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The optimal timing of continuous renal replacement therapy for patients with sepsis-induced acute kidney injury

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Abstract

Purpose   High mortality in the intensive care unit (ICU) is probably associated with sepsis-induced acute kidney injury (AKI). The aim of this study is to explore which stage of AKI may be the optimal timing for continuous renal replacement therapy (CRRT).

Methods   A retrospective analysis of 160 critically ill patients with septic AKI, treated with or without CRRT was performed in Binzhou medical college affiliated hospital ICU. The parameters including 28-days mortality rate, renal recovery, ventilation time and ICU stay between CRRT group and control group were assessed.

Results   Renal recovery, defined as independence from dialysis at discharge, was documented for 64/76 (84.2 %) of the surviving patients (48.1 % of total subjects included in the study). The mortality rate increased proportionally with acute kidney injury Network stages in CRRT subgroups ($P = 0.001$) and control groups ($P = 0.029$). CRRT initiation at stage 2 of AKI significantly reduced the 28-day mortality ($P = 0.048$) and increased the 28-day survival rate ($P = 0.036$) compared with those in control group. In addition, the ICU stay and ventilation time were shorter in CRRT group than that of control group in stage 2 of AKI.

Conclusion   The stage 2 AKI might be the optimal timing for performing CRRT.

Keywords   Sepsis-induced acute kidney injury · Continuous blood purification · Acute kidney injury network · Renal recovery

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Introduction

Sepsis is a complication frequently encountered in critically ill patients, with a reported incidence rate of 0.3 % and increasing rate of 8.7 % per year worldwide. The overall mortality of severe sepsis ranges from 25 to 30 %; however, the mortality of sepsis-induced acute kidney injury (AKI) is more than 70 % [1]. Noticeably, patients with septic AKI are generally sicker, with a higher burden of illness and have greater abnormalities (greater acuity of illness, lower blood pressure, higher heart rates, worse pulmonary function, greater acidaemia and higher white cell counts) in acute physiology compared with patients with non-septic AKI [2]. Moreover, septic AKI is independently associated with higher odds of death and longer duration of hospitalization [2]. With the development of continuous veno-venous hemodiafiltration (CVVHDF) technique, a form of continuous renal replacement therapy (CRRT), the outcome of sepsis has been dramatically improved. CVVHDF can remove various cytokines from blood continuously and efficiently by using a polymethyl-methacrylate membrane hemofilter [3]. It is widely accepted today that cytokines play pivotal roles in the pathophysiology of severe sepsis and septic shock [4–6]. Therefore, it is critical to apply various CRRT techniques to treat critical illnesses, such as septic AKI in which humoral and cytokine responses play important roles.

However, it still remains unclear, which stage of AKI may be the optimal timing for CRRT. Several criteria have been used to define the timing of the initiation of CRRT, such as blood urea nitrogen (BUN) [7], urine output [8], time from admission to CRRT [9], and RIFLE (R, risk; I, injury; F, failure; L, loss; E, end stage of disease) [10]. However, there is a concern that most of these criteria may cause significant delay in initiating appropriate therapy [1]. Fortunately, the acute kidney injury network (AKIN) working group developed the evidence-based AKIN classification system for AKI [11]. This system proposed refinements to the RIFLE criteria. In particular, the AKIN system sought to increase the sensitivity of the RIFLE criteria by recommending that a smaller change in serum creatinine (Cr) ($\geq$26.2 μmol/L) be used as a threshold to define the presence of AKI and identify patients with stage 1 AKI.

This study aims to define the optimal timing for CRRT initiation for septic AKI based on AKIN classification and to identify the factors associated with patient outcomes.

Methods

All human studies have been approved by China Ethics Committee and performed in accordance with the ethical standards.

Patients and grouping

Septic patients were confirmed according to 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference when they have more than two of the following criteria: body temperature >38 or <36 °C; heart rate >90/min; hyperventilation evidenced by respiratory rate >20/min or $PaCO_2$ <32 mmHg; and WBC count >12,000 cells/μl or <4,000/μl [12]. The septic AKI is considered when septic patients had concomitant AKI, which diagnosed and staged according to the AKIN criteria in 2005: stage 1: Cr $\geq$26.4 μmol/l or >150–200 % from baseline and urine <0.5 ml/kg/h for more than 6 h; stage 2: Cr >200–300 % from baseline and urine <0.5 ml/kg/h for more than 12 h; stage 3: Cr >300 % from baseline or $\geq$354 μmol/l with an acute increase of $\geq$44 μmol/l and urine <0.3 ml/kg/h for 24 h or anuria for 12 h [11].

Septic AKI patients treated with CRRT or only standard therapy from November 15th, 2009 to December 31st, 2011, in a 22-bed intensive care unit (ICU) were enrolled in this retrospective study. Exclusion criteria included patients <12 years; patients with chronic renal illness or were terminally ill; patients with pre-admission CRRT or used to treatment with CRRT for non-renal indications;

patients underwent CRRT for <24 h; patients with an ICU stay of <72 h.

Then, patients in AKI stage 1, AKI stage 2 and AKI stage 3 group were further divided into two subgroups including CRRT group and control group based on whether they underwent CRRT treatment. The patients in control group were the septic patients had concomitant AKI, which was also diagnosed and staged according to the AKIN criteria in 2005, while they abandoned CRRT treatment for personal reasons.

Informed consent was waived because this study did not interfere with clinical decisions related to patient care, and there was no breach of privacy.

CRRT procedure

CRRT was performed with the Baxter system in the ICU. Bicarbonate-buffered solution was used with a replacement fluid amounting to 30–40 ml/kg/h, with a blood flow rate of 150–200 ml/min. Heparin or unfractionated heparin was used as anticoagulant in the treatment modalities. Dosage of heparin or unfractionated heparin was regulated according to the patient's blood coagulation state. Changes in blood and replacement fluid flow rates and dialysate composition as well as type of anticoagulant were dictated by the patients' clinical condition. The treatment was initiated by ICU physicians and then carried out by nurses. The ICU physicians were mainly responsible for the duration, mode and dose of CRRT treatment, constructing venous channel and observing the symptoms and vital signs of patients. Then machine was operated, and the vital signs of patients were recorded once hourly by the nurse.

Data collection

All the data were collected from ICU daily care nursing records. Laboratory data were extracted from electronic medical records. Data abstraction included demographics (gender, age, admission dates), CRRT data (time of onset, duration, blood anticoagulation, complications), cause of AKI, other system involvement, survival and renal recovery (independent from dialysis at discharge) status for the index hospitalization. Biochemistry data such as BUN, Cr, WBC and total fluid balances (including urine outputs) were recorded upon ICU admission. In addition, clinical parameters and severity scores, such as use and/or change in doses of vasopressor drugs, mean arterial pressure (MAP), Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were also collected.
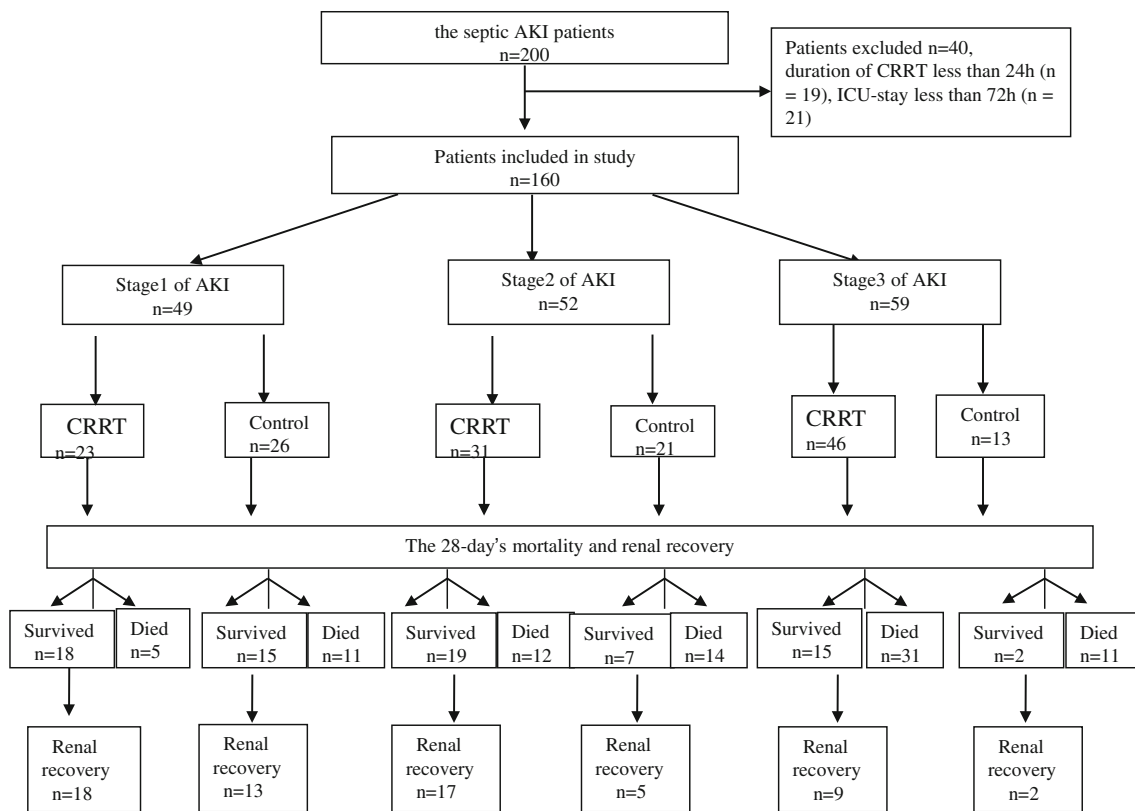
Fig. 1 Flow diagram of the clinical course, 28-day's prognosis and renal recovery of the septic AKI patients. Renal recovery defined as the absence of need for dialysis at time of hospital discharge. *CRRT* continuous renal replacement therapy, *AKI* acute kidney injury

Variable definitions

Organ function failure was defined when the SOFA score of an organ ≥3 points according to SOFA criteria [1]. CRRT time was the actual time for hemofiltration from the start to the end of CRRT in ICU. The renal function in admission was defined as the baseline renal function. For the patients undergoing CRRT, the assignment to an AKIN classification was decided by the patient's serum Cr or urine output at the start of CRRT. Similarly, the patients in control group were selected based on their serum Cr or urine output. Renal recovery was independent from dialysis at discharge. Renal recovery rate was defined as the ratio between the number of patients achieving renal recovery in survived patients and the total number of the survived patients.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as number and percent. The 28-day cumulative survival was calculated according to the Kaplan–Meier method. Univariate analyses including logistic regression analysis, Chi-square test and Fisher's exact test were applied to identify and select significant risk factors for the outcomes of death. Multivariate logistic regression analysis was performed to determine the most significant risk factors. P value <0.05 were considered statistically significant.

Results

A total of 200 patients were enrolled in this study, and 40 patients were excluded because duration of CRRT was <24 h ($n = 19$), or ICU stay was <72 h ($n = 21$). At last, a total of 160 eligible patients were selected in this study. Of these 160 patients, 49 patients were assigned to AKI stage 1 group (CRRT, $n = 23$; Control, $n = 26$), 52 patients were assigned to AKI stage 2 group (CRRT, $n = 31$; Control, $n = 21$), and 59 patients were assigned to AKI stage 3 group (CRRT, $n = 46$; Control, $n = 13$), respectively (Fig. 1).

The demographics of patient population and causes of AKI are summarized in Table 1. There was no significant difference in mean age and sex percentage between CRRT and control subgroup of each stage.

The baseline of BUN, Cr, urine output, WBC, MAP, APACHE II score and SOFA score also had no difference

in statistics. However, the 72-h MAP of stage 3 AKI was significantly lower in control subgroup than that in CRRT subgroup (90.8 ± 19.1 vs. 72.8 ± 17.3, $P < 0.01$). Vasopressor drug use was found to be higher in control subgroup compared with those in CRRT subgroup in stage 1 AKI and stage 3 AKI (46.2 vs. 21.7 % in stage 1 AKI and 84.6 vs. 50.0 % in stage 3 AKI, all $P < 0.05$). The positive bacteria of stage 1 AKI were significantly lower in the CRRT subgroup than that in the control subgroup (73.1 vs. 43.5 %, $P < 0.05$). For stage 1 AKI, no difference in ICU stay was identified between CRRT and control subgroup

($P = 0.172$) However, shorter ICU stay was found in CRRT subgroup compared with control subgroup for stage 2 AKI ($P = 0.045$). While longer ICU stay was observed in CRRT subgroup compared with control subgroup for stage 3 AKI ($P = 0.045$). Moreover, assessment of ventilation revealed that CRRT subgroup has shorter ventilation time compared with control group only in stage 2 AKI (stage 1, $P = 0.090$; stage 2, $P = 0.050$; stage 3, $P = 0.938$).

The 28-days mortality for all three stages of AKI is shown in Fig. 2. As anticipated, the mortality rate

Table 1 Baseline demographics and clinical characters for patients with septic AKI in different stages ($n = 160$)

	AKI stage 1		AKI stage 2		AKI stage 3	
	$n = 49$		$n = 52$		$n = 59$	
	CRRT group $n = 23$	Control group $n = 26$	CRRT group $n = 31$	Control group $n = 21$	CRRT group $n = 46$	Control group $n = 13$
Sex (male)	18 (78.3 %)	18 (69.2 %)	22 (71.0 %)	16 (76.2 %)	39 (84.9 %)	10 (76.9 %)
Age (years)	48.3 ± 15.3	54.7 ± 17.0	54.35 ± 20.5	61.0 ± 11.6	50.6 ± 19.5	55.4 ± 21.3
Baseline BUN (mmol/L)	11.4 ± 4.6	12.3 ± 5.5	17.7 ± 8.1	17.9 ± 10.2	23.5 ± 12.2	27.4 ± 13.1
Baseline creatinine (μmol/L)	149.5 ± 29.9	145.6 ± 26.6	199.5 ± 55.2	200.9 ± 42.2	394.3 ± 215.6	356.4 ± 226.2
Median urine output (mL)						
Day 1	2,278 ± 2,106	2,267 ± 1,345	1,512 ± 1,299	1,462 ± 814	1,207 ± 1,176	1,317 ± 1,459
Day 2	2,310 ± 1,760	2,329 ± 1,238	1,540 ± 1,149	1,510 ± 962	1,090 ± 1,259	1,112 ± 1,005
Day 3	2,385 ± 2,205	2,374 ± 1,217	1,939 ± 1,740	1,755 ± 900	1,122 ± 1,379	952 ± 824
Baseline WBC ($\times 10^9$/L)	11.6 ± 6.4	13.7 ± 7.6	13.1 ± 8.6	17.2 ± 15.2	16.7 ± 9.8	16.2 ± 7.6
MAP (mmHg)						
0 h	86.1 ± 21.6	82.4 ± 16.2	80.2 ± 21.3	90.6 ± 14.2	90.5 ± 19.2	78.8 ± 19.3
72 h later	86.7 ± 21.7	91.6 ± 17.8	84.4 ± 14.4	84.3 ± 15.1	90.8 ± 19.1**	72.8 ± 17.3
Vasopressor (%)	5 (21.7 %)*	12 (46.2 %)	19 (61.3 %)	11 (52.4 %)	23 (50.0 %)*	11 (84.6 %)
Bacteria (%)	10 (43.5 %)*	19 (73.1 %)	22 (71.0 %)	18 (85.7 %)	35 (76.1 %)	10 (83.3 %)
APACHE II score	12.9 ± 5.0	15.3 ± 4.2	19.0 ± 5.6	18.3 ± 3.7	21.8 ± 5.0	20.5 ± 3.2
SOFA score	7.6 ± 2.8	8.4 ± 2.3	9.3 ± 2.9	9.6 ± 1.5	10.0 ± 2.3	11.2 ± 1.8
ICU stay (days)	9.20 ± 5.20	11.31 ± 5.35	10.75 ± 5.39*	14.40 ± 6.60	14.65 ± 7.51*	8.17 ± 6.13
Ventilation time (h)	84.60 ± 168.34	165.29 ± 159.24	117.27 ± 107.28*	203.52 ± 173.52	153.88 ± 166.89	148.78 ± 176.38
Causes of disease						
Pneumonia	6	13	12	9	17	8
Abdominal infection	5	4	7	4	7	3
Trauma	3	4	5	4	4	0
Acute pancreatitis	5	2	3	1	3	0
Toxicosis	1	1	0	0	3	1
Epidemic hemorrhagic fever	1	0	0	0	3	0
Skin tissue infection	0	1	1	1	1	1
Viral encephalitis	0	0	1	1	3	0
Hepatopathy	1	1	1	1	3	0
Thermoplegia	1	0	1	0	0	0

MAP mean arterial pressure, *APACHE II scores* Acute Physiology and Chronic Health Evaluation II scores, *SOFA scores* Sequential Organ Failure Assessment scores

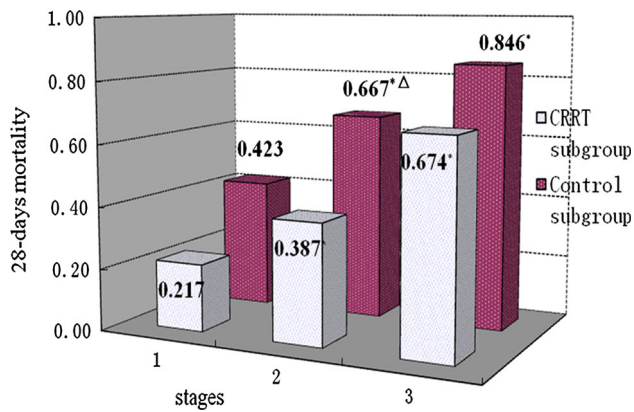* $P < 0.05$, ** $P < 0.01$, compared with control group for each stage

Fig. 2 Comparison of 28-day mortality between CRRT and control group. $^{\triangle}P < 0.05$ between CRRT group and control group in each stage, $*P < 0.05$ among three stages in CRRT group and control group

increased proportionally with AKIN stages whether patients receiving CRRT ($P = 0.001$) or not ($P = 0.029$). However, the mortality rate was reduced when patients were treated with CRRT at stage 2 AKI ($P = 0.048$). Therefore, it was concluded that the stage 2 AKI might be optimal timing for implementing CRRT.

Additionally, renal recovery, which was defined as independent from dialysis at discharge, was documented for 64/76 (84.2 %) of the surviving patients (48.1 % of total subjects included in study). We compared the renal recovery between CRRT group and control group of each stage and found no significant difference in three stages of AKI (Table 1).

Univariate analysis and multivariate logistic regression analysis were performed on factors impacting mortality (Tables 2 and 3). Univariate analysis revealed that age of older than 65 years, use of vasopressor, ventilator use, CRRT therapy, bacteria, urine output ≤500 ml and APACHE II ≥20 were all significantly associated with mortality (Table 2). Then, multivariate logistic regression analysis confirmed a significantly association of mortality and age of older than 65 years ($P = 0.013$) and CRRT therapy ($P = 0.033$; Table 3).

Discussion

Sepsis is the most common cause of AKI in critical illness, but there is limited information on timing of initiation of CRRT in patients with septic AKI. In this study, we conducted a large, observational, retrospective study to investigate the clinical outcomes that are associated with CRRT treatment in critically ill patients and demonstrated the optimal timing of CRRT for these patients. Our findings showed that the mean 28-day mortality was 42.3 % in stage

Table 2 Risk factors for mortality considered and analyzed using univariate analysis

Risk factors	Odds ratio	P value
Age (≥65 years)	9.978	0.002
MAP (<60 mmHg)	1.614	0.204
Use of vasopressor	6.827	0.009
Ventilator use	9.987	0.002
Oxygenation index (<100)	2.167	0.141
CRRT therapy	0.177	0.017
ALB at baseline (<25 g/L)	1.722	0.189
Total bilirubin (>34.2 μmol/L)	4.484	0.636
Creatinine at baseline (>240.5 μmol/L)	4.238	0.227
Plt at baseline (<100 × 10^9/L)	0.001	0.679
WBC at baseline (>10 × 10^9 or <4 × 10^9)	8.929	0.738
Bacteria (%)	7.490	0.006
Urine output		
Day 1 (≤500 ml)	16.915	<0.001
Day 2 (≤500 ml)	17.005	<0.001
Day 3 (≤500 ml)	14.471	<0.001
Lac (>2.0 mmol/L)	1.374	0.241
APACHE II scores (≥20)	5.001	0.025
SOFA scores (≥10)	3.061	0.080

Table 3 Odds ratio, 95 % CI, and P values for factors determined from multivariate logistic regression analysis of risk factors for mortality

Factors	Odds ratio	95 % CI	P value
Age (≥65 years)	4.943	(1.391, 17.558)	0.013
CRRT therapy	0.254	(0.072, 0.897)	0.033

CRRT continuous renal replacement therapy; *95 % CI* 95 % confidence interval

1 AKI, 66.7 % in stage 2 AKI and 84.6 % in stage 3 AKI, respectively, for patients in control group and that was 21.7, 38.7 and 67.4 %, respectively, for patients underwent CRRT. These results suggest that higher degree of AKIN classification is related to higher mortality. Similar trends for the association of AKI stage and hospital mortality rate were reported in a previous publication. Vencent et al. demonstrated that RIFLE class R, class I and class F had hospital mortality rates of 8.8, 11.4 and 26.3 %, respectively [13]. Moreover, CRRT group had lower 28-days mortality than that of control group at all three AKI stages. Therefore, CRRT is necessary for patients with septic AKI.

A multi-center prospective observational study showed that lower mortality was found in early dialysis group (RIFLE-0 or Risk) compared to late dialysis group (RIFLE-LD, RIFLE-Injury or Failure), suggesting that RIFLE-R stage of AKI may be optimal timing of CRRT initiation [14]. Additionally, Li et al. [15] also reported that prior to

RIFLE-F stage should be the optimal timing of initiating CRRT. However, the major limitation of these previous studies was the lack of information about control group (without dialysis) with the same disease. In this current study, we constructed CRRT group and control group of each stage of septic AKI and also examined additional thresholds of clinical, physiological and laboratory factors. Our results indicated that the significant differences in mortality, increase survival rate, ICU stay and ventilation time were only found at stage 2 AKI. Therefore, we speculated stage 2 AKI might be the optimal timing of CRRT initiation. Moreover, we found that age was an independent risk factor for prognosis, and CRRT was an important protecting factor for prognosis. So, it is highly recommended that old patients with septic AKI should accept CRRT when the renal function at stage 2 of AKI.

It needs to be emphasized that this investigation was carried out in a clinical setting. This leads to heterogeneity in our cohort, making the AKIN criteria useful. The data on the prognostic abilities of AKIN must, however, be seen in light of limitations of this single-center study and small number of participants. The higher mortality in the stage 3 AKI does not mean that AKIN can be used as a predictor of treatment with impunity. Moreover, we cannot extrapolate these data to all cases of AKI—this study focused on CRRT. It would have been interesting to study all patients with AKI, but we did not have that opportunity. We are currently using the AKIN criteria in a new project where all patients with septic AKI are included, with CRRT and without CRRT. Also, the results of this study may be affected by other factors such as CRRT <24 h, ICU stay <72 h or automatic discharge. A prospective multicenter clinical study of large sample is still required.

In conclusion, the mortality of patients with septic AKI is highly associated with AKIN classification and CRRT. Age was found to be an independent risk factor of 28-day mortality in septic AKI patients. More importantly, we found that stage 2 AKI may be optimal timing for initiating CRRT. Because of single-center study restriction and aforementioned limitations, the results of this study should be regarded as informative. A lager, randomized, multiple-center study is still warranted to investigate the appropriate timing of CRRT. What's more, other forms of renal replacement therapy also need to be evaluated in our further study.

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