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Association between Prolonged Intermittent Renal Replacement Therapy and All-Cause Mortality in COVID-19 Patients Undergoing Invasive Mechanical Ventilation: A Retrospective Cohort Study

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Keywords
Prolonged intermittent renal replacement therapy · Coronavirus disease 2019 · Invasive mechanical ventilation · Mortality

Abstract
Background: The mortality rate of critically ill patients with coronavirus disease 2019 (COVID-19) was high. We aimed to assess the association between prolonged intermittent renal replacement therapy (PIRRT) and mortality in patients with COVID-19 undergoing invasive mechanical ventilation. ***Methods:*** This retrospective cohort study included all COVID-19 patients receiving invasive mechanical ventilation between February 12 and March 2, 2020. All patients were followed until death or March 28, and all survivors were followed for at least 30 days. ***Results:*** For 36 hospitalized COVID-19 patients receiving invasive mechanical ventilation, the mean age was 69.4 (±10.8) years, and 30 patients (83.3%) were men. Twenty-two (61.1%) patients received PIRRT (PIRRT group), and 14 cases (38.9%) were managed with conventional strategy (non-PIRRT group). There were no differences in age, sex, comorbidities, complications, treatments, and most of the laboratory findings. During the median follow-up period of 9.5 (interquartile range 4.3–33.5) days, 13 of 22 (59.1%) patients in the PIRRT group and 11 of 14 (78.6%) patients in the non-PIRRT group died. Kaplan-Meier analysis demonstrated prolonged survival in patients in the PIRRT group compared with that in the non-PIRRT group ($p = 0.042$). The association between PIRRT and a reduced risk of mortality remained significant in 3 different models, with adjusted hazard ratios varying from 0.332 to 0.398. Increased IL-2 receptor, TNF-α, procalcitonin, prothrombin time, and NT-proBNP levels were significantly associated with an increased risk of mortality in patients with PIRRT. ***Conclusion:*** PIRRT may be beneficial for the treatment of COVID-19 patients with invasive mechanical ventilation. Further prospective multicenter studies with larger sample sizes are required.

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Introduction

Coronavirus disease 2019 (COVID-19) is an epidemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. In Wuhan, the fatality rate of COVID-19 was 5.1% (2,538/50,006). Of note, critically ill patients with COVID-19 have a much higher mortality rate. In a study of 52 critically ill patients in Wuhan, 32 (61.5%) patients had died after 28 days, and the mortality rate was 81.1% (30/37) in patients requiring mechanical ventilation [2]. Accumulated evidence has strongly demonstrated that systemic inflammatory response, acute kidney injury (AKI), and fluid overload were associated with high mortality in severe sepsis [3–5]. In critically ill patients with COVID-19, an overwhelming inflammatory response involving C-reactive protein, interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor α (TNF-α) was observed [6–9], which is similar to that observed in patients suffering from SARS-CoV [10] and Middle East respiratory syndrome (MERS)-CoV [11].

Renal replacement therapy (RRT) is of great help in the treatment of critically ill patients, not only controlling electrolyte and acid-base imbalance but also clearing inflammatory mediators and improving oxygenation in the case of fluid overload [12–14]. RRT has been applied to critically ill patients, including SARS-CoV, MERS-CoV, and other viral infectious diseases such as Ebola virus disease [13, 15]. There is still no consensus on the benefits of RRT in critically ill patients [16]. RRT can significantly reduce IL-6 level and hospital mortality in children with severe sepsis, especially acute respiratory distress syndrome [17]. In addition, a meta-analysis showed a significant reduction in mortality in patients receiving RRT compared with conventional treatment [18]. However, RRT was associated with increased mortality in MERS-CoV patients [15]. The relationship between RRT and patient prognosis varied among patients with different diseases and was influenced by RRT modalities, anticoagulant use, vascular access management, start-up time, and intensity [16, 19, 20].

Prolonged intermittent renal replacement therapy (PIRRT), as a cost-effective alternative, has been used in the intensive care unit [21, 22]. To date, no specific treatment has been proven effective for COVID-19, and supportive care remains critical. In this retrospective cohort study, we aimed to investigate the association between PIRRT and all-cause mortality in patients with COVID-19 undergoing invasive mechanical ventilation.

Materials and Methods

Study Design and Participants

This retrospective cohort study included COVID-19 patients undergoing invasive mechanical ventilation at the Optical Valley Branch of Tongji Hospital, Wuhan, from February 12 to March 2. The subjects were divided into 2 groups (PIRRT group and non-PIRRT group) according to the use of PIRRT treatment.

Inclusion and Exclusion Criteria

All included patients met the COVID-19 diagnostic criteria of the New Coronavirus Pneumonia Prevention and Control Program (Fifth Edition, in Chinese) published by the National Health Commission of China [23]. Invasive mechanical ventilation was defined as mechanical ventilation through an endotracheal tube or tracheostomy. There were no exclusion criteria.

Procedures

Baseline data were collected and recorded for each patient at the start of invasive mechanical ventilation, including age, sex, comorbidities, complications, laboratory data, and treatments. All information was obtained and managed through established data collection forms. Two researchers independently reviewed and collected the data.

PIRRT Procedures

We performed PIRRT using commercially available pump-driven machines (PrismaFlex, Gambro, Sweden; or multiFiltrate, Fresenius, Germany) and appropriate circuit set with filter (M150 set, Gambro; Oxiris set, Baxter; or multiFiltrate cassette with AV1000s, Fresenius). For the patients with AKI, hemofiltration plus hemodialysis was performed. The blood flow rate, the ultrafiltration rate, and the clearance rate were set at 2.5–4 mL/kg/min, 0–5 mL/kg/h, and 35–70 mL/kg/h, respectively. Central venous catheterization circuit was obtained with a 24-cm long 13.5-F central venous catheter (Covidien, MA, USA) in the femoral vein. The filter circuit was prewashed with saline containing 5,000–6,250 IU/L heparin. PIRRT modalities were venovenous hemodiafiltration in 22.7% (5/22) of the patients and venovenous hemofiltration in 77.3% (17/22) of the patients. Patients received 8 h of PIRRT once a day or every other day.

The indications for PIRRT were as follows: (1) nonobstructive oliguria (urine output <200 mL/12 h) or anuria or AKI stage 3 (serum Cr increase ≥3 times baseline with 7 days); (2) hyperkalemia (K+ >6.5 mmol/L); (3) acidemia (PH <7.1); (4) clinically significant organ edema (especially pulmonary edema); (5) uremic complications (pericarditis/encephalopathy/neuropathy/myopathy); (6) azotemia (urea >30 mmol/L); (7) (optional) increased inflammatory cytokines (anyone of IL-1β, IL-2 receptor, IL-6, IL-8, or TNF-α ≥5 times of upper limit of normal range).

Outcomes

All patients were followed through hospital electronic medical records. The primary outcome was death, with all patients followed up to death or March 28, and all survivors followed up for at least 30 days. There was no loss to follow-up for patients.

Statistical Analyses

Numerical data were presented as the mean and SD or median (interquartile range [IQR]) and analyzed using Student's *t* test or

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

Parameters	All patients	PIRRT group	Non-PIRRT group	*p* value
N	36	22	14	–
Age, years				
Mean	69.4	67.5	72.6	0.167[a]
SD	10.8	11.4	9.1	
Range	44.0–86.0	44.0–86.0	58.0–86.0	
Sex, *n* (%)				
Male	30 (83.3)	19 (86.4)	11 (78.6)	0.658[c]
Female	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]
Hospitalization, median (IQR), days	6.0 (4.0–9.0)	5.5 (2.8–8.0)	7.5 (4.0–10.0)	0.171[a]
Comorbidities, *n* (%)				
Hypertension	14 (38.9)	8 (36.4)	6 (42.9)	0.738[c]
Diabetes	10 (27.8)	6 (27.3)	4 (28.6)	1.000[c]
Cardiac disease	12 (33.3)	6 (27.3)	6 (42.9)	0.472[c]
Cerebrovascular disease	2 (5.6)	0 (0)	2 (14.3)	0.144[c]
Chronic lung disease	7 (19.4)	4 (18.2)	3 (21.4)	1.000[c]
Malignant tumor	2 (5.6)	2 (9.1)	0 (0)	0.511[c]
Chronic viral hepatitis	3 (8.3)	3 (13.6)	0 (0)	0.267[c]
Any of comorbidity	30 (83.3)	18 (81.8)	12 (85.7)	0.759[c]
Complications, *n* (%)				
MODS	13 (36.1)	10 (45.5)	3 (21.4)	0.175[c]
Heart failure	7 (19.4)	5 (22.7)	2 (14.3)	0.681[c]
Acute kidney injury	8 (22.2)	5 (22.7)	3 (21.4)	1.000[c]
Arrhythmia	12 (33.3)	8 (36.4)	4 (28.6)	0.727[c]
ARDS	36 (100)	22 (100)	14 (100)	1.000[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]
IL-1β, median (IQR), pg/mL	6.3 (5.0–9.2)	6.3 (5.0–10.9)	6.4 (5.0–8.6)	0.667[b]
IL-2 receptor, median (IQR), U/mL	891.0 (636.0–1,465.0)	1,436.0 (724.3–1,593.0)	755.5 (558.3–887.3)	0.018[b]
IL-6, median (IQR), pg/mL	56.6 (21.9–188.9)	56.6 (20.9–161.3)	71.1 (23.7–270.0)	0.733[b]
IL-8, median (IQR), pg/mL	31.5 (20.1–110.8)	33.1 (17.7–122.3)	31.5 (21.3–47.8)	0.886[b]
IL-10, median (IQR), pg/mL	6.9 (5.0–13.7)	10.0 (5.0–19.2)	5.8 (5.0–8.8)	0.065[b]
TNF-α, median (IQR), pg/mL	13.7 (10.3–22.0)	13.2 (9.7–20.5)	14.0 (11.1–23.2)	0.516[b]
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	1,140.0 (799.0–1,983.0)	1,264.0 (795.4–2,108.0)	1,077.0 (806.4–1,933.0)	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, *]
BUN, 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 Cr, 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, *]
Serum bicarbonate, 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]

Table 1 (continued)

Parameters	All patients	PIRRT group	Non-PIRRT group	*p* value
Treatments, *n* (%)				
Moxifloxacin hydrochloride	24 (66.7)	16 (72.7)	8 (57.1)	0.472[c]
Abidol	28 (77.8)	17 (77.3)	11 (78.6)	1.000[c]
Lopinavir/ritonavir	10 (27.8)	8 (36.4)	2 (14.3)	0.255[c]
Hydroxychloroquine	3 (8.3)	2 (9.1)	1 (7.1)	1.000[c]
Other antibiotic treatment	34 (94.4)	21 (95.5)	13 (92.9)	1.000[c]
Antifungal treatment	5 (13.9)	5 (22.7)	0 (0)	0.134[c]
Other antiviral treatment	4 (11.1)	1 (4.5)	3 (21.4)	0.134[c]
Traditional Chinese medicine	20 (55.6)	12 (54.5)	8 (57.1)	1.000[c]
Glucocorticoid	29 (80.6)	17 (77.3)	12 (85.7)	0.681[c]
Diuretics	27 (75.0)	15 (68.2)	12 (85.7)	0.432[c]
Human albumin	34 (94.4)	21 (95.5)	13 (92.9)	1.000[c]
Gamma globulin	29 (80.6)	18 (81.8)	11 (78.6)	1.000[c]
Heparin	29 (80.6)	17 (77.3)	12 (85.7)	0.681[c]
IABP	2 (5.6)	1 (4.5)	1 (7.1)	1.000[c]
ECMO	3 (8.3)	3 (13.6)	0 (0)	0.267[c]
Duration of invasive mechanical ventilation to initiation of PIRRT, median (IQR), days	–	3.5 (2.0–6.3)	–	–

COVID-19, coronavirus disease 2019; APACHE II, acute physiology and chronic health evaluation II; SOFA, sepsis-related organ failure assessment; PIRRT, prolonged intermittent renal replacement therapy; MODS, multiple organ dysfunction syndrome; IABP, intra-aortic balloon counterpulsation; IQR, interquartile range; ARDS, acute respiratory distress syndrome; IL, interleukin; TNF-α, tumor necrosis factor-α; hCRP, hypersensitive C-reactive protein; hs-cTnI, high sensitive cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECMO, extracorporeal membrane oxygenation. * $p < 0.05$. [a] *t* test. [b] Mann-Whitney U test. [c] Fisher's exact test.

the Mann-Whitney U test according to data distribution. Categorical variables were displayed as frequencies and percentages and analyzed using Fisher's exact test. Paired *t* test or Wilcoxon matched-pairs signed rank test were used to evaluate the differences of variables between before and after PIRRT. The Kaplan-Meier method was used to estimate survival, and the log-rank test was used to evaluate differences between the 2 groups. Univariate and multivariate Cox proportional hazards regression analyses were performed for all-cause mortality. SPSS 23.0 (IBM Corporation, Armonk, NY, USA) statistical software and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) were used for statistical analysis and visualization. A *p* value of 0.05 or less was considered significant.

Results

Description of the Cohort

In total, 36 COVID-19 patients subjected to invasive mechanical ventilation were enrolled in the study. Table 1 shows the baseline characteristics of the cohort patients. There were 30 men (83.3%) and 6 women (16.7%) ranging in age from 44 to 86 years. Thirty patients (83.3%) had at least 1 comorbidity, and the common comorbidity factors in COVID-19 patients with invasive mechanical ventilation were hypertension ($n = 14$, 38.9%) and cardiac disease ($n = 12$, 33.3%).

We divided the subjects into 2 groups based on PIRRT. Twenty-two patients received PIRRT (PIRRT group) while 14 patients did not (non-PIRRT group). There was no difference between the 2 groups in baseline characteristics including age, sex, acute physiology, and chronic health evaluation (APACHE) II scores, sepsis-related organ failure assessment (SOFA) scores, comorbidities, complications, treatments, or most laboratory findings, except for patients who received PIRRT with higher levels of aspartate aminotransferase ($p = 0.034$) and serum Cr ($p = 0.017$).

The indications for PIRRT ($n = 22$) were as follows: (1) AKI at stage 3 with or without hyperkalemia or pulmonary edema: $n = 4$; (2) hyperkalemia: $n = 1$; (3) acidemia: $n = 1$; (4) pulmonary edema: $n = 1$; (5) (optional) increased inflammatory cytokines (anyone of IL-1β, IL-2, IL-6, IL-8 receptors or TNF-α ≥5 times of upper limit of normal range): $n = 15$. There was no definite indication of PIRRT for patients in the non-PIRRT group. Our evaluation of dialysis indications was consistent in all patients, except for inflammatory cytokines. Furthermore,

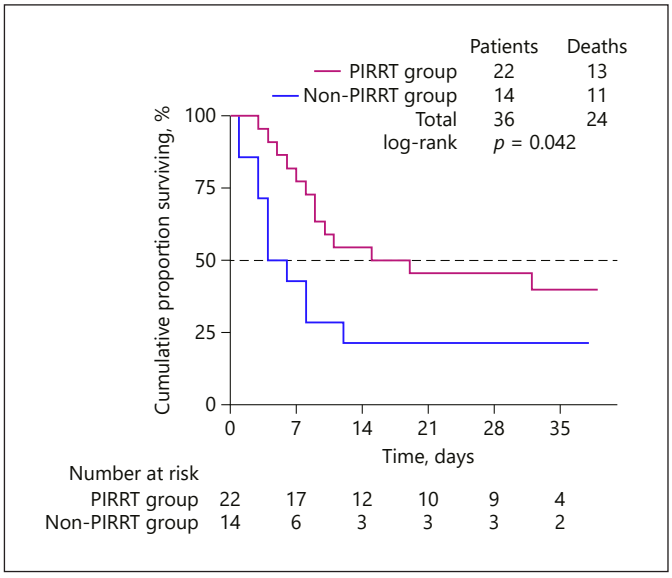

Fig. 1. Kaplan-Meier curve of overall patient survival according to with or without PIRRT treatment. Patient survival was significantly better for the PIRRT group than for the non-PIRRT group (log-rank test, $p = 0.042$). PIRRT, prolonged intermittent renal replacement therapy.

Color version available online

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

PIRRT versus non-PIRRT	Adjusted hazard ratio (95% CI)	*p* value
Model A	0.350 (0.147, 0.830)	0.017
Model B	0.398 (0.171, 0.924)	0.032
Model C	0.332 (0.119, 0.925)	0.035

Model A, adjusted for APACHE II scores, SOFA scores, and any of comorbidity; Model B, adjusted for acute kidney injury, APACHE II scores, sex; Model C, adjusted for IL-6, APACHE II scores, IL-2 receptor. COVID-19, coronavirus disease 2019; PIRRT, prolonged intermittent renal replacement therapy; APACHE II, acute physiology and chronic health evaluation II; SOFA, sepsis-related organ failure assessment.

in the PIRRT group, IL-6 showed a significant difference before and after PIRRT (before vs. after PIRRT: median 221.35, IQR 111.23–427.40 vs. median 48.53, IQR 12.93–119.23, pg/mL, $p = 0.001$).

Association between PIRRT and All-Cause Mortality in COVID-19 Patients Undergoing Invasive Mechanical Ventilation

All survivors were followed for at least 30 days. During the median follow-up period of 9.5 (IQR 4.3–33.5) days, 13 of 22 (59.1%) patients in the PIRRT group and 11 of 14 (78.6%) patients in the non-PIRRT group died. Kaplan-Meier analysis indicated that the survival time of patients in the PIRRT group was prolonged compared with the non-PIRRT group ($p = 0.04$) (shown in Fig. 1).

Three different models were used in the Cox regression analysis to analyze the adjusted hazard ratio for PIRRT treatment. Consistently, the association between PIRRT treatment and reduced risk of mortality remained significant, while the adjusted hazard ratio for PIRRT treatment fluctuated between 0.332 and 0.398 (Table 2). Univariate Cox proportional hazard regression analysis showed that increased IL-6 (HR = 1.004, 95% CI [1.001–1.007]) and TNF-α (HR = 1.040, 95% CI [1.007–1.073]) were associated with increased risk of mortality of all patients with invasive mechanical ventilation.

Risk Factors Associated with All-Cause Mortality for COVID-19 Patients Undergoing Invasive Mechanical Ventilation with PIRRT Treatment

We further conducted a univariate Cox proportional hazard regression analysis of all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation with PIRRT. We found that increased IL-2 receptor, TNF-α, procalcitonin, prothrombin time, and NT-proBNP levels were significantly associated with an increased risk of all-cause mortality (Table 3).

Discussion

To our knowledge, this study is the first cohort to estimate the association between PIRRT treatment and mortality in COVID-19 patients receiving invasive mechanical ventilation. Invasive mechanical ventilation was performed on 36 COVID-19 patients, of whom 22 received PIRRT. During follow-up, 59.1% of the patients in the PIRRT group and 78.6% in the non-PIRRT group died. PIRRT was independently associated with prolonged survival and reduced risk of mortality in COVID-19 patients requiring invasive mechanical ventilation. The research has been published on medRxiv [24].

Excessive inflammation previously characterized by uncontrolled release of pro-inflammatory cytokines into circulation is the leading cause of death in patients with sepsis [25, 26] and viral infectious diseases, such as influenza virus [27], Ebola virus [28], MERS-CoV [29], and SARS-CoV [30]. In our study, we found that the cytokine storm might

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

Parameters	Hazard ratio (95% CI)	*p* value
Age (per year)	1.048 (0.998, 1.100)	0.059
Sex (male vs. female)	0.959 (0.209, 4.397)	0.957
APACHE II score (per 1 score)	1.038 (0.942, 1.143)	0.453
SOFA score (per 1 score)	1.093 (0.948, 1.261)	0.221
Any of comorbidity (with vs. without)	1.720 (0.379, 7.816)	0.483
Acute kidney injury (with vs. without)	2.219 (0.674, 7.313)	0.190
White blood cell count (per 10^9/L)	0.980 (0.918, 1.047)	0.553
IL-2 receptor (per U/mL)	1.002 (1.001, 1.003)	0.004*
IL-6 (per pg/mL)	1.005 (0.999, 1.011)	0.085
TNF-α (per pg/mL)	1.046 (1.002, 1.092)	0.041*
Procalcitonin (per ng/L)	2.306 (1.098, 4.842)	0.027*
Prothrombin time (per s)	1.808 (1.229, 2.659)	0.003*
D-dimer (per μg/mL [FEU])	1.034 (0.964, 1.109)	0.346
hs-cTnI (per pg/mL)	1.000 (1.000, 1.000)	0.257
NT-proBNP (per μg/mL)	1.181 (1.056, 1.320)	0.003*
Alanine aminotransferase (per U/L)	0.998 (0.992, 1.004)	0.479
Aspartate aminotransferase (per U/L)	0.998 (0.994, 1.003)	0.442
Plasma albumin (per g/L)	1.010 (0.856, 1.191)	0.910
BUN (per mmol/L)	1.021 (0.950, 1.099)	0.569
Serum Cr (per μmol/L)	1.000 (0.987, 1.012)	0.963

* $p < 0.05$. COVID-19, coronavirus disease 2019; PIRRT, prolonged intermittent renal replacement therapy; APACHE II, acute physiology and chronic health evaluation II; SOFA, sepsis-related organ failure assessment; IL, interleukin; TNF, tumor necrosis factor; FEU, fibrinogen equivalent units; hs-cTnI, high-sensitive cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide.

play a crucial role in severe cases of COVID-19. The mean/median levels of inflammatory markers, including IL-1β, IL-2 receptor, IL-6, IL-8, and IL-10, white blood cell count, neutrophil count, hCRP, procalcitonin, and ferritin were higher than normal. In our study, univariate Cox proportional hazard regression analysis showed that increased IL-6 and TNF-α were both associated with increased risk of mortality in all patients with invasive mechanical ventilation. Besides, in patients receiving PIRRT, a significant difference of IL-6 before and after PIRRT was observed: before versus after PIRRT: 221.35 (IQR 111.23–427.40) versus 48.53 (IQR 12.93–119.23), $p = 0.001$.

Cytokine storms may be caused by several factors. First, SARS-CoV-2 infects patients by binding to human angiotensin (Ang)-converting enzyme 2 (ACE2) [31, 32], which is widely expressed in multiple organs throughout the body [33]. SARS-CoV-2 might lead to multisystem inflammation through the ACE/Ang II/AT1R pathway and the ACE2/Ang [1–7]/Mas receptor pathway [34, 35]. Second, it has been reported that antibody-dependent enhancement of SARS-CoV-2 due to previous exposure to other coronaviruses may also be associated with COVID-19 [36]. Third, coinfection may lead to a more severe systemic inflammatory response. Indeed, in our study, some patients were infected with other pathogens (e.g., influenza virus and fungi) in other organs (such as urinary tract and blood). Last, shock, hypoxemia, and abnormal coagulation pathways in critically ill patients can aggravate systemic inflammatory response, forming a life-threatening vicious cycle [37, 38].

In our study, PIRRT was associated with prolonged survival in COVID-19 patients on invasive mechanical ventilation. The primary goal of RRT is to compensate for the loss of renal function and associated sequelae, including uremic toxicity, electrolyte disturbances, metabolic acidosis, and volume overload [22, 39]. In addition, RRT can also clear cytokines from the blood. Emerging evidences have shown that RRT is associated with significantly reduced mortality in patients with severe sepsis [17, 18, 40]. Besides, in patients with acute respiratory distress syndrome, RRT could clear inflammatory mediators, regulate immune function, and regulate oxygenation, thereby improving patient prognosis [41–43]. PIRRT is a widely used blood purification therapy that achieves a high solute clear-

ance rate through diffusion and convection [44]. In intensive care units, PIRRT has been shown to encompass the benefits of both continuous RRT in terms of hemodynamic stability and intermittent hemodialysis in terms of cost-efficiency [22, 45]. In practical clinical work, PIRRT may be more flexible, realistic, and timely in the face of a large number of critically ill COVID-19 patients with different demands for treatment.

However, the available data on whether PIRRT is beneficial for viral pneumonia appears somewhat contradictory. RRT has been reported to have a positive effect on the treatment of adenovirus pneumonia [46]. Other studies have shown that PIRRT is a risk factor for mortality in MERS-CoV patients [15, 47]. Yang et al. [48] also found a higher percentage of non-survivors receiving RRT in COVID-19 patients. In our study, PIRRT was associated with a reduced risk of mortality in COVID-19 patients requiring invasive mechanical ventilation after adjusting for confounders. COVID-19 is a novel infectious disease caused by a novel coronavirus, and the pathophysiological process related to organ involvement is still unclear. In addition, the population in our cohort study was different from that of Yang et al. [48], which focused on all critically ill patients, while we focused on patients receiving invasive mechanical ventilation. Further research is needed to improve patient care and prognosis.

There were some limitations to our study. First, the design is retrospective, and prospective double-blind randomized controlled studies are warranted in the future. Second, the sample size of this study is not large enough. Third, because it is a single-center study, it needs to be confirmed by multicenter study. Last, the variety of PIRRT prescriptions leads to the lack of consistency in treatment. More uniform prospective studies are needed.

In summary, we demonstrate that PIRRT can improve the survival of COVID-19 patients and may be an independent protective factor for COVID-19 patients undergoing invasive mechanical ventilation. Prospective multicenter studies with larger sample sizes are also needed.

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Statement of Ethics

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

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

F.H., G.X., S.G., and Y.Y. conceived and designed the study. Y.N., J.L, Q.L., S.G., and F.H. were in charge of management of patients. Y.Y., J.S., X.X., Y.W., A.C., and F.H. screened, reviewed, and recorded the data. Y.Y., J.S., and S.G. performed statistical analyses. Y.Y., J.S., and S.G. drafted the manuscript. All authors provided critical revisions to the manuscript text. All authors read the manuscript and approved the final version.

References

1 Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–33.
2 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475–81.
3 Zarbock A, Gomez H, Kellum JA. Sepsis-induced acute kidney injury revisited: pathophysiology, prevention and future therapies. Curr Opin Crit Care. 2014;20(6):588–95.
4 Vincent JL. Fluid management in the critically ill. Kidney Int. 2019;96(1):52–7.
5 Xie J, Wang H, Kang Y, Zhou L, Liu Z, Qin B, et al. The epidemiology of sepsis in Chinese ICUs: a national cross-sectional survey. Crit Care Med. 2020;48(3):e209–18.
6 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
7 Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020 Jul 28;71(15):762–8.

8 Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 May;46(5):846–8.
9 Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med. 2020 Apr 30;382(18):1708–20.
10 Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004;136(1):95–103.
11 Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine. 2018;104:8–13.
12 Forni LG, Joannidis M. IDEAL timing of renal replacement therapy in critical care. Nat Rev Nephrol. 2019;15(1):5–6.
13 Wolf T, Kann G, Becker S, Stephan C, Brodt HR, de Leuw P, et al. Severe Ebola virus disease with vascular leakage and multiorgan failure: treatment of a patient in intensive care. Lancet. 2015;385(9976):1428–35.
14 Rewa OG, Villeneuve PM, Lachance P, Eurich DT, Stelfox HT, Gibney RTN, et al. Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review. Intensive Care Med. 2017;43(6):750–63.
15 Alfaraj SH, Al-Tawfiq JA, Assiri AY, Alzahrani NA, Alanazi AA, Memish ZA. Clinical predictors of mortality of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: a cohort study. Travel Med Infect Dis. 2019 May–Jun;29:48–50.
16 Karkar A, Ronco C. Prescription of CRRT: a pathway to optimize therapy. Ann Intensive Care. 2020;10(1):32.
17 Miao H, Shi J, Wang C, Lu G, Zhu X, Wang Y, et al. Continuous renal replacement therapy in pediatric severe sepsis: a propensity score-matched prospective multicenter cohort study in the PICU. Crit Care Med. 2019;47(10):e806–13.
18 Putzu A, Fang MX, Boscolo Berto M, Belletti A, Cabrini L, Cassina T, et al. Blood purification with continuous veno-venous hemofiltration in patients with sepsis or ARDS: a systematic review and meta-analysis. Minerva Anestesiol. 2017;83(8):867–77.
19 Fayad AII, Buamscha DG, Ciapponi A. Timing of renal replacement therapy initiation for acute kidney injury. Cochrane Database Syst Rev. 2018;12:CD010612.
20 Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database Syst Rev. 2016;10:CD010613.
21 Allegretti AS, Endres P, Parris T, Zhao S, May M, Sylvia-Reardon M, et al. Accelerated veno-venous hemofiltration as a transitional renal replacement therapy in the intensive care unit. Am J Nephrol. 2020;51(4):318–26.
22 Sethi SK, Mittal A, Nair N, Bagga A, Iyenger A, Ali U, et al. Pediatric Continuous Renal Replacement Therapy (PCRRT) expert committee recommendation on prescribing prolonged intermittent renal replacement therapy (PIRRT) in critically ill children. Hemodial Int. 2020 Apr;24(2):237–51.
23 China NHCo. The new coronavirus pneumonia prevention and control program. 5th ed. China; 2020.
24 Yang Y, Shi J, Ge S, Guo S, Xing X, Wang Y, et al. Association between prolonged intermittent renal replacement therapy and all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation: a retrospective cohort study. medRxiv. 2020 July. https://doi.org/10.1101/2020.03.16.20036780.
25 Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39(5):517–28.
26 Giamarellos-Bourboulis EJ. Failure of treatments based on the cytokine storm theory of sepsis: time for a novel approach. Immunotherapy. 2013;5(3):207–9.
27 Chen S, Liu G, Chen J, Hu A, Zhang L, Sun W, et al. Ponatinib protects mice from lethal influenza infection by suppressing cytokine storm. Front Immunol. 2019;10:1393.
28 Kennedy JR. Phosphatidylserine's role in Ebola's inflammatory cytokine storm and hemorrhagic consumptive coagulopathy and the therapeutic potential of annexin V. Med Hypotheses. 2020;135:109462.
29 Lau SK, Lau CC, Chan KH, Li CP, Chen H, Jin DY, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol. 2013;94(Pt 12):2679–90.
30 Li Y, Chen M, Cao H, Zhu Y, Zheng J, Zhou H. Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. Microbes Infect. 2013;15(2):88–95.
31 Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (novel coronavirus 2019): recent trends. Eur Rev Med Pharmacol Sci. 2020;24(4):2006–11.
32 Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020 Apr 16;181(2):271–80.e8.
33 Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–7.
34 Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). Physiol Rev. 2018;98(1):505–53.
35 Sun ML, Yang JM, Sun YP, Su GH. [Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(0):E014.
36 Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect. 2020 Mar;22(2):72–3.
37 Bar-Or D, Carrick MM, Mains CW, Rael LT, Slone D, Brody EN. Sepsis, oxidative stress, and hypoxia: are there clues to better treatment? Redox Rep. 2015;20(5):193–7.
38 Chakraborty RK, Burns B. Systemic inflammatory response syndrome. Treasure Island, FL: StatPearls; 2020.
39 Joannidis M, Forni LG. Clinical review: timing of renal replacement therapy. Crit Care. 2011;15(3):223.
40 Matsuda K, Moriguchi T, Oda S, Hirasawa H. Efficacy of continuous hemodiafiltration with a cytokine-adsorbing hemofilter in the treatment of acute respiratory distress syndrome. Contrib Nephrol. 2010;166:83–92.
41 Elbahlawan L, West NK, Avent Y, Cheng C, Liu W, Barfield RC, et al. Impact of continuous renal replacement therapy on oxygenation in children with acute lung injury after allogeneic hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2010;55(3):540–5.
42 Han F, Sun R, Ni Y, Hu X, Chen X, Jiang L, et al. Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. Am J Med Sci. 2015;349(3):199–205.
43 DiCarlo JV, Alexander SR, Agarwal R, Schiffman JD. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. J Pediatr Hematol Oncol. 2003;25(10):801–5.
44 Edrees F, Li T, Vijayan A. Prolonged intermittent renal replacement therapy. Adv Chronic Kidney Dis. 2016;23(3):195–202.
45 Fathima N, Kashif T, Janapala RN, Jayaraj JS, Qaseem A. Single-best choice between intermittent versus continuous renal replacement therapy: a review. Cureus. 2019;11(9):e5558.
46 Ha SO, Kim HS, Park S, Jung KS, Jang SH, Han SJ, et al. Severe ARDS caused by adenovirus: early initiation of ECMO plus continuous renal replacement therapy. Springerplus. 2016;5(1):1909.
47 Cha RH, Joh JS, Jeong I, Lee JY, Shin HS, Kim G, et al. Renal complications and their prognosis in Korean patients with middle east respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. J Korean Med Sci. 2015;30(12):1807–14.
48 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475–81.