Corona Virus Disease 2019; ICU, intensive care unit; IQR, interquartile range.

SI conversion factors: To convert alanine aminotransferase, aspartate aminotransferase, creatine kinase and lactate dehydrogenase to μkat/L, multiply by 0.0167;

P values indicate differences between survivors and non-survivors. *P* < .05 was considered statistically significant.

Table 3: **Course of the disease in patients infected with COVID-19 on admission to ICU**

	Day 1 (n=36)	Day 3 (n=36)	Day 5 (n=34)	Day 7 (n=32)	Day 10 (n=22)
HR	86(78-108)	78(73-87)	80(70-92)	87(79-103)	87(77-99)
Survivors	87(78-111)	74(64-80)	76(62-82)	81(74-97)	78(71-83)
Non-survivors	84(80-105)	83(79-99)	92(78-100)	91(85-115)	99(87-114)
P value	0.762	0.001	0.005	0.017	0.002
MAP	94(86-105)	83(77-95)	83(76-94)	86(78-91)	88(74-99)
Survivors	94(86-106)	84(79-95)	83(76-98)	87(79-92)	84(77-104)
Non-survivors	94(83-101)	81(71-99)	82(79-91)	80(76-93)	90(73-98)
P value	0.599	0.339	0.690	0.416	0.573
PaO2	68.6(53.9-99.6)	70.7(58.0-131.5)	69.8(60.7-89.0)	79.4(60.5-109.0)	63.2(51.0-107.1)
Survivors	62.3(48.7-79.9)	64.6(49.6-117.5)	65.3(55.2-86.9)	66.4(58.0-108.3)	54.7(45.4-73.3)
Non-survivors	84.6(60.3-175.8)	82.7(67.3-150.3)	72.5(63.0-111.0)	82.2(62.4-115.8)	73.0(59.2-123.0)
P value	0.022	0.067	0.488	0.329	0.053
PaO2/FiO2 ratio	115(87-190)	154(84-225)	139(110-184)	161(94-239)	136(100-207)
Survivors	114(80-170)	162(89-225)	145(110-196)	172(96-239)	131(102-244)
Non-survivors	117(91-204)	140(66-222)	126(105-178)	132(90-221)	141(98-206)
P value	0.633	0.626	0.466	0.406	0.879
PaCO2	33.8(31.7-38.6)	37.5(34.2-42.9)	42.0(36.7-48.8)	42.1(36.0-50.7)	44.0(37.8-49.9)
Survivors	32.7(30.2-36.1)	35.7(31.7-40.0)	39.3(34.6-43.1)	38.8(33.4-43.5)	38.9(35.7-43.1)
Non-survivors	35.4(32.7-40.9)	41.6(37.1-45.8)	50.4(43.0-58.3)	48.7(41.5-61.7)	49.7(45.5-54.7)
P value	0.115	0.012	0.001	0.004	0.001
PEEP	10.0(6.8-10.0)	10.0(9.5-10.0)	10.0(8.0-12.0)	10.0(9.0-10.0)	10.0(10.0-10.0)
Survivors	8.0(6.5-10.0)	10.0(7.5-10.0)	8.0(6.0-10.0)	8.0(6.0-10.0)	NA

Non-survivors	10.0(6.5-12.5)	10.0(10.0-13.0)	10.0(10.0-12.0)	10.0(10.0-11.5)	10.0(10.0-10.0)
P value	0.386	0.126	0.023	0.024	NA
% on vasopressors	7(19.4)	9(25.0)	8(23.5)	7(21.9)	6(26.1)
Survivors	2(10.0)	2(10.0)	3(15.8)	1(5.6)	0(0.0)
Non-survivors	5(31.3)	7(43.8)	5(33.3)	6(42.9)	6(26.1)
P value	0.204	0.049	0.417	0.027	0.003
% on neuromuscular blockade agents	7(19.4)	11(30.6)	7(20.6)	7(21.9)	4(17.4)
Survivors	3(15.0)	5(25.0)	1(5.3)	1(5.6)	0(0.0)
Non-survivors	4(25.0)	6(37.5)	6(40.0)	6(42.9)	4(17.4)
P value	0.675	0.483	0.028	0.027	0.029
SOFA	4.0(3.0-7.0)	5.0(4.0-7.0)	5.0(3.0-8.0)	5.5(3.0-9.0)	4.0(3.5-8.5)
Survivors	4.0(3.3-6.0)	4.5(4.0-7.0)	5.0(3.0-7.0)	6.0(3.3-6.8)	4.0(3.0-7.0)
Non-survivors	4.5(3.0-8.0)	6.0(3.0-7.0)	5.0(3.0-8.0)	4.5(3.0-9.3)	7.0(3.8-13.0)
P value	0.784	0.923	0.586	0.900	0.174
LIS	3.00(2.70-3.50)	3.00(2.37-3.25)	3.00(2.25-3.08)	2.84(2.00-3.50)	2.50(2.00-3.00)
Survivors	3.00(3.00-3.42)	3.00(2.37-3.00)	2.33(2.00-3.00)	2.25(2.00-3.00)	2.00(1.67-3.00)
Non-survivors	3.42(2.63-3.50)	3.00(2.37-3.63)	3.00(2.70-3.50)	3.41(2.59-3.50)	2.84(2.50-3.75)
P value	0.585	0.233	0.008	0.052	0.036

Abbreviations: COVID-19, Corona Virus Disease 2019; FiO2, fraction of inspiration O□; HR, heart rate; ICU, intensive care unit; LIS, Lung Injury Score; MAP, mean arterial pressure; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

P values indicate differences between survivors and non-survivors. $P < .05$ was considered statistically significant.

Table 4: **Treatments and outcomes of patients infected with COVID-19 in ICU**

Treatments and outcomes	Patients (number and percentage, n=50)
Modes of respiratory supports	
HFNC+NIMV	14(28.0)
IMV	19(38.0)
IMV+ECMO	17(34.0)
IMV+Prone ventilation	15(30.0)
Medications	
Antiviral therapy	37(74.0)
Glucocorticoid therapy	38(76.0)
Antibiotics	45(90.0)
Complications	
ARDS	47(94.0)
Shock	22(44.0)
Arrhythmia	19(38.0)
Acute cardiac injury	13(26.0)
AKI	11(22.0)
Secondary infection	17(34.0)

Data expressed as the median (percentage).

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, Corona Virus Disease 2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; HFNC, high-flow nasal cannula oxygen therapy; NIMV, non-invasive mechanical ventilation.

Table 5: **Univariate and Multivariate Analysis of Risk Factors Associated with Death of patients infected with COVID-19 in ICU**

Variable	Univariable		Multivariable	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age, years	1.058(0.999-1.122)	0.056	1.157(0.957-1.400)	0.133
APACHE II	1.082(0.976-1.199)	0.134		
LIS	1.335(0.485-3.673)	0.576		
Cstat	0.907(0.831-0.990)	0.030	0.866(0.734-1.021)	0.087
White blood cell count, × 10⁹/L	1.244(1.014-1.526)	0.037	3.572(0.090-142.287)	0.498
Neutrophil count, × 10⁹/L	1.250(1.013-1.542)	0.037	0.379(0.009-15.891)	0.611
IL-6	1.010(0.998-1.022)	0.103		

Abbreviations: APACHE II, Acute Physiology, and Chronic Health Evaluation II; COVID-19, Corona Virus Disease 2019; Cstat, compliance score; ICU, intensive care unit; LIS, Lung Injury Score.

Figures

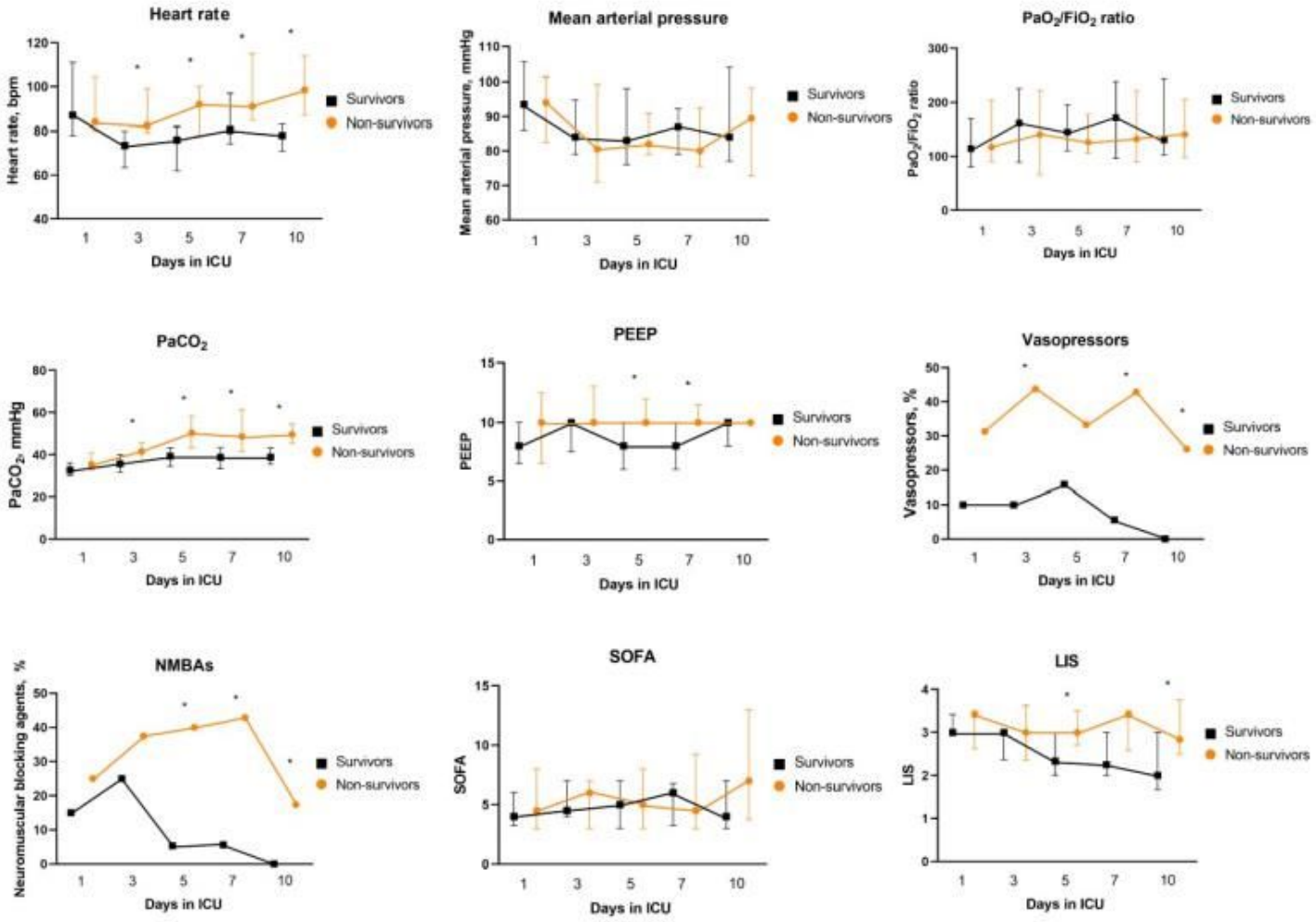

Figure 1

Fig. 1 Timeline charts illustrate several parameters in 36 discharged patients with COVID-19 (16 non-survivors and 20 survivors) every other day Data expressed as median (IQR). Abbreviations: COVID-19, Corona Virus Disease 2019; FiO2, fraction of inspiration O□; LIS, Lung Injury Score; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PEEP, positive end expiratory pressure; SOFA, Sequential Organ Failure Assessment. P values indicate differences between survivors and non-survivors. P < .05 was considered statistically significant.