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
| 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*  |
| 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*  |
| 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*  |
| SOFA score, median (IQR) | 6.0 (4.0–8.0) | 6.0 (3.8–8.0) | 6.0 (4.5–7.0) | 0.994*  |
| Hospitalization, median (IQR), days | 6.0 (4.0–9.0) | 5.5 (2.8–8.0) | 7.5 (4.0–10.0) | 0.171*  |
| Comorbidities, n (%) |              |             |                 |         |
| Hypertension | 14 (38.9) | 8 (36.4) | 6 (42.9) | 0.738*  |
| Diabetes   | 10 (27.8)    | 6 (27.3)    | 4 (28.6)        | 1.000*  |
| Cardiac disease | 12 (33.3) | 6 (27.3) | 6 (42.9) | 0.472*  |
| Cerebrovascular disease | 2 (5.6) | 0 (0) | 2 (14.3) | 0.144*  |
| Chronic lung disease | 7 (19.4) | 4 (18.2) | 3 (21.4) | 1.000*  |
| Malignant tumor | 2 (5.6) | 2 (9.1) | 0 (0) | 0.511*  |
| Chronic viral hepatitis | 3 (8.3) | 3 (13.6) | 0 (0) | 0.267*  |
| Any of comorbidity | 30 (83.3) | 18 (81.8) | 12 (85.7) | 0.759*  |
| Complications, n (%) |              |             |                 |         |
| MODS       | 13 (36.1)    | 10 (45.5)   | 3 (21.4)        | 0.175*  |
| Heart failure | 7 (19.4) | 5 (22.7) | 2 (14.3) | 0.681*  |
| Acute kidney injury | 8 (22.2) | 5 (22.7) | 3 (21.4) | 1.000*  |
| Arrhythmia | 12 (33.3)    | 8 (36.4)    | 4 (28.6)        | 0.727*  |
| ARDS       | 36 (100)     | 22 (100)    | 14 (100)        | 1.000*  |
| 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*  |
| Neutrophil count, mean (SD), 10^9/L | 12.7 (6.7) | 13.0 (8.0) | 12.2 (4.2) | 0.731*  |
| Lymphocyte count, mean (SD), 10^9/L | 0.6 (0.3) | 0.6 (0.3) | 0.6 (0.3) | 0.546*  |
| Hemoglobin, mean (SD), g/L | 122.4 (18.1) | 126.8 (18.6) | 115.5 (15.5) | 0.066*  |
| 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*  |
| Blood glucose, mean (SD), mmol/L | 9.8 (3.8) | 9.0 (2.8) | 11.0 (4.8) | 0.131*  |
| Total cholesterol, mean (SD), mmol/L | 3.3 (0.9) | 3.3 (1.0) | 3.2 (0.8) | 0.669*  |
| IL-1β, median (IQR), pg/mL | 6.3 (5.0–9.2) | 6.3 (5.0–10.9) | 6.4 (5.0–8.6) | 0.677*  |
| 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*  |
| 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*  |
| 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*  |
| 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*  |
| 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*  |
| hCRP, mean (SD), mg/L | 121.0 (76.1) | 124.7 (77.0) | 105.8 (80.9) | 0.667*  |
| 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*  |
| 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*  |
| 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*  |
| 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*  |
| hs-cTnI, median (IQR), pg/mL | 67.7 (16.0–284.9) | 79.3 (16.3–587.2) | 46.3 (14.6–162.0) | 0.373*  |
| 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*  |
| 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*  |
| 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*  |
| 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*  |
| 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*  |
| Serum bicarbonate, mean (SD), mmol/L | 24.7 (3.4) | 24.3 (2.9) | 25.4 (4.1) | 0.345*  |
| 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*  |
| 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*  |
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,
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-\( \alpha \) (HR = 1.040, 95% CI [1.007–1.073]) were associated with increased risk of mortality of all patients with invasive mechanical ventilation.

**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...
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-

### 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 10⁹/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) | 1.034 (1.005, 2.659) | 0.004* |
| D-dimer (per μg/mL [FEU]) | 1.000 (1.000, 1.000) | 0.003* |
| 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.
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.

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