Am J Transl Res 2024;16(8):3646-3653
www.ajtr.org /ISSN:1943-8141/AJTR0155779

Original Article

Efficacy of immediate versus delayed renal replacement therapy in septic patients undergoing continuous renal replacement therapy

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Received February 4, 2024; Accepted May 8, 2024; Epub August 15, 2024; Published August 30, 2024

Abstract: Objective: To compare the therapeutic efficacy of immediate versus delayed renal replacement therapy (RRT) in septic patients undergoing continuous RRT. Methods: We retrospectively analyzed 98 septic patients who received continuous RRT between August 2021 and January 2023. Patients were divided into two groups: RRT group (n=50, immediate RRT) and delayed RRT group (n=48), where RRT was delayed by 48 hours in the absence of renal function recovery. Demographic data, comorbidities, vital signs, laboratory results, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Sequential Organ Failure Assessment (SOFA) scores, and follow-up details were compared between the two groups. Results: The RRT group showed significantly lower serum interleukin-6 and creatinine levels at 1, 3, and 5 days of treatment (P=0.006, P=0.021, P=0.007; P=0.016, P=0.006, P=0.021, respectively) compared with the delayed RRT group. Additionally, the RRT group had shorter ICU stays, reduced duration of mechanical ventilation, and lower total treatment costs (P=0.016, P=0.003, P=0.029). Post-treatment, the RRT group exhibited significantly lower APACHE II and SOFA scores (P=0.031, P=0.018), a shorter average ICU stay (P=0.009), and a lower mortality rate (P=0.018) than the delayed RRT group. Conclusion: Immediate RRT in septic patients undergoing continuous RRT significantly reduces inflammatory markers, accelerates patient outcome, and decreases short-term mortality compared to delayed treatment.

Keywords: Renal replacement therapy, delayed treatment, continuous renal replacement therapy, sepsis, therapeutic efficacy, safety

Introduction

Sepsis is a critical condition that emerges from various severe insults, including infectious diseases, burns, trauma, shock and surgeries, profoundly disrupting human physiology [1, 2]. It remains one of the leading causes of death worldwide, posing a significant global health threat [3, 4]. Approximately 40% of patients admitted to intensive care units (ICU) are diagnosed with sepsis, which carries a high mortality rate of 25%-40%, primarily due to severe sepsis and septic shock [5].

Renal injury frequently complicates sepsis, representing the predominant cause of acute renal injury in ICUs. It is estimated that 40%-79% of acute renal injuries in the ICU are due to sepsis, with about half of critically ill septic patients developing this condition [6, 7]. Acute renal injury not only extends hospital stays and escalates treatment costs but is also a major mortality driver. The mechanisms behind sepsis-induced acute renal injury are complex and not fully understood [8]. So, there is a lack of definitive therapeutic standards for managing septic patients with this complication. Renal replacement therapy (RRT) has shown substantial promise in improving outcomes for these patients. By effectively managing fluid volume, maintaining acid-base balance, and correcting electrolyte imbalances, RRT helps eliminate inflammatory mediators thus serving a crucial therapeutic role [9, 10]. However, the optimal

https://doi.org/10.62347/XSTK3213

timing for initiating RRT is debated. While some studies suggest that early RRT initiation does not affect clinical outcomes, others report it may increase the risk of complications such as hypotension, hemorrhage, and arrhythmias [11]. Given these inconsistencies, this study aims to retrospectively analyze the differences in therapeutic efficacy between immediate RRT and delayed RRT (initiated 48 hours after non-recovery of renal function) in septic patients undergoing continuous RRT. By focusing on inflammatory markers and clinical indicators, this research seeks to refine our understanding of the impacts of RRT timing on septic patient outcomes, offering valuable insights for clinical decision-making.

Materials and methods

General data

This retrospective study included 98 septic patients who received continuous RRT between August 2021 and January 2023. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Hangzhou Fuyang Hospital of Traditional Chinese Medicine.

Inclusion criteria

(1) Patients who underwent continuous RRT at our facility with fully documented clinical information available in the hospital information system. This included baseline clinical data and pre- and post-treatment interleukin-6 (IL-6) levels, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, among other parameters; (2) Patients who were diagnosed with sepsis based on the 2021 Sepsis 3.0 criteria; (3) Patients aged 18 years or older.

Exclusion criteria

Patients with the following conditions were excluded: (1) patients who underwent continuous RRT without sepsis; (2) patients with incomplete clinical data; (3) patients who underwent renal transplant; (4) patients with a history of chronic renal insufficiency; (5) patients with prolonged use of immunosuppressive agents; (6) patients with autoimmune disorders; (7) patients with compromised immune function; (8) patients who underwent long-term dialysis treatment; (9) patients with psychiatric disorders.

Research methods

Grouping criteria: Ninety-eight patients with sepsis who received continuous RRT in our hospital from August 2021 to January 2023 were retrospectively collected and divided into an RRT group (n=50, receiving RRT within 12 h of acute renal injury onset) and a delayed RRT group (n=48, receiving RRT 48 h after non-recovery of renal function). The treatment protocols were determined after patients were informed of the pros and cons of each option, allowing them to make informed decisions accordingly.

Observation indicators

Primary observation indicators: (1) ICU length of stay, duration of mechanical ventilation, total treatment cost, and total duration of treatment were recorded in both groups. (2) Mortality rates at 28 d, 60 d, and 90 d of follow-up were collected and compared between the two groups.

Secondary observation indicators: (1) Baseline clinical data including sex, age, serum creatinine (Scr) levels, blood urea nitrogen (BUN) levels, and underlying diseases such as hypertension and diabetes were collected in both groups. (2) APACHE II scores [12] were assessed to evaluate acute physiological parameters, chronic health status, and age, with scores ranging from 0 to 71; higher scores indicate more severe conditions. Sequential Organ Failure Assessment (SOFA) scores [13] were used to evaluate multiple organ functions including respiratory, coagulation, liver, and cardiovascular systems, etc. The scores range from 0 to 4, with higher scores representing poorer prognosis. Both scores were collected from the patients of the two groups before treatment and at 5 d of treatment. (3) IL-6 levels were measured at baseline, and on days 1, 3, and 5 of treatment. (4) Serum creatinine (Scr) levels were similarly measured at baseline, and on days 1, 3, and 5 following the initiation of continuous RRT.

Quality control

To ensure the accuracy of the data, rigorous criteria were applied in the selection of participants at the beginning of the study. Patients were classified according to predefined grouping criteria. Comprehensive patient information

Table 1. Comparison of baseline clinical data between the two groups (mean ± SD)

General clinical data		Delayed RRT group (n=48)	RRT group (n=50)	t/χ^2	*P*
Sex	Male	30	32	0.024	0.878
	Female	18	18		
Average age (years)		63.75±9.83	62.23±6.03	0.927	0.356
Scr level (μmol/L)		166.97±31.48	165.43±38.58	0.216	0.829
BUN level (mmol/L)		13.71±3.17	12.34±3.75	1.812	0.072
IL-6 level (pg/ml)		527.15±222.94	558.35±250.68	0.650	0.517
SOFA score (point)		9.81±2.25	9.79±3.13	0.036	0.971
APACHE II score (point)		18.23±6.81	17.96±3.72	0.245	0.807
Underlying diseases	Hypertension	12	20	2.506	0.113
	Diabetes	9	11	0.159	0.690
	Chronic obstructive pulmonary disease	13	15	0.102	0.749

RRT: renal replacement therapy; Scr: serum creatinine; IL-6: interleukin-6; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

was collected systematically via the hospital's information systems. Data collection tasks were assigned to a dedicated staff member, while data verification was performed independently by two other individuals to mitigate any potential for error. The validated data were then inputted into statistical software for further analysis.

Statistical methods

Data management was performed using EXCEL 2021, while statistical analyses were conducted using SPSS 21.0. Measurement data, such as age and IL-6 levels, which conformed to a normal distribution, were expressed as mean ± standard deviation (SD). Independent samples t-test was used for comparison between groups. Repeated measures analysis of variance and post-hoc Bonferroni test, along with paired sample t-test were used for comparison of patients within the same group at different time points. Counting data were expressed as rate, and chi-square test was used for comparison between groups. Multivariate logistic regression analysis was conducted for the analysis of risk factors. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline clinical data

The comparisons of general clinical data, laboratory results, and underlying diseases of patients showed no statistically significant differences between the two groups ($P>0.05$) (**Table 1**).

Comparison of Scr levels before and after treatment between the two groups

Before treatment, the differences in Scr levels between the two groups were not statistically significant ($P>0.05$). However, at 1 d, 3 d, and 5 d of treatment, patients in the delayed RRT group exhibited significantly higher Scr levels than those in the RRT group, and the intergroup difference was statistically significant ($P=0.016$, $P=0.006$, $P=0.021$) (**Figure 1**).

Comparison of serum inflammatory factors before and after treatment between the two groups

Before treatment, the differences in serum IL-6 levels between the two groups were not statistically significant ($P>0.05$). However, at 1 d, 3 d, and 5 d of treatment, the serum IL-6 levels of patients in the RRT group were significantly lower than those in the delayed RRT group, exhibiting a statistically significant difference between the two groups ($P=0.006$, $P=0.021$, $P=0.007$) (**Figure 2**).

Comparison of hospitalization data between the two groups of patients

The ICU stay, duration of mechanical ventilation, and total treatment cost in the RRT group were all significantly lower than those in the delayed RRT group, exhibiting a statisti

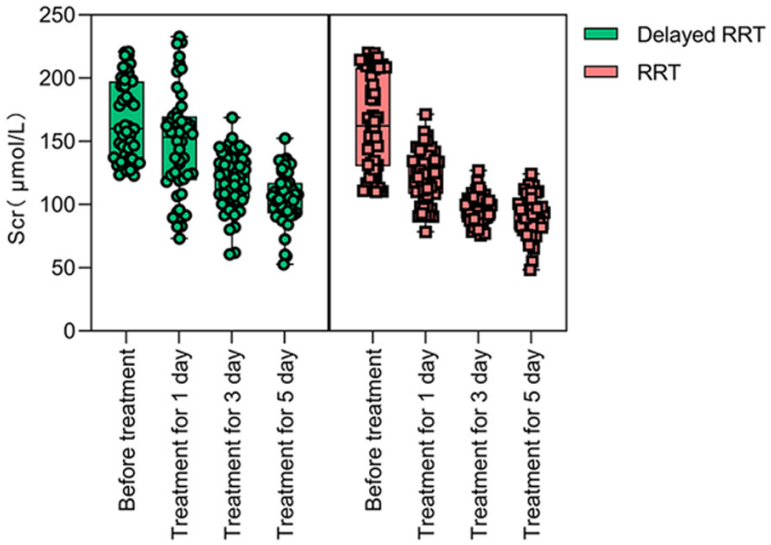

Figure 1. Comparison of Scr levels before and after treatment between the two groups. RRT: renal replacement therapy; Scr: serum creatinine.

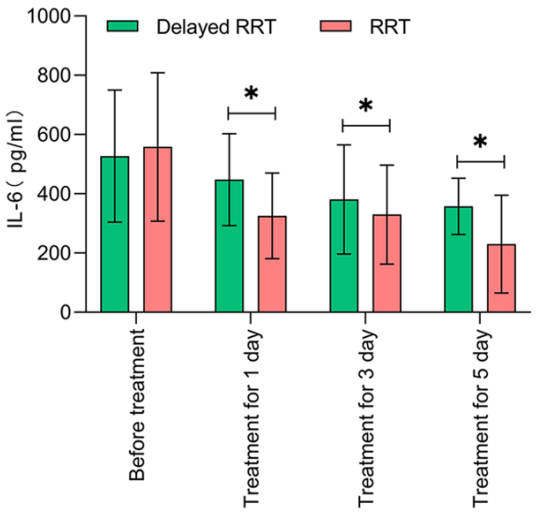

Figure 2. Comparison of serum inflammatory factors before and after treatment between the two groups. *P<0.05. RRT: renal replacement therapy; IL-6: interleukin-6.

cally significant difference (P=0.016, P=0.003, P=0.029). In terms of total duration of treatment, there was no significant difference between the two groups (P>0.05) (**Figure 3**).

Comparison of APACHE II and SOFA scores before and after treatment between the two groups

Before treatment, there were no significant differences in the APACHE II and SOFA scores between the two groups (P>0.05). After treatment, both groups exhibited significantly decreased APACHE II scores and SOFA scores compared with before treatment, and paired-sample t-test showed that the difference was statistically significant (P<0.05). Additionally, intergroup comparisons indicated that patients in the RRT group had significantly lower APACHE II scores and SOFA scores compared to the delayed RRT group, with a statistically significant difference between the groups (P=0.031, P=0.018) (**Figure 4**).

Comparison of follow-up data between the two groups

The average ICU stay in the RRT group was (11.65±2.70) d, which was significantly shorter than (15.17±3.27) d in the delayed RRT group, exhibiting a statistically significant difference between the two groups (P=0.009) (**Figure 5**). Comparisons of follow-up data showed that the mortality rates in the RRT group at 28 d, 60 d, and 90 d of follow-up were 16.00%, 24.00%, and 24.00%, respectively. In contrast, in the delayed RRT group, the mortality rates at 28 d, 60 d, and 90 d of follow-up were 25.00%, 47.92%, and 52.08%, respectively. A comparative analysis revealed that the mortality rates in the RRT group were significantly lower than those in the delayed RRT group at 60 d and 90 d of follow-up (P=0.020, P=0.018) (**Figure 6**).

Analysis of risk factors affecting prognosis in the patients

The follow-up clinical outcomes of the included patients were used as dependent variable (death =0, survival =1), and treatment timing, gender, age, Scr level, BUN level, etc., were used as independent variables. It was demonstrated that age and treatment timing were significant factors influencing the prognosis of septic patients (P<0.05). Furthermore, multivariate logistic regression analysis on the aforementioned factors revealed that treatment timing was an independent factor affecting the prognosis of the patients (P=0.01) (**Table 2**).

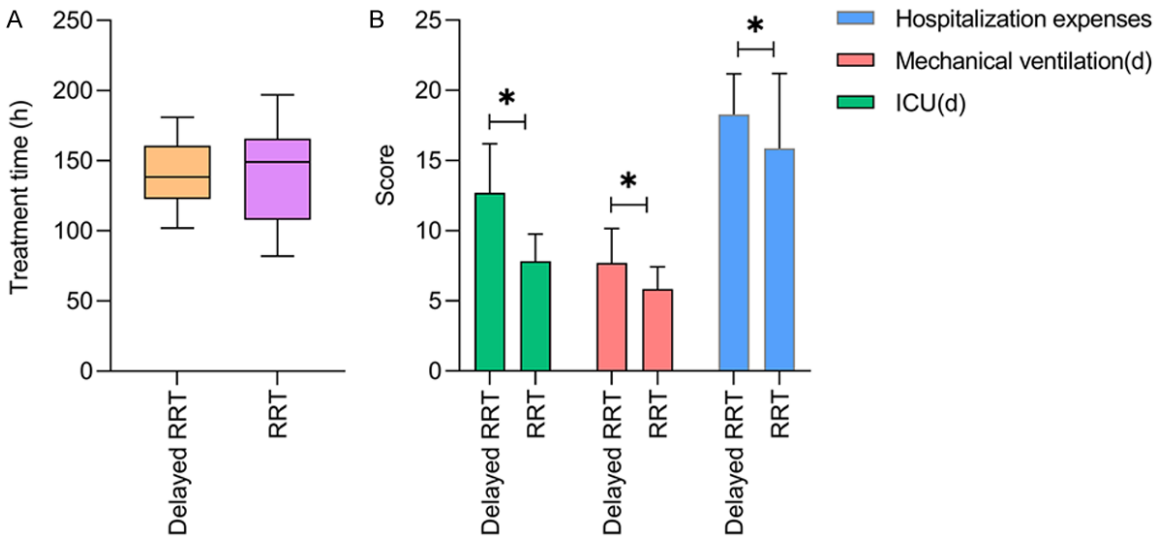

Figure 3. Comparison of hospitalization data between the two groups. A: Total duration of treatment; B: Length of ICU stay, duration of mechanical ventilation, and total cost of treatment. *P<0.05. ICU: intensive care unit; RRT: renal replacement therapy.

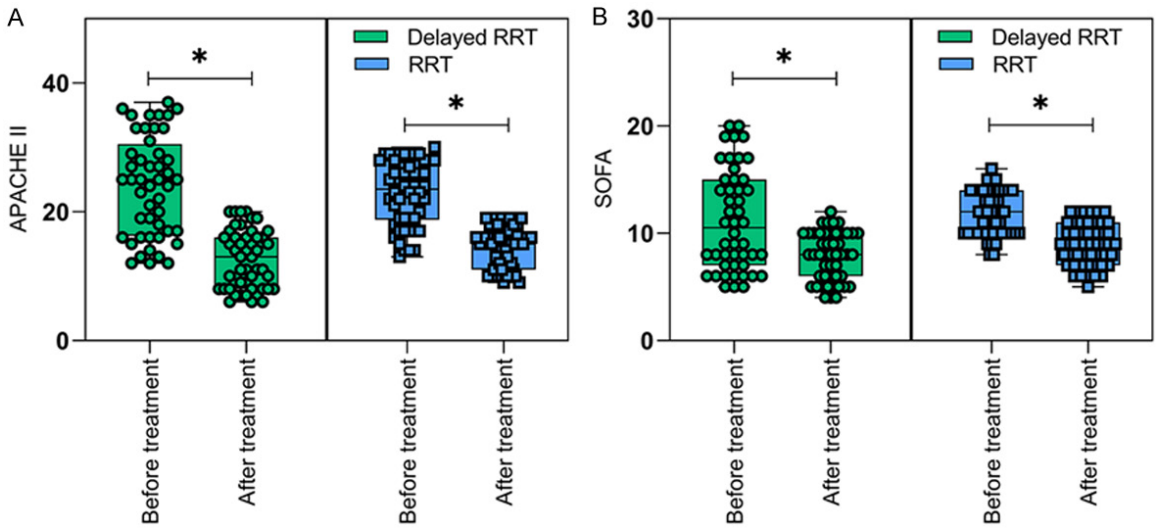

Figure 4. Comparison of APACHE II scores and SOFA scores before and after treatment between the two groups. A: APACHE II scores; B: SOFA scores. *P<0.05. RRT: renal replacement therapy; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

Discussion

The pathogenesis of sepsis is complex and multifaceted, involving factors such as exotoxins, signaling pathways, neuroendocrine-immune interactions, microbiota translocation, coagulation dysfunction, imbalances in inflammation and immune suppression, and genetic polymorphisms [14, 15]. Despite advances in medical technology and management, mortality rates for septic patients, particularly those experiencing septic shock, remain high (20%-50%), and survivors often face severe complications [16]. The dysregulated immune response in sepsis leads to excessive cytokine production, contributing to multi-organ dysfunction and mortality [17]. Continuous RRT has been shown to remove metabolic wastes and inflammatory cytokines from the body of septic patients [18], offering therapeutic benefits in managing sepsis.

This study compared the outcomes of immediate versus delayed RRT in septic patients

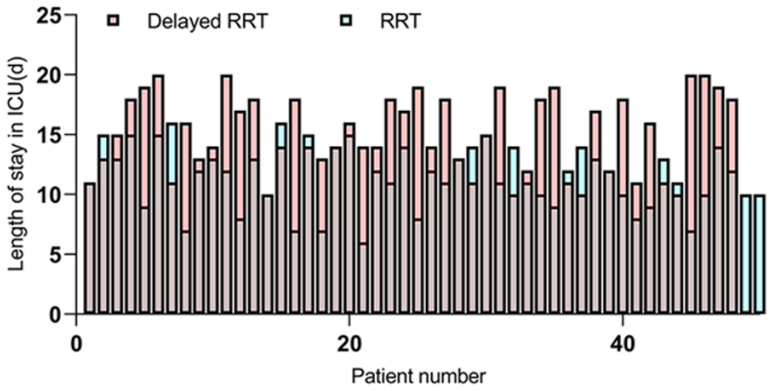

Figure 5. The length of ICU stay between the RRT group and the delayed RRT group. ICU: intensive care unit; RRT: renal replacement therapy.

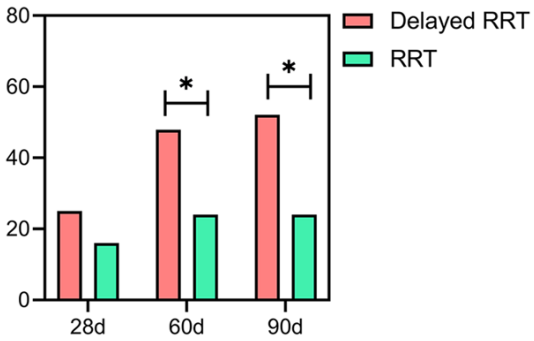

Figure 6. Difference in the follow-up mortality rates between the RRT group and the delayed RRT group. RRT: renal replacement therapy.

undergoing continuous RRT. The results showed that patients in the RRT group had significantly lower post-treatment Scr levels and IL-6 levels compared with those in the delayed RRT group. The kidney is one of the most susceptible target organs in sepsis, and most septic patients manifest acute renal impairment upon admission to medical facilities, leading to a significant increase in mortality [19]. Early initiation of RRT treatment can timely remove waste from the patients' body, contributing to the removal of inflammatory factors from the bloodstream. The reduction of these inflammatory factors is conducive to inhibiting the occurrence of the inflammatory cascade, which has a positive impact on the recovery of renal function, which is also a crucial reason why the Scr levels of patients in the RRT group were significantly lower than those in the delayed RRT group after treatment [20]. This finding is also supported by other studies, such as a retrospective report involving 370 septic patients undergoing RRT, in which patients were also differentiated according to the timing of intervention, and those who received early RRT had a more pronounced reduction in inflammatory factors after intervention [21].

Further results showed that the RRT group had shorter ICU stay, shorter duration of mechanical ventilation, and lower total cost of treatment compared with the delayed RRT group. These benefits likely stem from the early restoration of acid-base balance and timely elimination of toxins and inflammatory factors in the body. This helps to alleviate edema, contributing to a reduction in central venous pressure, accelerating the recovery of renal function, and promoting the restoration of the microcirculatory system [22]. In addition, early initiation of RRT facilitates the removal of inflammation cytokines, thereby restoring the patient's metabolic equilibrium and promptly managing the patient's condition to prevent the occurrence of subsequent complications. This assumption is supported by an additional study [23]. A Meta-analysis focusing on septic patients suggested that early initiation of RRT contributed to a reduced duration of mechanical ventilation, which is associated with the early stabilization of the internal environment in patients by RRT, along with the improvement of renal injury status, as confirmed by the comparisons of post-treatment APACHE II and SOFA scores between the two patient groups [24].

Regarding the comparison of mortality rates between the two groups, there is a discrepancy with the findings of some other studies. Presently, the majority of studies affirm the beneficial significance of RRT for septic patients. However, debates primarily focus on the timing of RRT initiation. A previous study [25] pointed out that the early RRT in patients with acute renal injury did not provide additional benefits and may, in fact, elevate the risk of adverse events during the treatment, whereas delayed RRT could facilitate comprehensive patient monitoring, thereby furnishing more precise recommendations for subsequent interventions. However, another report indicated

Table 2. Analysis of factors affecting the prognosis of septic patients undergoing continuous RRT

Risk factor	β	SE	Wald	P	OR	95% CI
Delayed RRT	0.881	0.231	6.891	0.01	0.782	0.671-0.981

SE: standard error; OR: odds ratio; 95% CI: 95% confidence interval.

that early RRT significantly reduced 90-d mortality in patients [26]. Early RRT does indeed possess certain drawbacks, such as a higher incidence of patient complications and increased utilization of medical resources [15]. However, delayed RRT carries the risk of irreversible progression of the patient's condition, rendering the benefit of RRT. Additionally, delayed RRT may be associated with risks of severe metabolic disruptions, organ failure, and fluid overload, all of which are strongly associated with patient mortality. Balancing these pros and cons, we recommend early initiation of RRT.

In summary, RRT has affirmed effects in septic patients undergoing continuous RRT. Early initiation of RRT contributes significantly to ameliorating inflammation, accelerating patient outcome, and reducing the short-term mortality of patients. However, the decision to initiate RRT should carefully weigh the potential risks and benefits, avoiding overly precipitous or delayed intervention. Therefore, it is necessary to comprehensively assess factors such as organ function, complications, medication usage, fluid balance, and other relevant factors to select the optimal timing for initiating RRT.

Disclosure of conflict of interest

None.

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