Early Renal-Replacement Therapy May Reduce the All-Cause Mortality of Severe COVID-19: An Observational Cohort Study

Jing Qian[a]   Mengjing Wang[a]   Huaizhou You[a]   Jianfeng Luo[b, c]   Shengqing Li[d]
Shu Chen[e]   Yijian Chen[f]   Xiantao Li[g, h]   Kangjie Wang[a]   Weichen Zhang[a]
Li Yuan[i]   Li Ni[a]   Jing Chen[a]

[a]Department of Nephrology, Huashan Hospital, Fudan University, Shanghai, China; [b]Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China; [c]Key Laboratory of Public Health Safety of Ministry of Education, Fudan University, Shanghai, China; [d]Department of Pulmonary and Critical Care Medicine, Huashan Hospital, Fudan University, Shanghai, China; [e]Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China; [f]Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, China; [g]Department of Neurology, Huashan Hospital, Shanghai, China; [h]Department of Critical Care Medicine, Huashan Hospital, Shanghai, China; [i]Department of Nursing, Huashan Hospital, Fudan University, Shanghai, China

Abstract

Introduction: The efficacy of renal-replacement treatment (RRT) remains to be validated in COVID-19. In this retrospective cohort study, we aimed to assess the efficacy of early initiation of RRT in intensive care unit (ICU) adults with severe COVID-19. ***Methods:*** Fifty-eight adult patients in ICU with critically ill or severe COVID-19 with a tendency of critical illness were recruited from February 9, 2020, to March 30, 2020. Early RRT were determined by the ICU medical team based on boom in cytokines levels, increased organs injury/failure, and rapid aggravation of condition. All participants were followed up from the first day of ICU admission to March 30, 2020. The primary outcome was all-cause mortality in ICU. ***Results:*** The mean age of the cohort was 68.4 ± 14.6 years, with 81.0% having at least one comorbidity before hospitalization. Twenty patients (34.5%) initiated early RRT after 24.1 ± 10.4 days from the onset and 6.4 ± 3.6 days from ICU admission. Thirty-four of 58 participants (58.6%) died during ICU follow-up. Univariate and multivariate Cox proportional-hazards model showed that early RRT was associated with a lower risk of all-cause mortality in ICU with an adjusted HR of 0.280 (95% CI: 0.106–0.738, $p = 0.010$). Sudden unexpected death (SUD) was remarkably reduced in the early RRT group, compared with the control group (0.2 vs. 2.9 per 100 person-day, $p = 0.02$). ***Conclusion:*** Early RRT can reduce the all-cause in-hospital mortality, especially SUD in patients with severe COVID-19, but not improve multi-organ impairment or increase the risk of AKI. Early initiation of RRT merits an optional strategy in critically ill patients with COVID-19 (ChiCTR2000030773).

© 2022 S. Karger AG, Basel

Jing Qian, Mengjing Wang, and Huaizhou You contributed equally to this work.

Karger

Correspondence to:
Li Ni, quickly-ni@hotmail.com
Jing Chen, chenjing1998@fudan.edu.cn

Introduction

COVID-19 has been confirmed in more than ten million people worldwide [1], carrying an overall in-hospital mortality of approximately 15–20% [2]. In patients requiring intensive care unit (ICU) admission, the mortality was up to 40% [2]. Unfortunately, the roles of current therapeutics remained controversial in reducing the mortality of critically ill patients with COVID-19 [3–7]. Therapies against "cytokine storm" might be of great importance in managing COVID-19 [8–12]. Renal-replacement treatment (RRT), which could effectively eliminate excess cytokines, endotoxin, or other harmful substances, might be a promising therapy in critically ill patients with COVID-19. However, there was controversy about the efficacy of RRT in critically ill patients [13–18]. The roles of early RRT in severe and critically ill patients with CO-VID-19 remain to be investigated [19–23]. In this retrospective cohort study, we aimed to assess the efficacy of early initiation of RRT in severe and critically ill ICU patients with COVID-19.

Materials and Methods

Study Design and Participants

We retrospectively conducted a consecutive cohort of adult patients with severe/critically ill COVID-19 in Huashan-Tongji ICU of Guanggu Branch, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). The ICU was entirely taken over by the medical team from Huashan Hospital (Shanghai, China) from February 9 to March 30, 2020. The indication of ICU admission was critically ill or severe CO-VID-19 with a tendency of critical illness.

A total of 70 patients admitted to ICU during this period were screened. Eligible patients were as follows: (1) ≥18 years old, (2) admitted to ICU, (3) confirmed (including clinically confirmed) with severe COVID-19 with a tendency of critical illness or critically ill COVID-19. Exclusion criteria included (1) patients on maintenance hemodialysis or peritoneal dialysis, (2) absolute contraindication for RRT including systolic blood pressure <80 mm Hg and no available vascular access, (3) died within 24 h after ICU admission, (4) pregnancy, (5) participated in other intervention research or refused to be enrolled into our study. Finally, 58 patients with confirmed severe/critically ill COVID-19 were recruited to our study. Twelve patients were excluded for the following reasons: one patient had a medical history of ESRD and maintenance hemodialysis twice a week, one patient had received CRRT before admission in ICU due to severe AKI 3 stage, and 10 patients received urgent resuscitation and died within 24 h after ICU admission. The flowchart for patient enrollment was illustrated in online supplementary Figure 1aS (for all online suppl. material, see www.karger.com/doi/10.1159/000524229).

The initiation of RRT in early stage was determined by the ICU medical team referring to the following criteria: (1) the cy-

Table 1. Baseline demographic and clinical characteristics of the study cohort before ICU admission (n = 58)

Variables	Total (n = 58)
Age, years	68.4±14.6
Male, n (%)	37 (63.8)
Comorbidities,[a] n (%)	
Hypertension	30 (53.6)
Diabetes	13 (23.2)
Coronary heart disease	7 (12.5)
Arrhythmia	6 (10.7)
Cerebrovascular disease	5 (8.9)
COPD	5 (8.9)
Pulmonary tuberculosis	2 (3.6)
CKD	4 (7.1)
Viral hepatitis	4 (7.1)
Symptoms and signs at onset,[a] n (%)	
Cough and dyspnea	52 (92.9)
Fever	46 (82.1)
Fatigue	18 (32.1)
Diarrhea & nausea	12 (21.4)
Headache	9 (16.1)
Muscular soreness	7 (12.5)
Diagnosis, n (%)	
Typical lung imaging features	58 (100)
SARS-CoV-2 RNA positive[b]	29 (70.7)

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; SARS-CoV, severe acute respiratory syndrome coronavirus; RNA, ribonucleic acid. [a] Present history and comorbidities were absent in 2 unconscious participants. [b] Only 41 patients had completed SARS-CoV-2 RNA test as the test kit was unavailable at the beginning.

tokine level increased rapidly, (2) increased organs injury/failure, (3) rapid aggravation of condition. The remaining patients had not received RRT unless they reached AKI stage 3. Other treatments were performed according to the latest edition of Diagnosis and Treatment Protocols of Pneumonia caused by Novel Coronavirus (SARS-CoV-2) by the National Health Commission of China including glucocorticoid and anticoagulant therapy unless with contraindication. All participants were followed up from the first day of ICU admission to the day of censoring for death, transferring to the general ward, or the end of the study (March 30, 2020).

The study was registered in the Chinese Clinical Trial Registry (ChiCTR2000030773) and complied with the Declaration of Helsinki and was approved by the local medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China (Approval number: 2020-062). Informed consent was waived by the Ethics Committee.

Clinical Data Collection

All clinical data including baseline demographics, clinical characteristics, laboratory data, and treatment data were extracted from the electronic medical records and then imported and double-checked in the database by at least two investigators.

Qian/Wang/You/Luo/Li/Chen/Chen/Li/
Wang/Zhang/Yuan/Ni/Chen

Table 2. Baseline clinical characteristics and laboratory findings of patients with COVID-19 at the first 24 h of ICU admission (n = 58)

Variables	Total (n = 58)	Variables	Total (n = 58)
Duration from the onset to ICU admission, median (IQR), days	15 (10, 22)	Complete blood count	
Medication treatment before ICU, n (%)		WBC, 10^9/L	10.7±5.3
Antivirals	40 (70.2)	Neutrophils, %	85.9±9.7
Antibiotics	37 (64.9)	Lymphocytes, %	8.2±5.8
Antifungal	3 (5.4)	Lymphocyte, 10^9/L	0.69±0.34
Glucocorticoid	26 (46.4)	Hemoglobin, g/L	124.2±21.3
Hydroxychloroquine, n (%)	2 (3.6)	Platelet, 10^9/L	178.4±98.5
Immunoglobulin	13 (23.2)	Coagulation profile	
LMWH	9 (16.1)	PT, s	16.5±7.0
Classification of COVID-19 pneumonia, n (%)		APTT, s	41.2±9.2
Severe	31 (53.5)	Fibrinogen, g/L	4.54±1.75
Critical ill	27 (46.6)	D-dimer, µg/mL FEU	9.16±8.24
Vital signs at admission of ICU		FDP, µg/mL	23.9 (7.8, 114.3)
Temperature (axillary), °C	36.4±0.9	Serum biochemical tests	
SBP, mm Hg	136.7±21.6	NT-proBNP, pg/mL	1,131 (321, 2091)
Diastolic blood pressure, mm Hg	79.8±12.0	hs-TnI, pg/mL	26.3 (8.8, 107.0)
Heart rate, bpm	93.9±15.6	Myoglobin, ng/mL	131.4 (67.6, 290.2)
Respiration rate, bpm	24.6±11.0	ALT, U/L	29.5 (17.0, 48.0)
SpO$_2$, %	90.9±9.5	Serum albumin, g/L	31.6±4.5
Assisted respiratory therapy at admission of ICU, n (%)		Total bilirubin, µmol/L	12.9 (9.1, 19.1)
Mechanical ventilation	3 (5.3)	AKP, U/L	98.9±42.6
Noninvasive ventilator	15 (26.3)	Serum creatinine, µmol/L	81.6±40.9
Nasal catheter or face mask	39 (68.4)	Urea nitrogen, mmol/L	9.4±5.4
Inflammation markers		Uric acid, µmol/L	241.8±130.6
hs-CRP, mg/L	104.8±77.5	Serum potassium, mmol/L	4.16±0.73
Serum ferritin, µg/L	993.5 (650.8, 2030.5)	Serum corrected calcium, mmol/L	2.18±0.11
Serum IL-2R, U/mL	884.0 (571.0, 1,412.0)	Serum bicarbonate, mmol/L	24.5±4.8
Serum IL-6, pg/mL	37.2 (14.0, 138.7)		
TNF-α, pg/mL	12.2±5.4		

Data were obtained at the first 24 h of ICU admission, unless otherwise noted. BP, blood pressure; SpO$_2$, pulse oxygen saturation; WBC, white blood cell; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrinogen degradation products; NT-proBNP, pro-brain natriuretic peptide; hs-TnI, high-sensitivity troponin; ALT, alanine aminotransferase; AKP, alkaline phosphatase; SBP, systolic blood pressure; IL-2R, interleukin-2R; TNF-α, tumor necrosis factor-α; LMWH, low-molecular-weight heparin.

Study Definitions

The diagnosis criteria and clinical classification (severe and critically ill) of COVID-19 was according to the 5th edition (Hubei province) of Diagnosis and Treatment Protocols of Pneumonia caused by Novel Coronavirus (SARS-CoV-2) by the National Health Commission of China [24]. Both confirmed and clinically confirmed COVID-19 cases were recruited in our study.

Organ injury/failure involved the following criteria: (1) acute respiratory failure: acute respiratory distress syndrome and need for mechanical ventilation; (2) acute kidney injury: fold change in serum creatinine from a baseline ≥1.5 within 1 week or increased creatinine ≥26.5 µmol/L within 48 h [25]; (3) acute liver injury: total bilirubin >26 mmol/L (above upper limit of normal); (4) acute myocardial injury: high-sensitivity troponin >156 pg/mL (above 10 × upper limit of normal); (5) coagulation system injury: platelet <100 × 10^9/L (under lower limit of normal). Those with two or more organ injuries after ICU admission were defined multi-organ impairment.

Study Outcomes

The primary outcome was all-cause mortality in ICU. The secondary outcomes were occurrence of multi-organ impairment and AKI after ICU admission.

Statistical Analyses

Continuous variables of participants' characteristics were expressed as mean ± standard deviation or median with interquartile range (IQR), and categorical variables were expressed as percentages or ratios. The differences between groups were examined using t tests, Wilcoxon rank-sum test, χ^2 test, or Fisher's exact test appropriately. The one-way analysis of variance or the Kruskal-Wallis test, followed by Bonferroni correction, was used for intergroup comparisons. The incidence rate was expressed as the number of cases per 100 person-years. The risks of all-cause mortality for the RRT group versus the control group were examined by the Kaplan-Meier curve and log-rank test and time-dependent Cox models. Three levels of adjustment were performed: (1) model 1

that included early RRT; (2) model 2 that included early RRT, mechanical ventilation, use of anticoagulant, and use of glucocorticoid; (3) model 3: adjusted for model 2 and time-dependent covariates of serum albumin, pro-brain natriuretic peptide, serum interleukin-6 (IL-6), D-dimer. All statistical analyses were performed with Stata, version 14.0 (StataCorp LCC). A p value less than 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics of the Study Cohort

The mean age of the 58 participants was 68.4 ± 14.6 years, including 37 men and 21 women. A total of 69.0% participants were older than 65 years, and 81.0% had at least one comorbidity before hospitalization. Abnormal lung imaging features were detected in all participants. SARS-CoV-2 ribonucleic acid was positive in 70.7% (29/41) patients who had completed the SARS-CoV-2 ribonucleic acid test (Table 1). The median (IQR) duration from the onset to ICU admission was 15 (10, 22) days.

At ICU admission, 53.5% participants were classified as the severe type and 46.6% as the critically ill type. Although 100% supported by assisted respiratory therapy, the mean pulse oxygen saturation was only 90.9%. A status of hyperfibrinolysis, hypermetabolism, and high consumption was presented in laboratory findings. Medication treatment before ICU admission and baseline laboratory findings of all patients in the first 24 h (24 h) of ICU admission were shown in Table 2.

Clinical and Laboratory Characteristics of the Early RRT Group versus the Control Group during ICU Follow-Up

Twenty of 58 patients (34.5%) initiated RRT in early stage (early RRT group) for not only nonrenal indications such as "cytokine storm" but also multiple organ failure with or without acute kidney injury, and the remaining 38 patients (65.5%) did not receive RRT unless reaching AKI stage 3 (control group) for renal support. The participants in the early RRT group initiated early RRT 24.1 ± 10.4 days after the onset and 6.4 ± 3.6 days after ICU admission. The modes of RRT included continuous veno-venous hemofiltration and continuous veno-venous hemodiafiltration (with/without hemoperfusion). Polysulfone membranes were mostly used in RRT. AN69 (Oxiris) was used in only a few patients in the late phase of the study. The dose of RRT was 20–25 mL/kg·h according to the AKI guideline of KDIGO. The vascular access was temporary central venous double-channel catheter in all
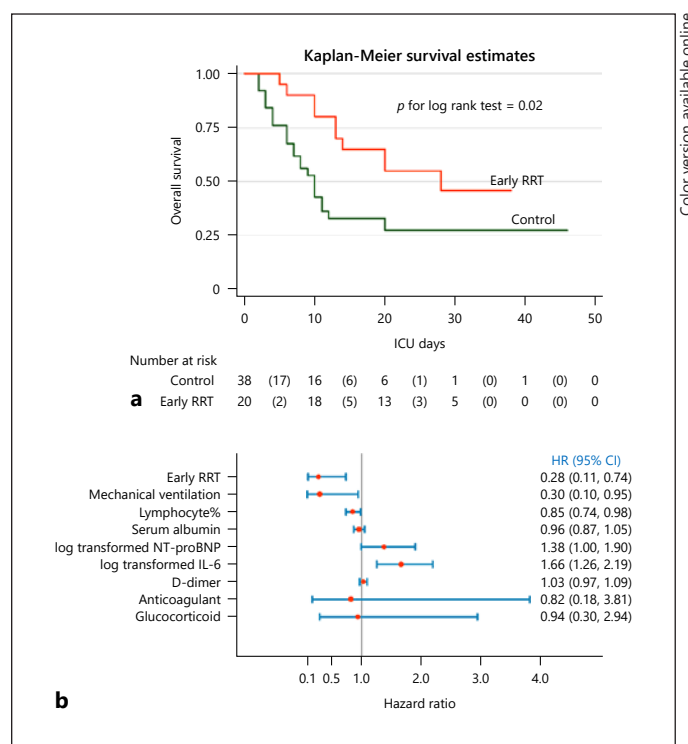
Fig. 1. Early RRT and risk for death. **a** Kaplan-Meier analysis (early RRT group vs. control group, log-rank p = 0.02). **b** Multivariate Cox analysis. RRT, renal-replacement treatment; IL-6, interleukin-6; NT-proBNP, pro-brain natriuretic peptide.

patients. The range of blood flow was 150–230 mL/min. The substitution flow rate was 2,000–4,000 mL/h, and the dialysate flow rate was 2,000 mL/h. The median (IQR) cumulative treatment time of RRT was 45.5 (16.8, 66.3) hours, and the ultrafiltration rate was 65.5 ± 65.2 mL/h. In the control group, only one (2.6%) participant received RRT when diagnosed as AKI stage 3 with oliguria.

During the whole ICU follow-up, the maximum of temperature, high-sensitivity C-reactive protein, and serum urea nitrogen were higher in early RRT group than that in the control group. No difference was found in maximum levels of serum inflammatory markers including interleukin-2R, IL-6, and tumor necrosis factor-α (online suppl. Table 1S).

Treatments and Prognosis of the Early RRT Group versus the Control Group during ICU Follow-Up
Early RRT Reduced the Incidence Rate of All-Cause Mortality in the ICU
Finally, 34 of 58 participants (58.6%) died during ICU follow-up (online suppl. Fig. 1bS). The all-cause mortality in the early RRT group was lower than that in the con-

Qian/Wang/You/Luo/Li/Chen/Chen/Li/
Wang/Zhang/Yuan/Ni/Chen

Table 3. Treatments and outcomes of ICU patients with and without early RRT during ICU (total *n* = 58)

Variables	Control group (*n* = 38)	Early RRT group (*n* = 20)	*p* value
Duration in ICU, days	10.9±9.4	21.8±10.1	<0.001
Life-support intervention, *n* (%)			
Mechanical ventilation	23 (60.5)	19 (95.0)	0.005
ECMO	0	5 (25.0)	0.003
Medication intervention, *n* (%)			
Antivirals	3 (8.1)	4 (20)	0.23
Antibacterial	30 (79.0)	20 (100)	0.04
Antifungal	7 (18.9)	5 (25)	0.74
Glucocorticoid	25 (67.6)	17 (85.0)	0.21
Hydroxychloroquine	5 (13.5)	7 (35.0)	0.09
Immunoglobulin	28 (75.9)	19 (95.0)	0.08
Anticoagulant	31 (83.8)	20 (100)	0.08
Outcomes			
Multi-organ impairment, *n* (%)	24 (63.2)	18 (90.0)	0.04
Multi-organ impairment, 100 person-day	5.8	4.1	0.28
AKI, *n* (%)	14 (36.8)	12 (60.0)	0.09
AKI, 100 person-day	3.4	2.6	0.60
Death, *n* (%)	24 (64.2)	10 (50.0)	0.33
Expected death, *n* (%)	12 (50.0)	9 (90.0)	0.05
Unexpected death,[a] *n* (%)	12 (50.0)	1 (10.0)	
Death, 100 person-day	5.8	2.3	0.01
Expected death, 100 person-day	2.9	2.1	0.44
Unexpected death,[a] 100 person-day	2.9	0.2	0.02

RRT, renal-replacement treatment; ECMO, extracorporeal membrane oxygenation; PT, prothrombin time; AKI, acute kidney injury. [a] Unexpected death was defined as a rapid death without new occurrence of multi-organ impairment.

trol group (50% in the early RRT group vs. 64.2% in the control group, $p = 0.33$). The survival time in the early RRT group (23 days, green lines) was longer than that in the control group (8 days, red lines) (online suppl. Fig. 1bS). The incidence rate of overall death in the early RRT group was 2.3 per 100 person-day, which was significantly lower than that in the control group (5.8 per 100 person-day, $p = 0.01$) (Table 3). Kaplan-Meier survival analysis showed that the all-cause mortality in ICU of the early RRT group was lower than that of the control group (log-rank $p = 0.02$) (Fig. 1a).

In the univariate Cox models performed for mortality, statistical significance was noted for early RRT with an unadjusted HR of 0.42 (95% CI: 0.20–0.89, $p = 0.024$) (online suppl. Table 2S). In the multivariate Cox regression model, after adjusted for mechanical ventilation, low-molecular-weight heparin, glucocorticoid, serum albumin, pro-brain natriuretic peptide, serum IL-6, and D-dimer, early RRT was still associated with a lower risk of all-cause mortality in the ICU with an adjusted HR of 0.280 (95% CI: 0.106–0.738, $p = 0.010$) (online suppl. Table 3S; Fig. 1b).

Early RRT Did Not Influence Occurrence of Multi-Organ Impairment

The crude incidence of multi-organ impairment during ICU in the early RRT group was higher than that in the control group (90% in early RRT group vs. 63.2% in control group, $p = 0.04$). However, by adjustment of follow-up time, the incidence rate of multi-organ impairment was 4.1 per 100 person-day in the early RRT group, similar to that in the control group (5.8 per 100 person-day, $p = 0.28$) (Table 3; online suppl. Fig. 1bS). In addition, there was no difference both in the morbidity and incidence rate of AKI between two subgroups. So, early RRT did not increase the risk of AKI (Table 3).

Early RRT Prevented Sudden Unexpected Death in Severe COVID-19

We further analyzed the characteristics of death in the 34 nonsurvivors. Interestingly, 13 (38.2%) nonsurvivors including 1 (10%) in the early RRT group and 12 (50%) in the control group featured a "sudden unexpected death." Sudden unexpected death (SUD) in COVID-19 is
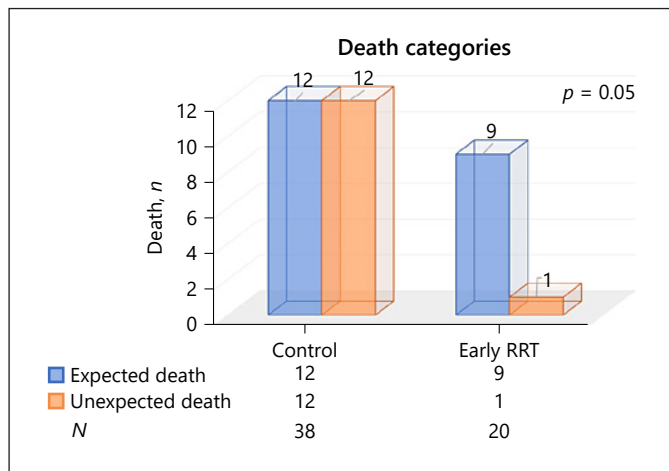
Fig. 2. Unexpected death during ICU admission in patients with/without early RRT. ICU, intensive care unit; RRT, renal-replacement treatment.

defined in our study as a rapid death within 24 h in a patient with COVID-19, presenting cardiac arrest, plunged blood pressure, or pulse oxygen saturation but without life-threatening organ injuries or fatal abnormalities in major laboratory features, which is not due to respiratory failure, septic shock, severe myocarditis, malignant arrhythmia, electrolyte disturbance, or other known causes. The incidence rate of SUD in the early RRT group was 0.2 per 100 person-day, much lower than 2.9 per 100 person-day in the control group ($p = 0.02$) (Fig. 2). It was inferred that the difference in the incidence of all-cause death between the two groups was caused by SUD.

We classified all the participants into three subgroups (survival, expected death, and unexpected death) to explore the risk factors of unexpected death. The severity and numbers of organ injury/failure were lower in nonsurvivors with unexpected death, compared with expected death. Less use of early RRT, older age, lower temperature and respiratory rate, shorter activated partial thromboplastin time, and lower tumor necrosis factor-α were associated with unexpected death in nonsurvivors with unexpected death in univariate analysis (online suppl. Fig. 2S).

Discussion

The retrospective cohort study indicated that early initiation of RRT could reduce the incidence rate of in-hospital all-cause death by preventing unexpected death, in ICU patients with severe/critically ill COVID-19. To our knowledge, these findings provide new evidence for the early application of RRT in treatment of severe and critically ill COVID-19.

High morbidity and mortality of severe to critically ill cases were observed in elderly population with COVID-19, especially those with multi-morbidities. The mean age of our ICU patients was higher than that of the whole population with COVID-19 in the same hospital [26]. So, close monitoring and active intervention should be performed for those elderly patients at high risk. In participants with early RRT, the mortality reduced to 50%, which was lower than that in other retrospective studies involving critically ill COVID-19 during the same period in Wuhan [26–28]. In general, RRT in the ICU was prescribed referring to the diagnosis of AKI stage 3 or even urgent complications [25]. Differently, the triggering time of RRT in our ICU had been moved up ahead of traditional indications. Early initiation of RRT reduced the risk of in-hospital overall mortality in ICU patients with COVID-19 by 72% in our study.

Several randomized controlled trials have focused on the "early" versus "late" initiation of RRT in critical care patients. In AKIKI [15] and IDEAL-ICU [18] studies, which mainly included sepsis patients, RRT in early strategy was started within 6–8 h when diagnosed as AKI stage 3 but without life-threatening complications related to AKI. No significant difference with regard to mortality was found in those two studies. The latest STARRT-AKI study among critically ill patients with AKI also indicated that an accelerated renal-replacement strategy in AKI stage 2 or 3 was not associated with a lower risk of death at 90 days compared to a standard strategy [16]. In contrast, in the ELAIN study which mainly enrolled postoperative patients with AKI [17], early RRT was initiated within 8 h of diagnosis of AKI stage 2, earlier than the above studies, and results showed that early RRT reduced mortality over the first 90 days.

In addition to renal function support, the main purpose of RRT application in sepsis or other cytokine storm-related diseases was to eliminate endotoxin, cytokines, or other harmful substances in the early stage, which had been considered to play an important role in severe acute respiratory syndrome, Middle-East respiratory syndrome, and other sepsis treatment [23, 29, 30]. So, the triggering time of RRT in our ICU was moved up before AKI development and multi-organ impairment, and our results demonstrated that it may be of great significance to start RRT earlier than the traditional indications in critically ill patients with COVID-19. Besides clinical signs in our study, it was worth to screen out the specific indicators of early RRT initiation in further studies [31,

Qian/Wang/You/Luo/Li/Chen/Chen/Li/
Wang/Zhang/Yuan/Ni/Chen

32]. Serum IL-6, one of the major pro-inflammatory cytokines of cytokine storm syndrome [33], might be the most potential candidate of triggers for the initiation of RRT, considering its strong association with mortality, which was also proven in our study.

Contrary to expectation, early RRT had not reduced the mean and the maximum levels of cytokines, as well as the incidence rate of multi-organ injuries, compared with the control group, nor did it increase the risk of AKI [28, 34, 35]. Interestingly, we found a remarkable reduction of SUD in COVID-19 in participants with early RRT.

SUD in COVID-19 has never been reported before but was found in nearly 20% severe to critically ill patients with COVID-19, which accounted for up to 30% of non-survivors in our study. No clinical signs or biomarkers can yet predict the SUD, so more public attention on SUD should be raised during clinical treatment of COVID-19.

The known causes of death in COVID-19 such as severe myocarditis, could not completely explain the rapid progression of the disease but the mild abnormalities in laboratory features in those seemingly "stable" patients with SUD in ICU. Thrombotic and microvascular complications most likely attributed to the SUD in COVID-19 [36]. Autopsy and clinical reports on high morbidity of thrombotic complications in patients with COVID-19 were increasingly prominent [37–45]. Even in patients receiving therapeutic anticoagulation, anticoagulation failure occurred as well. A recent cohort study revealed that endotheliopathy was present in COVID-19 and was likely to be associated with critical illness and death [46]. Experimental studies confirmed that SARS-CoV-2 directly invaded endothelial cells via angiotensin-converting enzyme 2, which was expressed on the endothelial cell surface, then the subsequent endothelial inflammation, complement activation, thrombin generation, platelet and leukocyte recruitment, and the initiation of innate and adaptive immune responses including cytokine storm syndrome culminate in immunothrombosis, ultimately causing thrombotic or microthrombotic complications such as deep vein thrombosis, pulmonary embolism, and stroke [47, 48]. COVID-19-associated coagulopathy, characterized by increased thrombotic and microvascular complications, was an important feature of SARS-CoV-2 pathogenesis. Given that thrombotic complications are central determinants of the high mortality rate in COVID-19, strategies to prevent thrombosis are of critical importance. Participants with SUD in our study had higher D-dimer and fibrinogen degradation product levels and shorter activated partial thromboplastin time, indicating a status of hyperfibrinolysis and high probability of thrombotic complications.

It is valuable that early RRT can prevent SUD in COVID-19 and then reduce the all-cause mortality, which may be of clinical utility in managing severe to critically ill patients with COVID-19. However, the underlying mechanisms are multiple and not entirely clear for now.

We proposed that early RRT might prevent thrombotic events not through therapeutic anticoagulation but by removing certain substances such as procoagulant substance or regulators of coagulation system in upstream and downstream, thus reducing SUD in critically ill COVID-19. The usage and dose of anticoagulant in participants with early RRT were similar with those without early RRT. Second, elevated serum levels of pro-inflammatory cytokines including IL-6 and IL-1β, as well as IL-2 and TNF, were exhibited substantially in severe and critically ill patients with COVID-19, characterized as a cytokine storm and could interact between inflammation and coagulation [48–50]. Early RRT could probably prevent the secondary endothelial inflammation by means of cutting the sudden fatal peak load of the cytokine storm. Moreover, early RRT as one of major life-support therapies could prolong survival time and gain time for key treatments of the primary disease.

Some study limitations should be considered in the interpretation of the results. First, this was a retrospective observational and small sample-size cohort study, so it was difficult to attribute direct causality between early RRT and the mortality of COVID-19. Second, the initiation of early RRT was decided by a medical treatment team, rather than randomization. Third, scoring systems in evaluating severity and prognosis such as sequential organ failure assessment (SOFA) were unavailable in most original medical records. Moreover, modes of RRT used in our target population included only continuous veno-venous hemofiltration/continuous veno-venous hemodiafiltration due to availability. Therefore, large sample-size randomized clinical trials on different modes of early RRT in COVID-19 will be needed in further studies.

Conclusions

In summary, early initiation of RRT can potentially prolong survival time and create necessary therapy opportunity, then reduce the all-cause in-hospital mortality, especially SUD in ICU patients with severe COVID-19, but not improve multi-organ impairment or increase the risk of AKI. Early initiation of renal-replacement therapy merits an optional strategy in severe to critically ill patients with COVID-19.

References

1 Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

2 Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782–93.

3 Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395(10236):1569–78.

4 Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020; 395(10238):1695–704.

5 Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med. 2020;382(19):1787–99.

6 Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational Study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;382(25): 2411–8.

7 Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ. 2020;369:m1849.

8 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH across speciality collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.

9 Zhang X, Tan Y, Ling Y, Lu G, Liu F, Yi Z, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature. 2020; 583(7816):437–40.

10 Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol. 2020;20(5):269–70.

11 Oberfeld B, Achanta A, Carpenter K, Chen P, Gilette NM, Langat P, et al. SnapShot: COVID-19. Cell. 2020;181(4):954–.e1.

12 Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529.

13 Pasin L, Boraso S, Tiberio I. Initiation of renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(19):1899–900.

14 Wierstra BT, Kadri S, Alomar S, Burbano X, Barrisford GW, Kao RL. The impact of "early" versus "late" initiation of renal replacement therapy in critical care patients with acute kidney injury: a systematic review and evidence synthesis. Crit Care. 2016;20(1):122.

15 Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016; 375(2):122–33.

16 STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group, et al. Timing of initiation of renal-Replacement rherapy in acute kidney injury. N Engl J Med. 2020;383(3):240–51.

17 Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of early versus delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016; 315(20):2190–9.

18 Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. IDEAL-ICU trial investigators and the CRICS TRIGGERSEP network. Timing of renal replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med. 2018;379(15):1431–42.

19 Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a Multicenter Retrospective Study from Wuhan, China. Crit Care. 2020;24(1): 394.

20 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

21 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.

22 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.

23 Huang D, Lian X, Song F, Ma H, Lian Z, Liang Y, et al. Clinical features of severe patients infected with 2019 novel coronavirus: a systematic review and meta-analysis. Ann Transl Med. 2020;8(9):576.

24 National Health Commission of the People's Republic of China. Diagnosis and treatment protocols of pneumonia caused by a novel coronavirus (revised trial version 5). 2020. Available from: http: //www.nhc.gov.cn/xcs/zhengcwj/202002/ d4b895337e19445f8d728fcaf1e3e13a/files/ab-6bec7f93e64e7f998d802991203cd6.pdf (accessed February 8, 2020).

25 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.

26 Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol. 2020;31(6):1157–65.

27 Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: a Cross-Sectional Study. Crit Care. 2020;24(1):219.

28 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;8(5):475–81.

29 Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005;67(2):698–705.

30 Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med. 2014;160(6):389–97.

31 Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8(7):738–42.

32 Ronco C, Bagshaw SM, Bellomo R, Clark WR, Husain-Syed F, Kellum JA, et al. Extracorporeal blood purification and organ support in the critically ill patient during COVID-19 pandemic: expert review and recommendation. Blood Purif. 2020;26:1–11.

33 Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39(5):517–28.

34 Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med. 2020;46(7):1339–48.

35 Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. cute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209–18.

36 Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(23):2950–73.

37 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18:1094–9.

38 Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020;173(5):350–61.

39 Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a Prospective Cohort Study. Ann Intern Med. 2020;15173(12):268.

40 Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? Lancet. 2020;395(10239):1758–9.

41 Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. Crit Care Med. 2020;48(9):1358–64.

42 Piagnerelli M, Cauchie P, Wautrecht JC. Optimizing the risk-benefit balance of thromboprophylaxis in critically ill patients with coronavirus disease 2019. Crit Care Med. 2020; 48(10):e988–9.

43 Trigonis RA, Holt DB, Yuan R, Siddiqui AA, Craft MK, Khan BA, et al. Incidence of venous thromboembolism in critically ill coronavirus disease 2019 patients receiving prophylactic anticoagulation. Crit Care Med. 2020;48(9): e805–e808.

44 Mirsadraee S, Gorog DA, Mahon CF, Rawal B, Semple TR, Nicol ED, et al. Prevalence of thrombotic complications in ICU-treated patients with coronavirus disease 2019 detected with systematic CT scanning. Crit Care Med. 2021;49(5):804–15.

45 Mohamed MFH. Caution is needed when reporting or pooling the prevalence of venous thromboembolism in critically ill coronavirus disease 2019 patients. Crit Care Med. 2021; 49(1):e114–5.

46 Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a Single-Centre, Cross-Sectional Study. Lancet Haematol. 2020;7(8):e575–82.

47 McFadyen JD, Stevens H, Peter K. The emerging threat of (micro) thrombosis in COVID-19 and its therapeutic implications. Circ Res. 2020;127(4):571–87.

48 Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020; 8(6):e46–7.

49 Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. Immunity. 2020;53(1):19–25.

50 Rizzo P, Vieceli Dalla Sega F, Fortini F, Marracino L, Rapezzi C, Ferrari R. COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Basic Res Cardiol. 2020; 115(3):31.