Effect of continuous renal replacement therapy on all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation: a retrospective cohort study

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Summary

Background Since December 2019, when coronavirus disease 2019 (COVID-19) emerged in Wuhan and rapidly spread throughout the world, critically ill patients have a high mortality rate. We aimed to assess the effect of continuous renal replacement therapy (CRRT) on all-cause mortality in patients with COVID-19 undergoing invasive mechanical ventilation.

Methods In this retrospective cohort study, we included all patients with COVID-19 undergoing invasive mechanical ventilation at Optical Valley Branch of Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology, Wuhan from February 12th to March 2nd, 2020. Demographic, clinical, laboratory, and treatment data were collected and analyzed. All patients were followed until death or end of follow up

(March 9th), and all survivors were followed for at least one week.

Findings Of 36 hospitalized COVID-19 patients with invasive mechanical ventilation, the mean age was 69.4 (±1.8) years and 30 (83.3%) were men. 22 (61.1%) patients received CRRT (CRRT group) and 14 cases (38.9%) were managed in conventional strategy (non-CRRT group). There was no difference in age, sex, comorbidities, complications, treatments and most of the laboratory findings, except for patients in the CRRT group with higher levels of aspartate aminotransferase and serum creatinine. During the average follow-up period of 10.4 days, 12 of 22 (54.5%) patients in CRRT group and 11 of 14 (78.6%) patients in non-CRRT group died. Kaplan–Meier analysis demonstrated a prolonged survival in patients in CRRT group than non-CRRT group (P=0.032). The association between CRRT treatment and a reduced risk of mortality remained significant after adjusting for confounding factors in seven different models, with an adjusted hazard ratio (aHR) varying between 0.283 and 0.424. Older age, higher levels of IL-1β, IL-2 receptor, hs-cTnI and NT-proBNP were independently associated with increased risk of mortality in patients with CRRT treatment.

Interpretation CRRT may be beneficial for the treatment of COVID-19 patients with invasive mechanical ventilation. Further prospective multicenter studies with larger sample sizes are required.

Funding National Natural Science Foundation of China; Science Foundation of Hubei Province of China

Keywords: Continuous renal replacement therapy, COVID-19, invasive mechanical ventilation, mortality

Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, officially named Coronavirus Disease 2019 (COVID-19), occurred in Wuhan and spread in more than 100 countries in the world.[1] SARS-CoV-2 has 75-80% genomic similarity to severe acute respiratory syndrome coronavirus (SARS-CoV) and 50% to Middle

East Respiratory Syndrome coronavirus (MERS-CoV).[2] As of March 9th, 2020, COVID-19 has infected more than 100,000 people worldwide and caused more than 3,500 deaths, and the data are still increasing; in Wuhan, the fatality rate of COVID-19 was 4.8% (2404/49965). Of note, critically ill patients with COVID-19 have a high mortality rate. In a study of 52 critically ill patients in Wuhan, 32 (61.5%) patients died at 28 days and the mortality rate was 81.1% (30/37) in patients requiring mechanical ventilation.[3] Accumulated evidence has strongly demonstrated that systemic inflammatory response, acute kidney injury (AKI) and fluid overload (FO) were associated with high mortality in severe sepsis.[4-6] In critically ill patients with COVID-19, the overwhelming inflammation including C-reactive protein (CRP) and interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor α (TNF-α) were observed,[7-10] which is consistent with patients suffering from SARS-CoV[11] and MERS-CoV.[12]

Continuous renal replacement therapy (CRRT) is a great help in critically ill patients not only to control of electrolyte, acid-base derangements but also to remove inflammatory mediators and improves oxygenation in fluid overload.[13-15] CRRT has been applied to critically ill patients, including patients with SARS-CoV, MERS-CoV and other viral infectious diseases such as Ebola virus disease.[14,16] However, the benefits of CRRT are still no consistent conclusion in critically ill patients.[17] CRRT significantly reduced the level of IL-6 and decreases hospital mortality rate in pediatric severe sepsis, especially in patients with acute respiratory distress syndrome (ARDS).[18] Besides, a meta-analysis revealed that patients who received CRRT had significantly lower mortality compared to conventional therapy.[19] Hoverer, CRRT was associated with increased mortality in patients with MERS-CoV.[16] The relationship between CRRT and patients' outcome varied in patients with the different disease and was effected by the modalities, anticoagulation, vascular access management, timing of initiation and intensity of CRRT.[17,20,21]

To date, no specific treatment has been confirmed to be effective for COVID-19, and supportive treatment remains essential. As far as we know, the effect of CRRT on critically ill patients with COVID-19 has not been reported. In this retrospective cohort study, we aimed to explore the effect of CRRT on all-cause mortality in patients with COVID-19 undergoing invasive mechanical ventilation and the risk factors for mortality in patients with CRRT treatment.

Methods

Study Design and Participants

In this retrospective cohort study, we included all patients with COVID-19 undergoing invasive mechanical ventilation at Optical Valley Branch of Tongji Hospital Affiliated with Tongji Medical College, Huazhong University of Science and Technology, Wuhan from February 12 to March 2. We divided the study participants into two groups according to the CRRT treatment (CRRT group) and non-CRRT group).

The study protocol and waived written informed consent was approved by the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology (No. TJ-C20200333).

Inclusion criteria

All included patients met the criteria for the diagnosis of COVID-19 according to the New Coronavirus Pneumonia Prevention and Control Program (5th edition, in Chinese) published by the National Health Commission of China, that is, the diagnosis of COVID-19 in Hubei is confirmed through the detection of SARS-CoV-2 pathogens and/or clinical diagnosis (clinical symptoms related to COVID-19 and features of viral pneumonia on chest CT imaging examinations).[22] Invasive mechanical ventilation was defined as mechanical ventilation through an endotracheal tube or tracheostomy.

Procedures

Each patient's baseline data were collected and recorded at the start of invasive mechanical ventilation, including age, sex, comorbidities (history of hypertension, diabetes, heart disease, cerebrovascular disease, chronic lung disease, malignant tumor, chronic viral hepatitis, and others), complications (including multiple organ dysfunction syndrome [MODS], heart failure, acute kidney injury, arrhythmia, and bacterial infection), and treatments (including the uses of moxifloxacin hydrochloride, abidol, lopinavir/ritonavir, hydroxychloroquine, other antibiotic treatment, antifungal treatment, other antiviral treatment, traditional Chinese medicine, glucocorticoid, glucocorticoid, diuretics, human albumin, gamma globulin, heparin, and

Intraaortic Balloon Counterppulsation [IABP]). The laboratory data were collected throughout the study as follows: routine blood test, blood glucose, total cholesterol, hypersensitive C-reactive protein (hCRP), procalcitonin, ferritin, coagulation function, liver and renal function, lactic acid, high sensitive cardiac troponin I （hs-cTnI）, N-terminal pro-brain natriuretic peptide (NT-proBNP), and inflammatory factors, including IL-1β, IL-2 receptor, IL-6, IL-8, IL-10, and TNF-α. All information is obtained and managed through established data collection forms. Two researchers independently reviewed and collected the data.

CRRT Procedures

We performed CRRT with an ultrafiltration rate of 25-75 mL/kg/hr, performed using commercially available pump-driven machines (PrismaFlex, Gambro, Sweden; or multiFiltrate, Fresenius, Germany) and filter (M150, Gambro; Oxiris, Baxter; or AV1000s, Fresenius). For the patients with AKI, hemofiltration plus hemodialysis were performed. The blood flow rate was set on 2.5-4 mL/kg/min, and the clearance rate was set on 40-75 mL/min. The filter circuit was prewashed with saline containing 5,000-6,250 IU/L heparin. Vascular access was obtained with 13.5F central venous catheters (Covidien, MA, USA) in femoral vein.

Outcomes

We followed up all patients through electronic hospital medical records. The outcome was death. All patients were followed until death or March 9th, and all survivors were followed for at least one week. There was no loss to follow-up patients.

Statistical analysis

Numeric data were presented as the means and standard deviation (SD) or medians (interquartile range [IQR]) and were analyzed using Student's t-test or the Mann-Whitney U test depending on the data distribution. Categorical variables were displayed as frequencies and percentages and were analyzed using the Chi-squared test. The Kaplan-Meier method was used to estimate survival, and the log-rank test was used to evaluate differences between the two groups. The Cox regression model was conducted to adjust for potential confounders, including age, sex, the baseline values, and the average values of all tests between the start of invasive

mechanical ventilation and the endpoint. Univariate Cox proportional hazards regression analyses were performed for all-cause mortality, the significant variants in the univariate analysis and the variables which have clinical significance were selected for inclusion in a multivariate "backward" stepwise Cox regression analysis. SPSS 23.0 (IBM Corporation, Armonk, NY) statistical software was used for statistical analysis. GraphPad Prism 6 (GraphPad Software, USA) was used for statistical analysis and visualization. A P-value of 0.05 or less was considered significant.

Role of the funding source

Research funders were not involved in study design, data collection, data analysis, data interpretation or report writing. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Description of the cohort

In total, 36 COVID-19 patients with invasive mechanical ventilation were enrolled in the study. Table 1 showed the baseline characteristics of the cohort patients. There were 30 men (83.3%) and 6 women (16.7%), ranging in age from 44 and 86 years. Common comorbidity factors in COVID-19 patients with invasive mechanical ventilation were hypertension (n=14, 38.9%) and cardiac disease (n=12, 33.3%). The mean/median level of inflammatory markers (including white blood cell count, neutrophil count, hCRP, procalcitonin, and ferritin) and cardiac injury biomarkers (including hs-cTnI and NT-proBNP) were higher than normal.

We divided the study participants into two groups according to the CRRT treatment. Twenty-two patients received CRRT (CRRT group) while fourteen patients did not (non-CRRT group). There was no difference between two groups in baseline age, sex, comorbidities, complications, treatments and most of the laboratory findings, except for patients received CRRT with higher levels of aspartate aminotransferase (p=0.034) and serum creatinine (p=0.017).

Association between CRRT and all-cause mortality of COVID-19 patients undergoing

invasive mechanical ventilation

The mean follow-up period was 10.4 days. During the follow-up, 12 of 22 (54.5%) patients in CRRT group and 11 of 14 (78.6%) patients in non-CRRT group died. Kaplan–Meier analysis indicated that patients in CRRT group fared prolonged survival than those in non-CRRT group (P=0.032) (Figure 1).

In Cox regression analysis, seven different models were used to analyze the adjusted hazard ratio of CRRT treatment. Consistently, the association between CRRT treatment and a reduced risk of mortality remained significant after adjusting for selected confounding factors, such as age, sex, the baseline laboratory findings, or the average values of all tests between the start of invasive mechanical ventilation and the endpoint. The adjusted hazard ratio (aHR) of CRRT treatment fluctuated between 0.283 and 0.424 (Table 2).

Risk factors for all-cause mortality of COVID-19 patients undergoing invasive mechanical ventilation with CRRT treatment

We further conducted univariate and multivariate Cox proportional hazard regression analysis for all-cause mortality of COVID-19 patients undergoing invasive mechanical ventilation with CRRT. After adjusting the prognostic significance of clinical factors including age, sex, inflammatory factors, coagulation function, liver, and renal function, and cardiac function, we demonstrated that older age (aHR=1.112, P=0.025), higher levels of IL-1β (aHR=1.292, P=0.012), IL-2 receptor (aHR=1.002, P=0.013), hs-cTNI (aHR=1.001, P=0.004), and NT-proBNP (aHR=1.256, P=0.008) were significantly associated with increased risk of all-cause mortality (Table 3).

Discussion

To our knowledge, this current study is the first cohort study to estimate the association between CRRT treatment and mortality of COVID-19 patients with invasive mechanical ventilation. We included 36 COVID-19 patients with invasive mechanical ventilation, of whom 22 patients received CRRT. During the follow-up, 54.5% of patients in CRRT group, and 78.6% of patients in non-CRRT group died. CRRT was independently associated with a prolonged survival and a lower risk of mortality in COVID-19 patients requiring invasive mechanical ventilation, with

aHR ranging from 0.283 to 0.424 in seven different models.

Excessive inflammation characterized by uncontrolled release of pro-inflammatory cytokines in circulation is the main cause of death from sepsis,[23,24] infection of influenza virus,[25] Ebola virus,[26] MERS-CoV,[27] SARS-CoV.[28] In our study, we found inflammatory storm might play a crucial role in critical COVID-19 patients. The mean/median level of inflammatory markers, IL-1β, IL-2 receptor, IL-6, IL-8, IL-10, white blood cell count, neutrophil count, hCRP, procalcitonin, and ferritin were higher than normal. For example, the average of peaks for IL-6 was 1081.7 pg/mL, which was more than 100 times higher than the upper limit of normal value (reference range: < 7 pg/mL). Inflammatory storm may originate from the following aspects. First, SARS-Cov-2 infects patients by binding human ACE2,[29,30] which is widely expressed in multiple organs throughout the body.[31] SARS-CoV-2 might lead to multi-system inflammation through ACE/Ang II/AT1R pathway and ACE2/Ang (1-7)/Mas receptor pathway.[32,33] Second, it was reported that antibody dependent enhancement (ADE) of SARS-CoV-2 due to prior exposure to other coronaviruses might also be involved in COVID-19. ADE can elicit sustained inflammation, lymphopenia, and/or cytokine storm, which makes it a possible explanation for the geographic limitation of severe cases.[34] Third, combined infections may lead to a more severe systemic inflammatory response. Indeed, in our study, some patients combined with infection in other organs (e.g. urinary tract, blood) and other pathogen (e.g. influenza virus, fungus). Fourth, shock, hypoxemia and coagulation pathway abnormalities in critical patients could aggravate systemic inflammatory response, which become a vicious cycle, threatening life.[35,36]

In our study, CRRT was associated with prolonged survival in COVID-19 patients with invasive mechanical ventilation. CRRT is a widely used blood purification therapy, which achieves a high solute clearance rate through diffusion, convection, ultrafiltration, and adsorption. The primary goal of CRRT is to compensate for the loss of renal function and associated sequelae, including uremic toxins, electrolyte disturbances, metabolic acidosis, and volume overload[37]. Besides these, CRRT can also remove cytokines from the bloodstream. Emerging evidence has shown that CRRT was associated with significantly lower mortality in patients with severe sepsis.[18,19,38] In addition, in patients with acute respiratory distress syndrome, CRRT could remove

inflammatory mediators, modulate immune function, unregulated oxygenation, thus improve patient's prognosis.[39-41]

However, it is controversial whether CRRT is beneficial in viral pneumonia. CRRT was reported to have a positive effect on the treatment of adenovirus pneumonia[42]. While other studies revealed that CRRT was a risk factor for mortality in patients with MERS-CoV[16,43]. Yang et al also found that non-survivors have a higher proportion of CRRT in patients with COVID-19[44]. In our study, CRRT was associated with a reduced risk of mortality in COVID-19 patients requiring invasive mechanical ventilation after adjusting for confounding factors. COVID-19 is a novel infectious disease caused by a novel coronavirus and the underlining pathophysiological process in organ involvement is still unclear. Besides, the population studied in our cohort was different from Yang et al study, as they focused on all critically ill patients while our patients all receive invasive mechanical ventilation. Further research is needed to improve its treatment and prognosis.

Although CRRT treatment improved patient survival, 54.5% of patients with CRRT treatment died during our follow-up. In patients with CRRT, we further explored the risk factors for death for better management and treatment. We derived that older age, and higher levels of IL-1β, IL-2 receptor, hs-cTnI, and NT-proBNP were independently associated with a higher all-cause mortality in patients with CRRT.

IL-1β is known as a lymphocyte-stimulating factor, produced by activated monocyte-macrophages.[45,46] It plays an immunomodulatory role to induce synthesis of acute phase protein causing fever and cachexia, active antigen-presenting cell and T cells, and promote the proliferation and secretion of antibodies of B cells in innate and acquired immunity.[47-49] IL-2 receptor is widely expressed on the surface of IL-2 target cells, including T cells, B cells, and monocyte macrophage, promoting cytotoxic action, secretion of the antibody, production of IFN-γ, TNF-β, TGF-β and non-specific cytotoxins.[50-52] Elevated levels of IL-1β and IL-2 receptor were associated with higher risk of all-cause mortality in patients with CRRT, indicating that overactive inflammation and immune responses might still be risk factors for death. Inflammatory mediators and biomarkers need to be timely monitored and other effective interventions need to be explored.

In our study, cTnI and NT-proBNP were associated with increased risk of mortality in patients with CRRT. cTnI, constituting cardiac troponin together with troponin T and C, is degraded from the cardiac muscle fiber in the event of myocardial cell injury. Elevated cTnI in serumreflects damage to cardiomyocytes with a high myocardial specificity.[53] Patients with increased cTnI levels showed higher in-ICU mortality of pneumonia.[54] NT-proBNP is a natural hormone with biological activity synthesized by cardiomyocytes and mainly expressed in the ventricle. The rapid synthesis and release of NT-proBNP into the blood due to myocardial dilation regulate the cardiac function among patients with left ventricular dysfunction. NT-proBNP cutoffs of 4000 pg/mL optimally predicted short-term mortality in patients with sepsis.[55] Therefore, COVID-19 patients with elevated cTnI and NT-proBNP should be given enough attention and active treatment.

There were some limitations to our experiment. First, it is retrospective in design, warranting a prospective double-blind randomized controlled study. Second, the sample size of this study is not large enough. Third, as it is just a single-center study; multicenter studies are needed for further confirmation.

In summary, we demonstrated that CRRT could improve COVID-19 patients' survival, and might be an independent protective factor for COVID-19 patients' survival, and might be an independent protective factor for COVID-19 patients with invasive mechanical ventilation. In patients undergoing CRRT, older age, and higher levels of IL-1β, IL-2 receptor, hs-cTnI, and NT-proBNP were independently associated with higher all-cause mortality. Further prospective multicenter studies with larger sample sizes are required.

Contributors

FH, GX, SWG and YY conceived and designed the study. YN, JUL, QQL, SMG, and FH were in charge of management of patients. YY, JS, XX, YNW, AYC, and FH screened, reviewed and recorded the data. YY, JS and SWG performed statistical analyses. YY, JS and SWG drafted the manuscript. All authors provided critical revisions to the manuscript text. All authors read the manuscript and approved the final version.

Declaration of interests

All authors declare that they have no competing interests.

Data sharing

With the permission of the corresponding authors, we can provide participant data without names and identifiers, but not the study protocol, statistical analysis plan, or informed consent form. Data can be provided after the Article is published. Once the data can be made public, the research team will provide an email address for communication. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided.

Acknowledgments

This study was funded by National Natural Science Foundation of China (NSFC 81974089, 81470994, 81873556, 81470948, 81670633, 81570667), international (regional) cooperation and exchange projects, (NSFC-DFG, Grant No. 81761138041), the Major Research plan of the National Natural Science Foundation of China (Grant No. 91742204), the National Key Research and Development Program (Grants 2016YFC0906103, 2018YFC1314000) and the National Key Technology R&D Program (Grant 2013BAI09B06, 2015BAI12B07) and Science Foundation of Hubei Province (2018CFB554).

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Figure legend

Figure 1: Kaplan–Meier curve of overall patient survival according to with or without CRRT treatment. Patient survival was significantly better for CRRT group than for non-CRRT group (log-rank test, P=0.027).

Table 1. Comparison of baseline demographics and clinical characteristics of COVID-19 patients undergoing invasive mechanical ventilation between patients with and without CRRT treatment in the cohort.

Parameters	All patients	CRRT group	Non-CRRT group	P
N	36	22	14	-
Age				0.167[a]
Mean, years	69.4	67.5	72.6	
SD	10.8	11.4	9.1	
Range, years	44.0-86.0	44.0-86.0	58.0-86.0	
Sex				0.541[c]
Male, n (%)	30 (83.3)	19 (86.4)	11 (78.6)	
Female, n (%)	6 (16.7)	3 (13.6)	3 (21.4)	
APACHE-II score, mean (SD)	13.7 (4.7)	13.4 (5.4)	14.1 (3.4)	0.633[a]
SOFA score, median (IQR)	6.0 (4.0-8.0)	6.0 (3.8-8.0)	6.0 (4.5-7.0)	0.994[a]
Comorbidities				
Hypertension, n (%)	14 (38.9)	8 (36.4)	6 (42.9)	0.697[c]
Diabetes, n (%)	10 (27.8)	6 (27.3)	4 (28.6)	0.933[c]
Cardiac disease, n (%)	12 (33.3)	6 (27.3)	6 (42.9)	0.334[c]
Cerebrovascular disease, n (%)	2 (5.6)	0	2 (14.3)	0.068[c]
Chronic lung disease, n (%)	7 (19.4)	4 (18.2)	3 (21.4)	0.810[c]
Malignant tumor, n (%)	2 (5.6)	2 (9.1)	0	0.246[c]
Chronic viral hepatitis, n (%)	3 (8.3)	3 (13.6)	0	0.149[c]
Complications				
MODS, n (%)	13 (36.1)	10 (45.5)	3 (21.4)	0.143[c]
Heart failure, n (%)	7 (19.4)	5 (22.7)	2 (14.3)	0.533[c]
Acute kidney injury, n (%)	8 (22.2)	5 (22.7)	3 (21.4)	0.929[c]
Arrhythmia, n (%)	12 (33.3)	8 (36.4)	4 (28.6)	0.629[c]

Laboratory findings				
White blood cell count, mean (SD), 10^9/L	14.0 (7.1)	14.3 (8.5)	13.4 (4.4)	0.700[a]
Neutrophil count, mean (SD), 10^9/L	12.7 (6.7)	13.0 (8.0)	12.2 (4.2)	0.731[a]
Lymphocyte count, mean (SD), 10^9/L	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.546[a]
Hemoglobin, mean (SD), g/L	122.4 (18.1)	126.8 (18.6)	115.5 (15.5)	0.066[a]
Platelet, median (IQR), 10^9/L	156.0 (99.8-213.0)	159.0 (94.0-203.0)	156.0 (110.3-221.5)	0.580[b]
Blood glucose, mean (SD), mmol/L	9.8 (3.8)	9.0 (2.8)	11.0 (4.8)	0.131[a]
Total cholesterol, mean (SD), mmol/L	3.3 (0.9)	3.3 (1.0)	3.2 (0.8)	0.669[a]
hCRP, mean (SD), mg/L	121.0 (76.1)	124.7 (77.0)	105.8 (80.9)	0.667[a]
Procalcitonin, median (IQR), ng/mL	0.32 (0.19-0.83)	0.3 (0.2-1.0)	0.3 (0.3-0.9)	0.538[b]
Ferritin, median (IQR), μg/L	1140.0 (799.0-1983.0)	1264.0 (795.4-2108.0)	1077.0 (806.4-1933.0)	0.637[b]
Prothrombin time, median (IQR), s	15.5 (14.5-16.3)	15.1 (14.1-16.3)	15.7 (14.9-16.6)	0.299[b]
Activated partial thromboplastin time, median (IQR), s	38.7 (36.0-44.7)	38.7 (35.4-43.7)	39.0 (37.0-51.9)	0.158[b]
hs-cTnI, median (IQR), pg/mL	67.7 (16.0-284.9)	79.3 (16.3-587.2)	46.3 (14.6-162.0)	0.337[b]
NT-proBNP, median (IQR), μg/mL	1.2 (0.6-3.0)	1.1 (0.6-2.8)	1.2 (0.5-3.6)	0.781[b]
Alanine aminotransferase, median (IQR), U/L	34.5 (21.5-45.5)	36.0 (29.0-53.0)	30.5 (16.0-43.3)	0.081[b]
Aspartate aminotransferase, median (IQR), U/L	30.5 (22.5-54.0)	43.5 (24.0-63.3)	29.5 (20.0-34.0)	0.034[b]*
Blood urea nitrogen, median (IQR), mmol/L	10.7 (6.7-14.4)	10.8 (6.4-14.9)	10.3 (6.9-13.6)	0.923[b]
Serum creatinine, median (IQR), μmol/L	83.5 (66.0-126.3)	94.5 (67.0-136.0)	72.0 (51.0-82.3)	0.017[b]*
$HCO3^-$, mean (SD), mmol/L	24.7 (3.4)	24.3 (2.9)	25.4 (4.1)	0.345[a]
Potassium, median (IQR), mmol/L	4.1 (3.5-4.6)	4.1 (3.5-4.8)	4.2 (3.6-4.6)	0.968[b]
Lactic acid, median (IQR), mmol/L	2.3 (1.8-2.9)	2.4 (1.9-2.8)	2.3 (1.8-3.0)	0.811[b]
Treatments				
Moxifloxacin hydrochloride, n (%)	24 (66.7)	16 (72.7)	8 (57.1)	0.334[c]
Abidol, n (%)	28 (77.8)	17 (77.3)	11 (78.6)	0.929[c]
Lopinavir/ritonavir, n (%)	10 (27.8)	8 (36.4)	2 (14.3)	0.149[c]

Hydroxychloroquine, n (%)	3 (8.3)	2 (9.1)	1 (7.1)	0.836[c]
Other antibiotic treatment, n (%)	34 (94.4)	21 (95.5)	13 (92.9)	0.740[c]
Antifungal treatment, n (%)	5 (13.9)	5 (22.7)	0	0.055[c]
Other antiviral treatment, n (%)	4 (11.1)	1 (4.5)	3 (21.4)	0.116[c]
Traditional Chinese medicine, n (%)	20 (55.6)	12 (54.5)	8 (57.1)	0.879[c]
Glucocorticoid, n (%)	29 (80.6)	17 (77.3)	12 (85.7)	0.533[c]
Diuretics, n (%)	27 (75.0)	15 (68.2)	12 (85.7)	0.236[c]
Human albumin, n (%)	34 (94.4)	21 (95.5)	13 (92.9)	0.740[c]
Gamma globulin, n (%)	29 (80.6)	18 (81.8)	11 (78.6)	0.810[c]
Heparin, n (%)	29 (80.6)	17 (77.3)	12 (85.7)	0.533[c]
IABP, n (%)s	2 (5.6)	1 (4.5)	1 (7.1)	0.740[c]
Duration of invasive mechanical ventilation to initiation of CRRT, median (IQR), days	-	3.5 (2.0-6.3)	-	-
Outcomes				
Follow-up time, mean (SD), days	10.4 (6.2)	12.2 (5.7)	7.5 (6.1)	0.025[a]*
Death, n (%)	23 (63.9)	12 (54.5)	11 (78.6)	0.143[c]

Values are expressed as mean (SD), median (25^{th}–75^{th} percentile) or n (%). COVID-19=Coronavirus disease 2019; APACHE II=Acute physiology and chronic health evaluation II; SOFA=sepsis-related organ fai lureassessment; CRRT=Continuous renal replacement therapy; MODS=Multiple organ disfunction syndrome; IABP=Intra aortic balloon counterpulsation; SD=Standard deviation; IQR=Interquartile range; hCRP=Hypersensitive C-reactive protein; hs-cTnI, High sensitive cardiac troponin I; NT-pro BNP=N-terminal pro-brain natriuretic peptide. *P<0.05. [a]t-test, [b]Whitney U test, [c]Chi-square test.

Table 2. Models of multivariate Cox proportional hazard regression analysis for CRRT treatment (reference group: non-CRRT treatment) for all-cause mortality of all COVID-19 patients undergoing invasive mechanical ventilation in the cohort.

CRRT versus non-CRRT	Adjusted Hazard Ratio (95% CI)	P
Model A	0.424 (0.185, 0.969)	0.042
Model B	0.404 (0.175, 0.932)	0.033
Model C	0.415 (0.179, 0.962)	0.040
Model D	0.332 (0.115, 0.959)	0.042
Model E	0.333 (0.133, 0.833)	0.048
Model F	0.283 (0.110, 0.732)	0.009
Model G	0.324 (0.118, 0.893)	0.029

Model A: Adjusted for age and sex;

Model B: Adjusted for age, sex, blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, plasma albumin, high sensitive cardiac troponin I, myoglobin (the baseline values);

Model C: Adjusted for age, sex, blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, plasma albumin, high sensitive cardiac troponin I, myoglobin (the average of all tests between the start of invasive mechanical ventilation and the end point);

Model D: Adjusted for age, sex, IL-1β, IL-2 receptor, IL-6, IL-8, IL-10 and TNF-α (the baseline values);

Model E: Adjusted for age, sex, IL-1β, IL-2 receptor, IL-6, IL-8, IL-10 and TNF-α (the average of all tests between the start of invasive mechanical ventilation and the end point);

Model F: Adjusted for age, sex, IL-1β, IL-2 receptor, IL-6, IL-8, IL-10, TNF-α, white blood cell count, neutrophil count, lymphocyte count, hemoglobin, platelet, prothrombin time, activated partial thromboplastin time (the baseline values);

Model G: Adjusted for age, sex, IL-1β, IL-2 receptor, IL-6, IL-8, IL-10, TNF-α, white blood cell count, neutrophil count, lymphocyte count, hemoglobin, platelet, prothrombin time, activated partial thromboplastin time (the average of all tests between the start of invasive mechanical ventilation and the end point).

Table 3. Univariate and multivariate Cox proportional hazard regression analysis for all-cause mortality of COVID-19 patients undergoing invasive mechanical ventilation with CRRT treatment in the cohort.

Parameters	Univariate Cox regression		Multivariate Cox regression	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Age (per year)	1.060 (1.003, 1.120)	0.037	1.112 (1.013, 1.220)	0.025
Sex (male versus female)	0.728 (0.156, 3.387)	0.686	-	
IL-1β (per pg/mL)	1.012 (0.910, 1.126)	0.822	1.292 (1.059, 1.578)	0.012
IL-2 receptor (per U/mL)	1.002 (1.000, 1.003)	0.006	1.002 (1.000-1.004)	0.013
IL-6 (per pg/mL)	1.006 (1.000, 1.012)	0.066	-	
IL-8 (per pg/mL)	1.003 (1.000, 1.005)	0.021	-	
IL-10 (per pg/mL)	1.009 (0.971, 1.050)	0.636	1.054 (0.996, 1.116)	0.067
TNF-α (per pg/mL)	1.051 (1.008, 1.097)	0.021	-	
Prothrombin time (per s)	1.831 (1.234, 2.717)	0.003	-	
Plasma albumin (per g/L)	1.064 (0.878, 1.290)	0.524	-	
Serum creatinine (per μmol/L)	1.002 (0.990, 1.015)	0.712	-	
hs-cTnI (per pg/mL)	1.000 (1.000, 1.000)	0.373	1.001 (1.000-1.002)	0.004
NT-proBNP (per μg/mL)	1.179 (1.055, 1.318)	0.004	1.256 (1.062, 1.485)	0.008

COVID-19=Coronavirus disease 2019; CRRT=Continuous renal replacement therapy; IL= interleukin; TNF= tumor necrosis factor; hs-cTnI, high sensitive cardiac troponin I; NT-proBNP=N-terminal pro-brain natriuretic peptide.