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Original Article

Timely renal replacement therapy linked to better outcome in patients with sepsis-associated acute kidney injury

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ABSTRACT

Background: Recent studies suggest that acute kidney injury (AKI) can be treated with renal replacement therapy (RRT). However, its benefits to patients with sepsis-associated AKI (SA-AKI), which is linked to high mortality and morbidity rates, remain under debate. The aim of this study was to compare the outcomes of different RRT strategies for patients with SA-AKI.

Methods: This retrospective study evaluated patients who were admitted to the hospital with sepsis and developed SA-AKI during hospitalization from 1st January 2014 to 31st January 2019. Mortality, renal recovery, and systemic organ function at 90 days following admission were compared between the RRT group (RG) and non-RRT group (NRG), as well as the early-RRT group (EG) and delayed-RRT group (DG). The groups were defined according to the time from admission to RRT initiation (criterion 1, EG1 and DG1) and Kidney Disease Improving Global Outcomes (KDIGO) classification (criterion 2, EG2 and DG2). Categorical and continuous variables were compared using the chi-squared test or Fisher's exact test and Student's *t*-test or Wilcoxon test. Kaplan–Meier curves were constructed to determine the unadjusted survival rates for the different subgroups.

Results: A total of 116 patients were included in this study; of those, 38 received RRT and 46 expired within 90 days. Among different strategies of RRT, there were no significant differences found in 90-day mortality (RG *vs.* NRG: χ^2=0.610, *P*=0.435; EG1 *vs.* DG1: χ^2 =0.835, *P*=0.360; EG2 *vs.* DG2: χ^2=0.022, *P*=0.899) and renal recovery. However, the values of change in sequential organ failure assessment $(\Delta SOFA)_{max-min}$ of patients in the EG and RG were significantly higher than those recorded in the NRG ($\Delta SOFA_{RG}$=7.0, $\Delta SOFA_{NRG}$=3.60, $\Delta SOFA_{EG1}$=9.00, $\Delta SOFA_{EG2}$=6.30; *P*<0.050). Also, the 90-day renal recovery in the EG was better than that noted in the DG with criterion 1 (87.5% *vs.* 38.5%, respectively, χ^2=10.425, *P*=0.032), suggesting that RRT (especially timely RRT) may be beneficial to the restoration of systemic organ function in patients with SA-AKI.

Conclusion: RRT did not reduce the 90-day mortality among patients with SA-AKI. However, timely RRT may benefit the restoration of systemic organ function, thereby improving the quality of life of patients.

Introduction

Acute kidney injury (AKI) is one of the most serious complications of sepsis.[1–4] Research studies have shown that AKI occurs in 50% of patients with sepsis, with a mortality rate of approximately 60% at 3 months.[2,5–8] Therefore, the discovery of effective therapeutic strategies for patients with sepsis-associated AKI (SA-AKI) is urgently warranted.

Renal replacement therapy (RRT) has been used for the treatment for AKI, and several studies have suggested that it may benefit some additional patient groups.[9] However, a recent study reported that RRT exerts a limited effect on the recov-

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ery of patients with AKI.[10] Moreover, some studies proposed that early RRT may be an independent risk factor in patients with AKI.[11] In addition, the optimal timing for the use of RRT in critically ill patients who are not at risk of a potentially life-threatening complication directly related to renal failure remains unknown.

Currently, the strategies for the initiation and discontinuation of RRT for AKI vary considerably worldwide.[9] Several multicenter randomized trials[10] and some observational studies on the use of RRT in these patients[12–14] have yielded conflicting results. Furthermore, few of those studies focused on patients with SA-AKI. Therefore, the aim of this single-center retrospective study was to investigate the specific outcomes of different strategies of RRT in patients with SA-AKI.

Methods

Study design, setting, and population enrolled

This single-center retrospective study screened 546 patients and enrolled 116 patients who were admitted to the emergency center with a diagnosis of sepsis from 1st January 2014 to 31st January 2019 and subsequently developed SA-AKI during hospitalization [Figure 1]. In all cases, RRT was provided as an optional treatment.

In the present study, following the diagnosis of sepsis, we evaluated the microcirculation through laboratory testing (e.g., lactic acid levels). In patients with sufficient capacity and absence of shock, standard treatment was administered. For patients with sepsis-induced hypoperfusion or septic shock, ≥30 mL/kg of intravenous crystalloid fluid was administered within the first 3 h of resuscitation, according to guidelines.[15]

The inclusion criteria were: (1) age >18 years and (2) admission to hospital with a diagnosis of sepsis and development of Kidney Disease Improving Global Outcomes (KDIGO)[16] stage 2 or 3 AKI during hospitalization.

The exclusion criteria were: (1) diagnosis of AKI not associated with sepsis; (2) receipt of treatment for AKI before admission; (3) presence of pre-existing diseases requiring maintenance treatment, including RRT, or any prior RRT; (4) KDIGO stage other than 2 or 3 at diagnosis; (5) severe disease requiring RRT as the only possible method to preserve life; (6) expected death within 24 h; and (7) concurrent presence of tumors, pregnancy, or other existing kidney diseases not related to sepsis.

We divided the patients into two groups, namely the RRT group (RG) and non-RRT group (NRG). Patients in the RG were further divided into the early-RRT group (EG) and delayed-RRT group (DG) based on two criteria described below.

Definitions

Definition of sepsis

Sepsis was defined according to the Sepsis 3.0 criteria.[17] These criteria provide a new definition of sepsis, which depends on either an increase of two or more points on the Sequential Organ Failure Assessment (SOFA) score or meeting two or more of the quick SOFA criteria.

Definition of AKI

AKI was defined and classified according to the KDIGO criteria, based on specific increases in serum creatinine (SCr) levels and reduction in urine output.

Stage 1: Increase in SCr by 1.5–1.9 times baseline; or increase in SCr by ≥0.3 mg/dL (≥26.5 μmol/L); or urine output <0.5

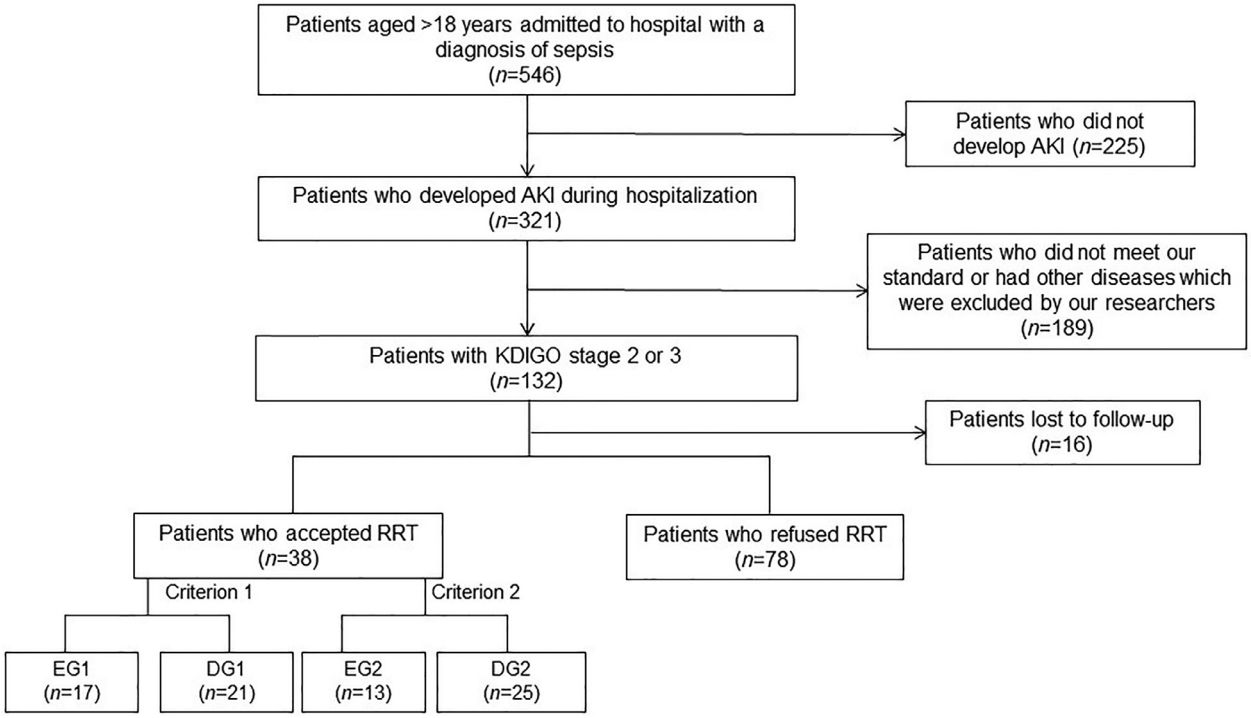

Figure 1. Study flow chart. Criterion 1: The groups were defined according to the time from admission to RRT initiation(EG1<24 h, DG1>24 h); Criterion 2: The groups were defined according to KDIGO stage of patients at admission (EG2: stage 3, DG2: stage 2).
AKI: Acute kidney injury; DG: Delayed-RRT group; EG: Early-RRT group; KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal replacement therapy.

mL/kg/h for 6–12 h; Stage 2: Increase in SCr by 2.0–2.9 times baseline; or urine output <0.5 mL/kg/h for ≥12 h; Stage 3: Increase in SCr by 3.0 times baseline; or increase in SCr to 4.0 mg/dL (353.6 μmol/L); or initiation of RRT; or in patients <18 years, decrease in estimated glomerular filtration rate (eGFR) to 35 mL/min/1.73 m^2; or urine output <0.3 mL/kg/h for ≥24 h; or anuria for ≥12 h.[18]

Decision to use RRT and definition of early or delayed RRT

The decision to initiate RRT and all RRT prescription details, including when to initiate therapy, were at the discretion of the attending doctors (RG: *n*=38; NRG: *n*=78). We collected the indications for the initiation of RRT. The provided RRT modality and dose[19] were in agreement with current guidelines.[20] Two different criteria were used to define the EG and DG, and to explore the differences between RRT strategies. Criterion 1 defined the EG and DG as patients who received RRT within and after 24 h, respectively, of the diagnosis of SA-AKI (EG1: *n*=17; DG1: *n*=21). Criterion 2 classified patients admitted with KDIGO stage 2 as the EG2 (*n*=13); patients admitted with KDIGO stage 3 as the DG2 (*n*=25), suggesting that those patients developed more severe impairment prior to RRT [Figure 1].

Definition of renal recovery

Renal recovery conditions were determined according to the examination performed at a 90-day return visit. We divided renal recovery conditions into full recovery, partial recovery, and non-recovery, using criteria of classification referred to in the International Consensus Criteria[21] and prior literature.[22]

Full renal recovery was defined as: (1) SCr levels at discharge <144 μmol/L; (2) return of spontaneous urine output ≥1000 mL/24 h (or ≥2000 mL/24 h with diuretics) for a minimum of 24 h without RRT during the hospital stay; or (3) return of SCr levels to <150% of the baseline. Partial recovery was defined as SCr >144 μmol/L and <350 μmol/L at discharge. Non-recovery was defined as the inability to maintain renal function without RRT during the hospital stay or SCr ≥350 μmol/L without RRT.

All patients who expired within 90 days (*n*=46) were excluded from the statistical analysis because the recovery of renal function could not be estimated.

Data collection and database construction

Data were collected by trained research nurses and clinical doctors using a standardized and validated data form. The collected data included admission status, the course of disease during hospitalization, and 90-day outcome. Admission data for each patient included sex, age, urea and SCr levels, SOFA scores at admission, and blood tests in the first 24 h. In addition, the history of underlying diseases (e.g., atrial fibrillation, deep vein thrombosis, chronic heart failure, chronic obstructive pulmonary disease, and chronic kidney disease) was recorded.

Data collected during the hospitalization included the occurrence of shock, details for the administration of RRT, and the respiratory condition, including partial pressure of arterial oxygen (PaO_2) and PaO_2/fractional inspired oxygen (PaO_2/FiO_2). Outcome data, involving the primary endpoints of death and renal recovery at 90 days, consisted of the SCr and urea levels at discharge or at the last assessment before death and the maximum recorded values. In-hospital death, as well as time to death and SOFA scores at discharge were also collected. For RRT-treated patients who expired, the SOFA score was evaluated based on the last data obtained in the intensive care unit (ICU). As in the ICU, laboratory examinations for critically ill patients were conducted at least once daily.

Data from the medical records were checked by at least two investigators to ensure quality.

Study endpoints

First, we used 90-day renal recovery and 90-day death as two of the primary endpoints. The occurrences of mechanical ventilation and shock were secondary endpoints. We also analyzed the changes in SCr and urea nitrogen levels, as well as alterations in the SOFA scores between admission and discharge.

Second, we used the SOFA score at discharge, as well as the ΔSOFA (maximum–minimum) and ΔSOFA (admission–discharge), as the primary endpoint to determine the organ recovery in living patients.

Statistical analysis

Baseline characteristics in each study group were described as frequencies and percentages for categorical variables, and as means ±standard deviations for continuous variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, while continuous variables were compared using Student's *t*-test or the Wilcoxon test. Kaplan–Meier curves were constructed to determine the unadjusted survival rates for the different subgroups.

Further stratification and adjustments for baseline prognostic factors ($P<0.1$ in a univariable Gray's model was used as a cutoff value for inclusion) were performed with a Cox semiparametric proportional-hazards model, using the 90-day death rate as the endpoint.

In this retrospective study, we used G*power (version 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) to calculate the power as a *post hoc* analysis to ensure the reliability of the results.

The RG *vs.* NRG, EG1 *vs.* DG1, and EG2 *vs.* DG2 *post hoc* power analyses showed the following: alpha = 0.485, 0.36, and 0.683; degree of freedom = 1; sample size = 116, 38, and 38; and power = 0.994, 0.828, and 0.895, respectively.

$P < 0.05$ denoted statistically significant differences. All analyses were conducted using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics

Data from admission to hospital death or discharge from the ICU, and 90-day follow-up was collected for 116 patients with SA-AKI (mean age: 72.51 years; 65 males [56.0%] and 51 females [44.0%]). Blood routine examination at admission showed that the average white blood cell count was 15.4×10^9/L, which was higher than the normal high threshold of 12.0×10^9/L. The average percentage of lymphocytes and neutrophils was 6.5% and 87.6%, and the neutrophil-to-lymphocyte ratio was 23.9. Among all patients, 51 (44.0%) were

Table 1
Basic characteristics of enrolled patients (*n*=116).

Characteristics	Data
Age (years)	72.51 ± 12.12
Sex	
male	65 (56.0)
female	51 (44.0)
Blood routine tests	
WBC ($\times 10^9$/L)	15.4 ± 7.8
Lymphocytes (%)	6.5 ± 5.1
Neutrophils (%)	87.6 ± 8.1
NLR	23.9 ± 20.4
PLT ($\times 10^9$/L)	131.0 ± 77.4
KDIGO Stage 3	65 (56.0)
Urea at admission (mmol/L)	
At admission	21.7 ± 12.1
Max	25.2 ± 13.0
At discharge*	16.2 ± 13.9
SCr (mmol/L)	
At admission	318.0 ± 211.8
Max	384.6 ± 222.2
At discharge*	213.1 ± 195.8
SOFA	
At admission	7.12 ± 3.71
Max	7.54 ± 3.70
At discharge*	2.33 ± 1.81
Shock	43 (37.1)
Mechanical ventilation	31 (26.7)
Vasopressor use	44 (37.9)
Receiving RRT	38 (32.7)
90-day death	46 (39.7)
Renal recovery at 90 days from ICU admission (*n*=70)	
Full recovery	45 (38.8)
Partial recovery	18 (15.5)
Non-recovery	7 (26.0)

Data are presented as *n* (%) or mean ± standard deviation.
ICU: Intensive care unit; KDIGO: Kidney Disease Improving Global Outcomes; NLR: Neutrophil-to-lymphocyte ratio; PLT: Platelet count; RRT: Renal replacement therapy; SCr: Serum creatinine; SOFA: Sequential Organ Failure Assessment.
* Scr, urea at discharge, and SOFA at discharge were obtained from patients who were discharged alive (*n*=76).

diagnosed with KDIGO stage 2 SA-AKI. During hospitalization, 38 patients received RRT, accounting for 32.7% of the total study population. Some patients developed shock (*n*=43, 37.1%) or required mechanical ventilation (including non-invasive ventilation and endotracheal intubation; *n*=31, 26.7%) during hospitalization, while 44 patients (37.9%) needed vasopressor to maintain adequate blood pressure. Among 116 patients, 40 expired in hospital and 46 expired within 90 days from admission. Moreover, we recorded the renal recovery in living patients at 90 days: 45 (38.8%) and 18 (15.5%) experienced full and partial recoveries, respectively, whereas 7 (26.0%) did not recover. The results are shown in Table 1. We also listed the sources of infection, underlying diseases of patients at admission, and causes of death [Figure 2].

RRT did not improve patient prognosis

Of the 116 patients, 38 received RRT (RG) and 78 patients did not (NRG). The baseline data, including age, sex, and the blood routine tests within 24 h, did not reveal significant differences between the two groups, except for the percentage of neutrophils (90.41% *vs.* 86.28%, respectively; *P*= 0.006).

During hospitalization, 20 (52.6%) and 23 (29.5%) patients developed shock in the RG and NRG, respectively (*P*=0.015). Table 2 shows that 17 (44.7%) and 14 (17.9%) patients in the RG and NRG, respectively, required mechanical ventilation (*P*=0.002).

The 90-day death rate (37.0% vs. 63.0%, *P*=0.435; Table 2) did not reveal significant difference between RG and NRG. We further compared 90-day renal recovery [Figure 3] and survival curves between them [Figure 4]. There was no significant difference of 90-day renal recovery rate (*P*=0.643; Figure 3A) between the two groups. Additionally, data on urea and SCr levels at discharge (*n*=116) and SOFA scores at discharge (*n*=76) did not show significant differences. The Kaplan–Meier survival curves [Figure 4A] showed a similar tendency for both groups and the log-rank test did not show significant differences between the groups regarding the death rate (*P*=0.579).

Comparison of EG and DG according to criterion 1 did not show significant differences

Patients who received RRT (38/116, 32.8%) were divided into the EG1 (*n*=17, 44.7%) and DG1 (*n*= 21, 55.3%) according to criterion 1. The basic conditions at admission were similar for

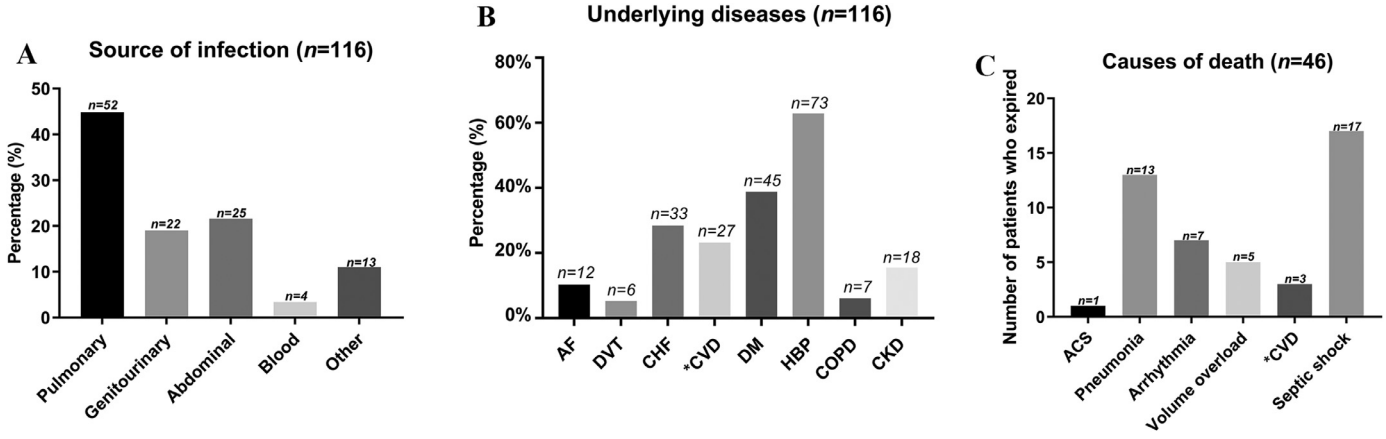

Figure 2. Baseline data of patients. A: Sources of infection which induced sepsis in patients (*n*=116); B: Underlying diseases (*n*=116); C: Causes of death (*n*=46); *CVD including coronary artery disease and ACS.
ACS: Acute coronary syndrome; AF: Atrial fibrillation; CHF: Chronic heart failure; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease; DM: Diabetes mellitus; DVT: Deep vein thrombosis; HBP: High blood pressure.

Table 2
Characteristics of RRT-group(RG) and Non-RRT group(NRG).

Characteristics	RG (n=38)	NRG (n=78)	95% CI	t/χ^2	P-value
Age (years)	69.42 ± 13.68	74.01 ± 1.08	−0.504—9.687	1.937	0.055
Sex (male)	22 (57.9)	43 (55.1)		0.079	0.778
Blood routine tests*					
WBC ($\times 10^9$/L)	16.2 ± 9.0	15.1 ± 7.2	−4.166—1.977	0.706	0.482
Lymphocytes (%)	5.3 ± 5.2	7.1 ± 4.9	−0.210—3.736	1.771	0.079
Neutrophils (%)	90.4 ± 6.8	86.3 ± 8.4	−7.030—1.238	2.836	0.006
NLR	28.64 ± 21.11	21.47±19.69	−15.351—1.014	1.747	0.085
PLT ($\times 10^9$/L)	125.2 ± 78.5	133.9 ± 77.1	−21.763— 39.188	0.566	0.572
KDIGO Stage 3	25 (65.8)	40 (51.3)	−0.339 —0.049		0.140
SOFA					
At admission	7.55 ± 3.49	7.15 ± 3.60	−1.795—0.998	0.566	0.573
Max	8.47 ± 3.70	7.09 ± 3.65	−2.821—0.053	1.908	0.059
At discharge†	1.52 ± 1.81	2.80 ± 1.61	0.345–2.199	2.789	0.009
Shock	20 (52.6)	23 (29.5)		5.867	0.015
Mechanical ventilation	17 (44.7)	14 (17.9)		9.364	0.002
Vasopressor use	21 (55.3)	23 (29.5)		7.211	0.007
90-day death	17 (37.0)	29 (63.0)		0.610	0.435
Death time (days) (n = 46)				3.568	0.191
≤30	14 (30.4)	27 (58.7)			
>30 and <60	1 (2.2)	2 (4.4)			
≥60	2 (4.4)	0 (0)			
Renal recovery at 90 days from ICU admission (n =70)				0.884	0.643
Full recovery	12 (57.1)	33 (67.3)			
Partial recovery	6 (28.6)	12 (24.5)			
Non-recovery	3 (14.3)	4 (8.2)			

Data are presented as n (%) or mean ± standard deviation.
CI: Confidence interval; ICU: Intensive care unit; KDIGO: Kidney Disease Improving Global Outcomes; NLR: Neutrophil-to-lymphocyte ratio; PLT: Platelet count; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment.
* Blood routine test results were obtained within the first 24 h after admission.
† SOFA scores at discharge were obtained from patients who were discharged alive (n=76).

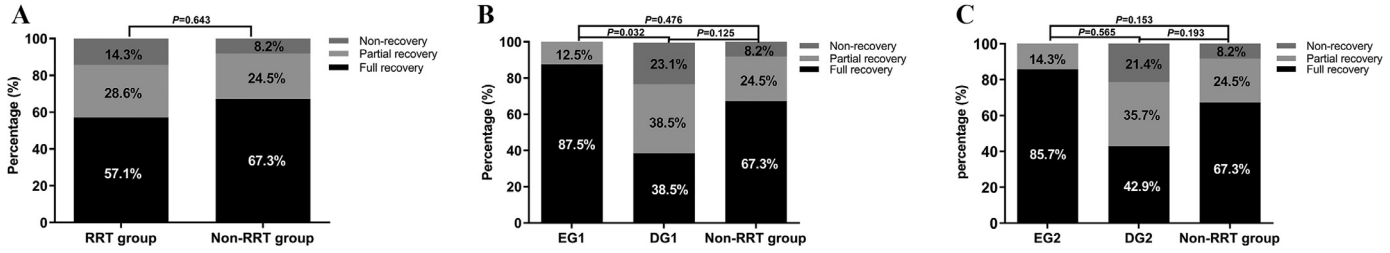

Figure 3. Comparison of renal recovery at 90 days among different groups. A: Comparison between RRT group and Non-RRT group; B: Comparison between EG, DG based on criterion 1(EG1, DG1) and Non-RRT group; C: Comparison between EG, DG based on criterion 2(EG2, DG2) and Non-RRT group.
Criterion 1: The groups were defined according to the time from admission to RRT initiation (EG1<24 h, DG1>24 h); Criterion 2: The groups were defined according to KDIGO stage of patients at admission (EG2: stage 3, DG2: stage 2).
Full renal recovery was defined as SCr levels at discharge 144 mol/L; return of spontaneous urine output 1000 mL/24 h (or 2000 mL/24 h with diuretics) for a minimum of 24 h without RRT during the hospital stay; or a return of SCr to 150% of the baseline.
DG: Delayed-RRT group; EG: Early-RRT group; KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal replacement therapy; SCr: Serum creatinine.

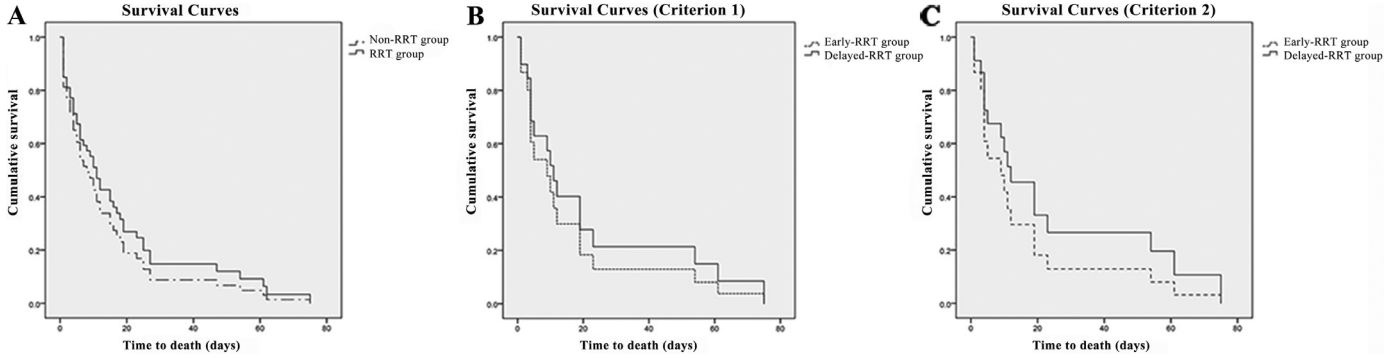

Figure 4. Kaplan-Meier survival curves. A: RRT group and Non-RRT group (P=0.579); B: Early-RRT group and Delayed-RRT group according to criterion 1 (P=0.421); C: Early-RRT group and Delayed-RRT group according to criterion 2 (P=0.899).
Criterion 1: The groups were defined according to the time from admission to RRT initiation (Early-RRT group <24 h, Delayed-RRT group >24 h); Criterion 2: The groups were defined according to KDIGO stage of patients at admission (Early-RRT group: stage 3, Delayed-RRT group: stage 2).
KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal replacement therapy.

Table 3
Characteristics of the patients in different groups (n=116).

Characteristics	EG1(n=17)	DG1(n=21)	EG2(n=13)	DG2(n=25)	NRG(n=78)
Age(years)*	71.00	68.10	69.10	69.60	74.00
Sex (male)	64.7	52.4	53.8	60.0	55.1
Urea (mmol/L)†					
At admission‡,§	16.8	24.3	13.6	24.8	22.1
Max‡,§,‖,¶	18.3	28.1	14.5	28.5	25.9
At discharge†	16.1	13.0	13.6	14.7	17.1
SCr (mmol/L)†					
At admission*,†,‡,§,¶	258.3	472.5	178.8	479.5	289.4
Max*,†,§	344.5	539.1	277.2	543.0	351.7
At discharge†	191.6	230.4	151.6	245.0	213.1
KDIGO Stage 3*,¶	47.6	81.0	NA	NA	51.3
SOFA					
At admission	8.29	6.95	6.92	7.88	7.15
Max‖,¶	9.88	7.33	8.92	8.24	7.09
Shock‡,§,‖,¶	70.6	38.1	84.6	36.0	29.5
ARDS‡,‖,¶	58.8	33.3	69.2	32.0	20.5
Mechanical ventilation‡,§,‖	58.8	33.3	69.2	32.0	17.9
Vasopressor use‡,§,‖,¶	70.6	33.3	92.3	36.0	29.5
90-day death	52.9	38.1	46.2	44.0	37.2

Data are presented as average number or percentage of the total.
The SCr and urea levels of the dead patients at discharge refer to the last test value obtained before death.
Criterion 1: The groups were defined according to the time from admission to RRT initiation (EG1<24 h, DG1>24 h); Criterion 2: The groups were defined according to KDIGO stage of patients at admission (EG2: stage 3, DG2: stage 2).
ARDS: Acute respiratory distress syndrome; DG: Delayed-RRT group; EG: Early-RRT group; KDIGO: Kidney Disease Improving Global Outcomes; NA: Not available; NRG: Non-RRT group; RRT: Renal replacement therapy; SCr: Serum creatinine; SOFA: Sequential organ failure assessment.
* DG1 *vs.* NRG,
† DG2 *vs.* NRG,
‡ EG2 *vs.* NRG,
§ EG2 *vs.* DG2,
‖ EG1 *vs.* NRG,
¶ EG1 *vs.* DG1, all P< 0.05.

both groups [Table 3]. We found that the ratio of patients with KDIGO stage 3 disease was significantly higher in DG1 than in EG1 (P=0.029). This suggests that patients in DG1 were in generally poorer health and could not tolerate early RRT compared with those in EG1.

During hospitalization, a significantly higher number of patients in EG1 developed shock (n=12, 70.6%) than those in DG1 (n=8, 38.1%; P=0.046). In addition, more patients in EG1 (n=10, 58.8%) required treatment with ventilation to maintain adequate blood pressure than those in DG1 (n=7, 33.3%; P=0.022).

At 90 days after admission to the ICU, 9 (52.9%) and 8(47.1%) deaths were recorded in the EG1 and DG1, respectively. There was no significant difference between the two groups in 90-day death rates (χ^2=0.835, P=0.360), and requirement for RRT at 90 days after admission to the ICU (P=0.243; Table 3). Though interedtingly, the 90-day renal recovery rate was significantly better in EG1 than DG1 (87.5% vs. 38.5%, respectively; χ^2=10.425, P=0.032) [Figure 3B]. The Kaplan–Meier survival curves [Figure 4B] and the overall comparison results (0.421 in log-rank analysis) did not show significant differences.

Comparison of EG and DG according to criterion 2 did not show significant differences

DG2 (n=25, KDIGO stage 3 disease at admission) had worse renal function with higher levels of urea (P<0.001) and SCr (P=0.056) than EG2. However, the two groups showed similar outcomes (90-day death rate: χ^2=0.022, P=0.899; 90-day renal recovery: P=0.153) [Figure 3C and 4C].

During hospitalization, EG2 had a significantly higher rate of shock than DG2 (84.6% *vs.* 36.0%, respectively; P=0.006). Meanwhile, patients in EG2 were more likely to require treatment with a vasopressor and mechanical ventilation to maintain their oxygen saturation and blood pressure; this was similar to the findings in EG1 [Table 3 and Figure 5].

Comparison of NRG with EG and DG

We compared the NRG with EG and DG. First, we discovered that regardless of criterion 1 or 2, the SCr levels at admission (criterion 1: 472.49 mmol/L; criterion 2: 479.53 mmol/L) and maximum levels of SCr (criterion 1: 539.14 mmol/L; criterion 2: 542.98 mmol/L) of the DG were significantly higher than those recorded in the NRG (289.39 mmol/L and 351.72 mmol/L). These data suggested that patients in the DG had more severe kidney injury during hospitalization than those in the NRG.

Moreover, in the EG, notwithstanding criterion 1 or 2, the occurrence rates of shock (criterion 1: 70.6%; criterion 2: 84.6%) and acute respiratory distress syndrome (criterion 1: 58.8%; criterion 2: 69.2%) were significantly higher than those noted in the NRG (29.5% and 20.5%). Furthermore, the number of patients who required mechanical ventilation in the EG (criterion 1: 58.8%; criterion 2: 69.2%) was greater than that recorded in the NRG (33.3% and 32.0%, P=0.001 and P<0.001, respectively) during hospitalization. This evidence suggested that the vital signs of the patients in the EG were more unstable. These results are shown in Table 3.

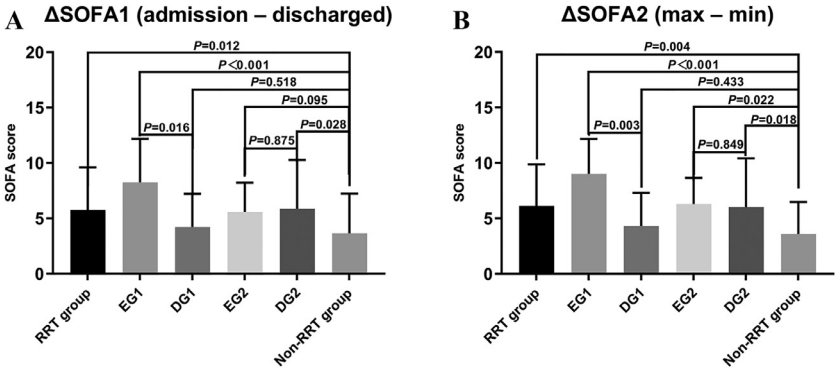

Figure 5. Comparison of SOFA score in patients who were alive at 90 days. A: Comparison of SOFA scores changes at admission and discharge; B: Comparison of SOFA scores changes at maximum and minimum during hospitalization.
Criterion 1: The groups were defined according to the time from admission to RRT initiation (EG1<24 h, DG1>24 h); Criterion 2: The groups were defined according to KDIGO stage of patients at admission (EG2: stage 3, DG2: stage 2).
DG: Delayed-RRT group; EG: Early-RRT group; KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal replacement therapy; SOFA: Change in Sequential Organ Failure Assessment.

Comparison of characteristics of patients who remained alive (EG vs. NRG, DG vs. NRG)

At day 90, 70 patients were alive. We selected and analyzed their data, and the results are shown in Table 4. The SCr levels at admission (criterion 1: 563.5 mmol/L; criterion 2: 588.0 mmol/L) and maximum levels of creatinine (criterion 1: 625.2 mmol/L; criterion 2: 657.2 mmol/L) during hospitalization were significantly higher in the DG than the NRG (at admission: 280.8 mmol/L; maximum levels: 331.6 mmol/L). Nevertheless, the SCr levels at discharge and renal recovery at 90 days was not significantly different between these groups (P=0.088 and P=0.095 at discharge with criterion 1 and 2, respectively), suggesting that even delayed RRT may improve the renal function of patients.

We also found that patients in the EG were more likely to develop shock during hospitalization (75.0% and 85.7% with criterion 1 and 2, respectively) than in the DG (30.8% and 28.6% with criterion 1 and 2, respectively); and more likely to require mechanical ventilation (62.5% and 57.1% with criterion 1 and 2, respectively) than in the DG (23.1% and 28.6% with criterion 1 and 2, respectively), suggesting that patients who received early RRT had more unstable vital signs. We also discovered that patients in EG1 have higher SOFA scores at admission and during hospitalization (8.75 and 9.50, respectively) than DG1 (5.62 and 6.46, respectively). At discharge, patients in EG1 and EG2 had lower SOFA scores (0.50 and 1.00; P<0.001 and P=0.006, respectively) compared with those in NRG (SOFA score: 2.80), indicating that patients in EG had better recovery of systemic organ function than those in NRGs.

Moreover, we found that ΔSOFA (maximum-minimum) of patients in the EG and RG were significantly higher than those recorded in the NRG ($\Delta SOFA_{AG}$=7.0, $\Delta SOFA_{NRG}$=3.6, $\Delta SOFA_{EG1}$=9.0, $\Delta SOFA_{EG2}$=6.3; P <0.50).

Discussion

Clinically, RRT is widely used as an important supportive treatment in patients with AKI. It can effectively control the state of liquids and electrolytes, remove uremic toxins, and prevent the occurrence of complications.[6,23,24] However, the timing of RRT initiation in patients with AKI remains controversial; two important studies conducted in 2016 reached contrasting conclusions.[10,25] The results of the randomized controlled trial conducted by Gaudry et al.[10] suggested that early RRT does not offer significant benefits to patients, while delayed RRT may protect some patients from overtreatment and reduce the incidence of related complications.In a study performed by Zarbock et al.,[25] patients who received early RRT had a significantly lower 90-day mortality rate and better recovery of renal function than those who received delayed RRT.

Compared with AKI caused by other causes, SA-AKI is often accompanied by more severe and complex inflammatory reactions, and the disease is also more serious, with a mortality rate reaching 30–50%.[26] Studies on SA-AKI suggested that early RRT may improve the short-term prognosis and reduce the 28-day mortality rate; nonetheless, it does not improve the overall mortality and ICU stay of patients with SA-AKI.[12,27–29] Sepsis is a serious disease involving systemic organ dysfunction caused by severe infection. The purpose of treatment is to improve kidney injury and the function of systemic organs. However, currently, there is limited research in this field.

Currently, there are marked differences in the definitions of early and delayed RRT. Therefore, we set up definitions of “early-RRT” and “delayed-RRT” based on two criteria. In brief, criterion 1 defines “early” and “delayed” based on the absolute time between the diagnosis and the initiation of RRT. Meanwhile, considering the improved sensitivity for the diagnosis of AKI and the stronger ability to predict the prognosis,[30] we utilized the course of disease (KDIGO stage) as criterion 2. Furthermore, we used the SOFA score to determine the function status of systemic organs.[31]

Although timely RRT has significant benefits on organ function, in this study, RRT and early RRT did not significantly reduce the 90-day mortality rate and ICU hospitalization time. Moreover, patients in the RG were more unstable; hence, more support measures were required to stabilize their vital signs. We hypothesized that the possible reasons were as follows. Patients with SA-AKI have special pathophysiological characteristics as some may have relatively good original renal function without basic kidney disease. Following the administration of anti-infection and other supportive treatments, their condition can be controlled and their renal function can recover spontaneously. In such cases, the advantages of RRT may be weakened; thus, there is no significant difference in mortality and hospital stay between the RG and NRG. In addition, RRT alters numerous inflammatory mediators in the body within a short period of time, which affect more in elderly patients group, who are more intolerant to changes in the internal environment and cannot rapidly adapt. Therefore, the vital signs after RRT were unstable, and other adjuvant treatments, such as the ventilator support or vasopressor drugs, were required.

Table 4
Characteristics of living patients (EG *vs.* NRG, DG *vs.* NRG) (*n*=70).

Characteristics	G1(*n*=8)	DG1(*n*=13)	EG2(*n*=7)	DG2(*n*=14)	NRG(*n*=49)
Age (years)	64.25	68.00	64.29	67.71	72.08
Sex (male)	62.5	46.2	42.9	57.1	51.0
Urea (mmol/L)*					
At admission†	18.1	27.6	15.5	28.1	20.9
Max*,†,‡	17.8	30.8	14.0	31.9	23.1
At discharge	11.4	11.8	9.9	12.5	10.4
SCr (mmol/L)*					
At admission†,‡,§	279.9	563.5	190.3	588.0	280.8
Max†,§	445.7	625.2	356.1	657.2	331.6
At discharge	112.9	219.9	106.3	215.5	144.1
KDIGO Stage 3*	50.0	76.9	NA	NA	46.9
Renal recovery at 90 days from admission to the ICU					
Full recovery	87.5	38.5	85.7	42.9	67.3
Partial recovery	12.5	38.5	14.3	35.7	24.5
Non-recovery	0	23.1	0	21.4	8.2
Requirement for RRT after 90 days	0.0	15.4	0.0	14.3	4.1
Shock*,‡,‖,¶	75.0	30.8	85.7	28.6	26.5
Mechanical ventilation*,†,‖	62.5	23.1	57.1	28.6	8.2
SOFA					
At admission‖	8.75	5.62	6.57	6.93	6.45
Max‖,¶	9.50	6.46	7.29	7.79	6.35
At discharge*,‖,¶	0.50	2.15	1.00	1.79	2.80
△SOFA1 (admission–discharge)†,‖,¶	8.25	4.25	5.57	5.86	3.65
△SOFA2 (max–min)*,†,‖,¶	9.00	4.31	6.30	6.00	3.60

Data are presented as the average number or percentage of the total.
Criterion 1: The groups were defined according to the time from admission to RRT initiation(EG1<24 h, DG1>24 h); Criterion 2: The groups were defined according to KDIGO stage of patients at admission (EG2: stage 3, DG2: stage 2).
DG: Delayed-RRT group; EG: Early-RRT group; KDIGO: Kidney Disease Improving Global Outcomes; NA: Not available; NRG: Non-RRT group; RRT: Renal replacement therapy; SCr: Serum creatinine; SOFA: Sequential organ failure assessment.
* EG2 *vs.* NRG,
† DG2 *vs.* NRG,
‡ EG2 *vs.* DG2,
§ DG1 *vs.* NRG,
‖ EG1 *vs.* NRG,
¶ EG1 *vs.* DG1, all $P< 0.05$.

Nonetheless, based on the subgroup analysis, the present study has yielded some interesting findings. First, our results suggested that RRT could support the recovery of organ function in patients with more severe systemic organ injury. In the RG, compared with the NRG, the SOFA score (admission) was higher (7.55 *vs.* 7.15, respectively) and patients with KDIGO stage 3 accounted for a larger proportion (65.8% *vs.* 51.3%, respectively). These findings suggested the presence of more serious renal injury and systemic organ injury in patients who received RRT at the baseline. Meanwhile, during hospitalization, patients in the RG were more prone to develop shock than those in the NRG (52.6% *vs.* 29.5%, respectively; P=0.015); additionally, they had a greater demand for non-invasive ventilator support (44.7% *vs.* 17.9%, respectively; P=0.002) and use of vasopressor drugs (55.3% *vs.* 29.5, respectively; P=0.007). These data suggested that the fluctuation of vital signs was greater in patients who received RRT compared with those who did not. Moreover, although the general condition of patients was poorer in the RG compared with the NRG, there was no significant difference in 90-day renal recovery (P= 0.643) and overall mortality (P=0.643) between the groups. Also, the organ function of patients who received RRT at discharge was significantly better than that recorded in the NRG (SOFA at discharge: 1.52 *vs.* 2.80, respectively; P=0.009). Therefore, in this study, RRT exerted a protective effect on long-term renal function and systemic organ function. The present findings are consistent with those of other studies, further demonstrating that RRT may eliminate and regulate inflammatory factors, strengthen fluid management in patients with sepsis, correct water and electrolyte disorders, and stabilize the internal environment.[30]

Second, we found that early RRT resulted in greater fluctuation in vital signs during hospitalization. However, it was conducive to the long-term recovery of renal function and other organ functions. Meanwhile, delayed RRT took a more stable supporting role in the recovery of renal function.

We found that the incidence of shock during hospitalization was higher in the EG than the other two groups (DG and NRG); also, the use of mechanical ventilation and vasopressor drugs was more frequent in this group. Nevertheless, there was no significant difference in mortality among the three groups. Furthermore, the 90-day renal recovery rate was significantly better in EG1 than DG1 (87.5% *vs.* 38.5%, respectively; χ^2=10.425, P=0.032), which further suggests that early and timely RRT may be of great benefit to the recovery of renal function in patients with SA-AKI. Meanwhile, although the degree of renal injury in DG1 was significantly higher than that noted in EG1 and NRG, there was no significant difference observed in the SCr levels at discharge and 90-day renal recovery among the DG1, EG1, and NRG. This indicates that delayed RRT may have certain benefits on the recovery of renal function.

A subgroup analysis of survivors at 90 days (n=70) suggested that early RRT may protect the systemic organ function of patients with severe kidney injury. We found that the SOFA score at discharge was significantly lower in EG1 *vs.* DG1 and NRG (P<0.001). We also found that the $\Delta SOFA_{admission–discharge}$ of EG1

was significantly higher than that of DG1 (P=0.016) and NRG (P<0.001). For DG2 (consisting of patients with more serious kidney injury), the protective effect of RRT on the systemic organ function was significantly stronger than that observed in NRG (P=0.028). However, regardless of the criteria, the fluctuation of vital signs in patients who received early RRT was significantly greater and the proportion of patients requiring shock and respiratory support were significantly higher than those recorded in the NRG, suggesting that patients who received early RRT required more supportive measures during hospitalization.

The present findings are consistent with those of other studies focusing on critically ill patients. In the study conducted by Chou et al.[12] which included 370 patients with SA-AKI, "early" or "delayed" were defined according to the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria. The results showed that the mortality rate at discharge in the EG (stage R) was significantly lower than that observed in the DG (stage I or F). Leite et al.[32] defined the early and delayed groups according to the AKI Network. Although the results showed that the mortality rates in the two groups were equal, the early group still exhibited an absolute advantage in terms of improved prognosis. In the ELAIN (early *vs.* late initiation of RRT in critically ill patients) trial,[25] "early" and "delayed" were defined based on the KDIGO stages. The early group showed a better prognosis in critically ill patients, in terms of 90-day death and renal function recovery. The differences between the present study and the ELAIN trial is that the previous investigation included patients with higher SOFA scores (mean SOFA score: 15.6–16.0) and had more diverse sources of patients. These differences indicate that patients in the ELAIN trials may have had more severe acute conditions than those in our study. In addition, the trial did not report data on the SOFA score at discharge. However, the early group had shorter hospitalization time compared with the delayed group, suggesting that timely RRT may have improved the whole health status and systemic organ function. Consistent results are shown in another *post hoc* analysis of the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial,[33] which focused on patients with septic shock who had more similar SOFA scores to those of our enrolled patients. Similar to the present study, the AKIKI trial did not report a significant difference in 60-day death rate between the early and delayed groups. Additionally, early RRT resulted in shorter length of hospital stay compared with delayed RRT (28 days *vs.* 37 days, respectively).

It has been demonstrated that RRT is a non-specific scavenger of inflammatory mediators, playing a key role in the occurrence and development of sepsis.[34,35] Studies have shown that higher concentrations of inflammatory mediators are associated with higher mortality rates.[36,37] In addition, RRT is able to downregulate the AKI markers of sepsis, such as neutrophil gelatinase-associated lipocalin (*NGAL*),[38] and promote the recovery of renal function. Therefore, early clearance of inflammatory mediators and reconstruction of immune homeostasis may improve the prognosis of patients with sepsis.

Based on the complex pathophysiology of patients with SA-AKI, RRT should be considered according to the clinical condition of each patient. In clinical practice, establishment of a set of standards is necessary to guide the strategy for the implementation of RRT. Nevertheless, the present study has some limitations. As a single-center retrospective study, the data volume is small; notably, the mortality rate among our patients was lower than that previously reported internationally. It is unclear whether this is due to the better condition of the patients or the provision of better medical support in the ICU. Moreover, the patients included in this research study were older (mean age: 72.51 ± 12.12 years) compared with those evaluated in the ELAIN trial[25] (mean age: 68.2 ± 12.7 years). Hence, there may be more underlying diseases in those patients, potentially leading to a bias with regard to their basic condition. In addition, we did not consider the details of clinical treatment, such as the mode and duration of RRT. Moreover, although we set a series of standards for the enrollment of patients, as a retrospective study, there were some differences between groups at baseline. Therefore, a larger, controlled, and prospective study is warranted to determine the optimal RRT strategy for patients with SA-AKI.

Conclusions

Although RRT had a limited effect on patient survival and 90-day mortality, timely RRT may improve the restoration of systemic organ function and long-term renal function recovery in patients with SA-AKI. This may help patients obtain a better quality of life. However, the vital signs of patients who received RRT were more unstable during hospitalization. Therefore, strong support measures are warranted.

Ethical Approval

This study was approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval number: XHEC-D-2020-058). The requirement for informed consent was waived due to the retrospective design of the study. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Data Availability

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

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