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Original Article

Early initiation of continuous renal replacement therapy improves outcome in sepsis-associated acute kidney injury

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Abstract: Objective: To investigate the effect of initiation timing of Continuous Renal Replacement Therapy (CRRT) on prognosis in Sepsis-Associated Acute Kidney Injury (SAKI). Methods: A total of 113 SAKI patients receiving CRRT were stratified by initiation timing: early-stage (ES, ≤ 12 h; n = 51), intermediate-stage (IS, 12-24 h; n = 35), and advanced-stage (AS, > 24 h; n = 27). Organ function (SOFA score), inflammatory markers (C-reactive protein, CRP; procalcitonin, PCT), renal function (serum creatinine, SCr), clinical course (ICU stay, mechanical ventilation, CRRT duration), and 90-day survival were compared. Results: The AS Group showed the most severe multi-organ dysfunction at day 3, with higher SOFA scores (12 vs. 8 in ES, P = 0.037), BNP (809 vs. 361 pg/mL, P < 0.001), and INR (2.21 vs. 1.53, P < 0.001). Inflammation markers were also highest in AS (CRP: 92.81 mg/L; PCT: 4.25 ng/mL; P = 0.009 and P = 0.002). By day 5, SCr was significantly higher in AS (165.77 μmol/L) than ES (127.17 μmol/L, P = 0.004). The AS Group had longer ICU stays (12.5 d vs. 9.5 d, P = 0.031) and mechanical ventilation (8.5 vs. 5.5 d, *P* = 0.046), but shorter CRRT duration (130.5 vs. 145.6 h, *P* = 0.035). Although 90-day mortality did not differ statistically (ES 45.1% vs. AS 63.0%; *P* = 0.767), survival analysis showed AS had a 4.83-fold higher mortality risk than ES (HR = 4.83, *P* < 0.001). Conclusion: Early CRRT (≤ 12 h) improved organ function, enhanced inflammatory control, and reduced mortality risk, while delayed initiation (> 24 h) correlated with worse outcome.

Keywords: Sepsis, acute kidney injury, continuous renal replacement therapy, treatment timing, prognosis analysis

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Acute kidney injury (AKI) is characterized by rapid decline in renal function [2], with sepsis-associated AKI (SAKI) being the leading cause of AKI in intensive care units (ICUs), accounting for 40%-79% of all cases [3]. Patients with SAKI face substantially higher mortality rates and longer hospital stays compared to those with sepsis alone or AKI from other causes [4]. SAKI involves complex mechanisms including hemodynamic disturbances, microthrombosis, and immune activation [5, 6]. The 2021 International Guidelines for Management of Sepsis and Septic Shock recommend renal replacement therapy for septic acute kidney injury (AKI) [7]. Continuous renal replacement therapy (CRRT) effectively removes toxins, and corrects imbalances [8], and has become a cornerstone of supportive care for critically ill SAKI patients. However, the optimal timing for initiating CRRT remains one of the most controversial issues in critical care nephrology. Well-established absolute indications for initiating CRRT include severe AKI with hemodynamic instability, life-threatening fluid overload (e.g., acute pulmonary edema), refractory electrolyte or acid-base disturbances, or severe infections, all of which warrant immediate intervention. For critically ill AKI patients, the 2012 KDIGO guidelines suggest considering CRRT at AKI Stage 2 [9]. However, controversy persists regarding when to initiate CRRT in SAKI patients without these life-threatening conditions. This lack of a standardized, universally accepted definition has led to inconsistent and often contradictory findings in the literature, making it difficult to derive clear guidance for clinicians.

Therefore, we designed this study to address these gaps by systematically evaluating the

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effect of CRRT initiation timing, defined specifically as the time from ICU admission, on a comprehensive set of outcomes in a well-defined cohort of SAKI patients at KDIGO stage 2. The innovative aspect of our study lies in its detailed stratified analysis not only of survival but also of dynamic changes to organ function (e.g., SOFA score), inflammatory control (CRP, PCT), and renal recovery patterns, aiming to identify the "therapeutic window" for CRRT. We hypothesized that delayed CRRT initiation (> 24 hours) would be associated with a constellation of persistent organ failures and worse survival, and we sought to characterize the specific clinical phenotype of these high-risk patients. By providing clearer evidence on the relationship between timing and outcomes, this study aimed to offer a rational basis for clinical decision-making, with the potential to improve the prognosis of this vulnerable patient population.

Patients and methods

Study design and case selection

This retrospective study enrolled 113 SAKI patients (KDIGO stage 2 AKI) receiving CRRT (January 2022-December 2024). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Dongying People's Hospital (Approval No: 2024101502). Given the retrospective nature of this study, the requirement for written informed consent was waived by the ethics committee. All patient data were kept strictly confidential and anonymized for analysis.

The inclusion criteria were as follows: (1) Age > 18 years; (2) Sepsis (Sepsis-3.0 criteria [10]) with AKI requiring CRRT; (3) Kidney Disease Improving Global Outcomes (KDIGO) stage 2 AKI [10]: SCr increase 200%-300% within 48 h, or urine output < 0.5 mL/(kg·h) for ≥ 12 h; (4) First-time CRRT recipients.

The exclusion criteria included: (1) Malignancy, AIDS, chronic renal insufficiency, kidney transplantation, pregnancy; (2) Long-term maintenance hemodialysis; (3) Contraindications to CRRT; (4) Incomplete medical records.

Experimental grouping basis: 113 patients meeting stage 2 AKI criteria were stratified into three groups based on CRRT initiation timing: Early-stage group (ES Group): n = 51; Intermediate-stage group (IS Group): n = 35; Advanced-stage group (AS Group): n = 27.

Intervention: CRRT protocol

All patients received sepsis management per 2021 guidelines.

Conventional Therapy included: Early fluid resuscitation; Antimicrobial therapy; Hemodynamic management; Mechanical ventilation; Correction of fluid-electrolyte and acid-base imbalances; Glycemic control; Nutritional support; Multi-organ support as needed.

CRRT initiation timing: (1) ES Group: CRRT within 12 hours of ICU admission; (2) IS Group: CRRT between 12-24 hours after ICU admission; (3) AS Group: CRRT > 24 hours post-ICU admission.

CRRT procedure: Vascular access: Double-lumen catheters (jugular/femoral); Mode: Venovenous hemofiltration (CVVH); Equipment: Dialysis machine: Gambro Prismaflex® (Sweden); Filter: Prismaflex ST100 Set; Membrane: AN-69ST (surface area: 1.0 m^2); Adjunctive Therapies (case-dependent): Plasma exchange/Hemoperfusion; Parameters: Blood flow: 200-220 mL/min; Replacement fluid: 20-30 mL/(kg·h); Anticoagulation: Low-molecular-weight heparin (non-bleeding risk): Target APTT 50-70 s; Regional citrate anticoagulation (bleeding risk): Citrate dose titrated to ionized calcium; Treatment Schedule: Initial session: > 72 hours; Subsequent sessions: Daily or every other day (8-12 hours/session).

Data collection and outcome measures

Data were extracted from electronic medical records: (1) General data: gender, age, infection site (pulmonary, intra-abdominal, biliary tract, urinary tract, skin/soft tissue, others), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, urine output, serum creatinine (SCr), mean arterial pressure (MAP), and vasoactive drug dose prior to CRRT; (2) Organ function at 3 days post-CRRT: SOFA score, oxygenation index (PaO_2/FiO_2 ratio, P/F ratio), body temperature, hemoglobin (Hb), platelet count (PLT), B-type natriuretic peptide

(BNP), international normalized ratio (INR), MAP, and lactate; (3) Renal function: SCr pre-CRRT and at 24 h, 3 d, and 5 d post-CRRT; (4) Infection markers: white blood cell count (WBC), procalcitonin (PCT), and C-reactive protein (CRP) pre-CRRT and at 3 d post-CRRT; (5) Prognostic outcomes: Intensive Care Unit (ICU) length of stay (LOS), mechanical ventilation duration (MV Duration), CRRT duration, and 90-day mortality (followed until death or 90 days).

Statistical analysis

SPSS 26.0 software (IBM Corp.) was used. Categorical variables were expressed as frequencies (%) and compared by χ^2 or Fisher's exact test. The normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation, while non-normally distributed or heteroscedastic data were expressed as median (interquartile range, IQR). For comparisons among the three groups (ES, IS, AS): Continuous variables with normal distribution and homogeneous variance (verified by Levene's test) were analyzed by one-way analysis of variance (ANOVA). If the ANOVA was significant, post-hoc pairwise comparisons were performed using the Bonferroni test. Non-normally distributed or heteroscedastic continuous variables were compared using the Kruskal-Wallis H test. If the Kruskal-Wallis test was significant, post-hoc pairwise comparisons were conducted using the Dunn's test with Bonferroni correction. For comparisons of continuous variables between two time points within the same group (e.g., pre- and post-treatment levels of WBC, CRP, PCT), the paired-samples t-test was used for normally distributed data, and the Wilcoxon signed-rank test was used for non-normally distributed data. Survival rates were analyzed with Kaplan-Meier curves, and group differences were assessed by the log-rank test. Cox proportional hazards regression models were used to quantify hazard ratios (HR) with 95% confidence intervals (CI). A two-sided $P < 0.05$ indicated statistical significance.

Results

Results of comparison of general patient data on admission

A comparison of the general data of patients in the three groups at admission showed no significant differences ($P > 0.05$) between the ES Group, IS Group, and AS Group in terms of age, gender, infection site, APACHE II score, SOFA score, mean arterial pressure, creatinine, urine output, or vasoactive drug dose. This indicated that the patients in the three groups were comparable, as shown in **Table 1**.

Results of organ function at day 3 post-CRRT

A comparison of organ function results among the three groups after 3 days of CRRT treatment is shown in **Table 2**. There were no significant differences ($P > 0.05$) in body temperature or lactate levels between the groups. However, significant differences ($P < 0.05$) were observed among the three groups for SOFA score, P/F ratio, Hb, PLT, BNP, INR, and MAP. The AS group exhibited the most severe multi-organ dysfunction, followed by the IS and then the ES group. SOFA scores increased progressively across the groups (ES: 8, IS: 9, AS: 12; $P = 0.037$). Similarly, BNP and INR levels were highest in the AS Group (809 pg/mL and 2.21, respectively), intermediate in the IS Group (532 pg/mL and 1.72), and lowest in the ES Group (361 pg/mL and 1.53) (both $P < 0.001$). Conversely, P/F ratios were lowest in the AS Group, intermediate in the IS Group, and highest in the ES Group (all $P < 0.05$). For Hb and PLT levels, the AS Group was significantly lower than both the ES and IS groups (both $P < 0.05$), which did not differ from each other. Post-hoc analyses for the key indexes are detailed as follows: For SOFA score, the AS Group was significantly higher than both the ES and IS Groups (both $P < 0.05$), while the difference between ES and IS groups was not significant. Similarly, for BNP and INR, levels in the AS Group were significantly elevated compared to both the ES and IS groups (all $P < 0.001$), and the IS Group also had higher values than the ES Group ($P < 0.05$ for both). Conversely, P/F ratios showed a stepwise decrease from the ES to the AS group (both $P < 0.05$).

Results of changes in serum creatinine levels before and after CRRT initiation in the three groups

Significant differences existed in baseline SCr levels before treatment among patients at different stages ($P < 0.05$). The AS Group had the highest median value, significantly exceeding those of the IS and ES groups. After receiving

Table 1. Comparison of general patient data on admission by group

Variable	ES Group (n = 51)	IS Group (n = 35)	AS Group (n = 27)	H/χ^2	P
Age (years)	53.45 (45.03, 60.79)	51.49 (45.15, 58.85)	55.17 (47.12, 62.32)	5.412	0.068
Male gender	36 (70.59%)	23 (65.71%)	19 (74.07%)	0.340	0.712
Infection site				N/A	0.992
Pulmonary infection	16 (31.37%)	10 (28.57%)	8 (29.63%)		
Abdominal infection	13 (25.49%)	11 (31.43%)	9 (33.33%)		
Biliary infection	10 (19.61%)	6 (17.14%)	5 (18.52%)		
Urinary infection	5 (9.80%)	3 (8.57%)	1 (3.70%)		
Skin/soft tissue	2 (3.92%)	1 (2.86%)	2 (7.41%)		
Other sites	5 (9.80%)	4 (11.43%)	2 (7.41%)		
APACHEII score	32 (29, 35)	31 (29, 35)	30 (28, 35)	5.254	0.073
SOFA score	19 (17, 22)	18 (14, 22)	19 (14, 23)	5.781	0.054
Mean arterial pressure (mmHg)	81 (68, 102)	79 (70, 98)	85 (71, 105)	5.091	0.078
Creatinine (μmol/L)	223.51 (163.97, 283.15)	222.35 (175.65, 297.53)	234.29 (170.69, 291.23)	5.698	0.057
Urine output [mL/(kg × h)]	0.07 (0.02, 0.55)	0.09 (0.05, 0.63)	0.09 (0.03, 0.64)	1.263	0.531
Vasoactive drug dose (μg/kg/min)	1.50 (0.20, 2.40)	1.50 (0.15, 1.90)	1.40 (0.40, 2.40)	4.769	0.093

Note: ES Group, Early-stage Group; IS Group, Intermediate-stage Group; AS Group, Advanced-stage Group; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment. Data presented as Median (Interquartile Range, IQR) or n (%). H = Kruskal-Wallis H test statistic; χ^2 = Chi-square statistic; Fisher's = Fisher's Exact Test was used for the overall infection site comparison due to small expected cell counts.

Table 2. Comparison of organ function after 3 days of CRRT treatment by group

Variable	ES Group (n = 51)	IS Group (n = 35)	AS Group (n = 27)	H	P
SOFA	8 (4, 11)[a]	9 (5, 13)[a]	12 (9, 16)[b]	4.156	0.037
P/F (mmHg)	289 (220, 328)[a]	220 (194, 281)[b]	183 (121, 257)[c]	17.035	< 0.001
Temperature (°C)	37.1 (36.8, 38.4)	37.4 (36.6, 38.5)	37.5 (36.9, 38.7)	0.079	0.913
Hb (g/dL)	8.8 (7.8, 9.5)[a]	9.3 (7.7, 10.3)[a]	7.9 (6.5, 8.9)[b]	3.571	0.016
PLT (10^9/L)	135 (68, 221)[a]	130 (75, 206)[a]	115 (56, 198)[b]	5.615	0.007
BNP (pg/mL)	361 (226, 451)[a]	532 (367, 652)[b]	809 (465, 955)[c]	15.042	< 0.001
INR	1.53 (0.91, 2.04)[a]	1.72 (1.12, 2.18)[b]	2.21 (1.85, 2.44)[c]	12.934	< 0.001
MAP (mmHg)	85 (63, 123)a	88 (68, 125)[a]	89 (73, 131)[b]	4.066	0.019
Lactate (mmol/L)	1.58 (1.32, 1.73)	1.65 (1.41, 1.76)	1.77 (1.53, 1.82)	2.513	0.349

Note: ES Group, Early-stage Group; IS Group, Intermediate-stage Group; AS Group, Advanced-stage Group; P/F, PaO_2/FiO_2 ratio (Oxygenation Index); Hb, Hemoglobin; PLT, Platelet count; BNP, B-type natriuretic peptide; INR, International Normalized Ratio; MAP, Mean Arterial Pressure; CRRT, Continuous Renal Replacement Therapy; SOFA, Sequential Organ Failure Assessment; Data presented as Median (Interquartile Range, IQR). Different superscript letters (a, b, c) indicate the results of post-hoc pairwise comparisons conducted after a significant Kruskal-Wallis H test. Groups that share the same letter are not statistically different from each other ($P \geq 0.05$), whereas groups with different letters are significantly different ($P < 0.05$). Letters are assigned in alphabetical order from the group with the lowest median value (a) to the highest (c), where applicable.

treatment, SCr levels significantly decreased over time in all three groups ($P < 0.05$ for the Friedman test within each group, with post-hoc Wilcoxon signed-rank tests confirming significant reductions from baseline to each subsequent time point). At 24 hours post-treatment, significant differences between groups remained ($P < 0.05$), with the AS Group exhibiting the highest levels. Notably, by day 3 post-treatment, the SCr levels of patients in the three groups converged, showing no significant inter-group differences ($P > 0.05$). However, by day 5 post-treatment, significant inter-group differences re-emerged ($P < 0.05$). The SCr level in the AS Group was significantly higher than in both the ES and IS groups, while the levels in the ES and IS groups were similar at this point. As shown in **Table 3**, inter-group differences in SCr levels were significant at all measured time points: before CRRT, at 24 hours, and at 5 days post-treatment (all $P < 0.05$), with the exception of day 3 ($P = 0.063$). Post-hoc tests for the significant time points revealed that before treatment and at 24 hours, the AS Group had significantly higher SCr than both the ES and IS groups (all $P < 0.001$), and the IS Group was also higher than the ES Group ($P < 0.05$). At day 5, the AS group's SCr remained significantly

Table 3. Changes in serum creatinine levels at different time points by group

SCr (μmol/L)	ES Group (n = 51)	IS Group (n = 35)	AS Group (n = 27)	H	P
Before treatment	234.13 (175.26, 296.85)[a]	259.13 (193.65, 317.53)[b]	334.15 (283.19, 379.32)[c]	35.034	< 0.001
24 h post-tx	191.53 (132.54, 251.23)[a]	225.14 (165.67, 285.75)[b]	273.13 (197.51, 331.56)[c]	17.193	< 0.001
3 days post-tx	175.17 (122.55, 210.31)[a]	178.53 (131.16, 211.54)[a]	176.63 (128.57, 209.15)[a]	3.504	0.063
5 days post-tx	127.17 (103.51, 149.18)[a]	135.09 (117.25, 151.63)[a]	165.77 (101.53, 209.15)[b]	5.634	0.004
$H_{within\ group}$	38.193	42.138	55.621		
$P_{within\ group}$	< 0.001	< 0.001	< 0.001		

Note: ES Group, Early-stage Group; IS Group, Intermediate-stage Group; AS Group, Advanced-stage Group; SCr, Serum Creatinine; tx, treatment. Data presented as Median (Interquartile Range, IQR). Different superscript letters (a, b, c) indicate the results of post-hoc pairwise comparisons conducted after a significant Kruskal-Wallis H test. Groups that share the same letter are not statistically different from each other ($P \geq 0.05$), whereas groups with different letters are significantly different ($P < 0.05$). Letters are assigned in alphabetical order from the group with the lowest median value (a) to the highest (c), where applicable.

Table 4. Changes in infection markers by group

Infection Marker	Time	ES Group (n = 51)	IS Group (n = 35)	AS Group (n = 27)	H	P
WBC (10^9/L)	Pre-treatment	15.23 (11.07, 18.35)	15.88 (11.64, 19.01)	16.29 (12.01, 20.63)	1.845	0.093
	Post-tx (3 days)	9.65 (8.53, 11.66)[*]	10.75 (7.65, 11.96)[*]	11.34 (7.84, 12.09)[*]	0.936	0.257
CRP (mg/L)	Pre-treatment	213.65 (195.35, 236.34)[a]	196.15 (183.53, 233.56)[a]	205.33 (189.16, 236.16)[a]	1.534	0.128
	Post-tx (3 days)	57.15 (40.03, 75.35)[a,*]	75.13 (51.23, 106.01)[b,*]	92.81 (65.29, 120.65)[c,*]	6.945	0.009
PCT (ng/mL)	Pre-treatment	3.63 (1.25, 9.16)[a]	5.63 (2.97, 10.39)[b]	8.91 (3.67, 13.46)[c]	8.157	< 0.001
	Post-tx (3 days)	2.73 (1.05, 4.19)[a,*]	3.08 (1.54, 6.44)[b,*]	4.25 (2.03, 6.97)[c,*]	7.751	0.002

Note: ES Group, Early-stage Group; IS Group, Intermediate-stage Group; AS Group, Advanced-stage Group; WBC, White Blood Cell count; CRP, C-Reactive Protein; PCT, Procalcitonin; tx, Treatment (CRRT). Data presented as Median (Interquartile Range, IQR). Different superscript letters (a, b, c) indicate significant intergroup differences at the same time point ($P < 0.05$) based on post-hoc pairwise comparisons after a significant Kruskal-Wallis H test. Groups sharing the same letter are not significantly different; groups with different letters are significantly different. Letters are assigned in alphabetical order from the group with the lowest median value (a) to the highest (c), where applicable. Asterisk (*) indicates a statistically significant difference ($P < 0.05$) compared to the pre-treatment value within the same group for that specific marker.

higher than both the ES and IS groups (both $P < 0.01$), but no difference was found between ES and IS groups.

Results of changes in infection markers after CRRT initiation

Three days after initiating CRRT treatment, WBC, CRP, and PCT levels decreased compared to pre-treatment levels in all groups. Inter-group comparisons showed that WBC levels at 3 days post-treatment did not differ significantly among the three groups ($P > 0.05$). However, significant differences were observed between the groups for CRP and PCT levels (CRP: $H = 6.945$, $P = 0.009$; PCT: $H = 9.851$, $P = 0.002$). Specifically, post-hoc analysis confirmed that both CRP and PCT levels in the AS Group were significantly higher than those in both the ES and IS groups ($P < 0.01$ for AS vs. ES, and AS vs. IS). Additionally, the IS Group had significantly higher CRP and PCT levels than the ES Group ($P < 0.05$). It is noteworthy that before treatment, only PCT showed a significant baseline difference between the groups ($P < 0.05$), with the AS Group having the highest level. This suggested that inflammation control in AS Group might be less optimal compared to the ES and IS groups. The higher baseline PCT level in AS Group also reflects a heavier initial infection burden. Furthermore, within each group, significant differences ($P < 0.05$) were found when comparing pre-treatment levels of WBC, CRP, and PCT to their respective levels at 3 days post-CRRT treatment, as determined by the Wilcoxon signed-rank test (for non-normally distributed CRP and PCT) and paired t-test (for normally distributed WBC) (all $P < 0.05$), as shown in **Table 4**.

Results of treatment course analysis in patients initiating CRRT

Analysis of the treatment course across the groups revealed significant differences ($P < 0.05$) in ICU LOS, MV duration, and CRRT duration of therapy among the three groups. Patients in the AS Group had significantly longer ICU LOS and MV duration than those in both the ES Group and the IS Group (AS Group > IS Group > ES Group). Conversely, the duration of CRRT therapy was longest in the ES Group and shortest in the AS Group, with the IS Group being intermediate and not significantly differ-

Table 5. Analysis of treatment course by group

Time	ES Group (n = 51)	IS Group (n = 35)	AS Group (n = 27)	H	P
ICU LOS (d)	9.5 (5.5, 14.5)[a]	11.5 (8.5, 19.0)[b]	12.5 (8.5, 20.5)[b]	4.351	0.031
MV Duration (d)	5.5 (4.0, 8.5)[a]	7.0 (4.0, 11.5)[b]	8.5 (5.5, 12.0)[b]	3.167	0.046
CRRT Duration (h)	145.6 (103.5, 201.5)[a]	137.5 (100.0, 191.5)[a]	130.5 (95.5, 189.5)[b]	4.035	0.035

Note: ES Group, Early-stage Group; IS Group, Intermediate-stage Group; AS Group, Advanced-stage Group; ICU LOS, Intensive Care Unit Length of Stay; MV, Mechanical Ventilation; CRRT, Continuous Renal Replacement Therapy; Data presented as Median (Interquartile Range, IQR). Different superscript letters (a, b) indicate the results of post-hoc pairwise comparisons conducted after a significant Kruskal-Wallis H test. Groups that share the same letter are not statistically different from each other ($P \geq 0.05$), whereas groups with different letters are significantly different ($P < 0.05$). Letters are assigned in alphabetical order from the group with the lowest median value (a) to the highest (b), where applicable.

Table 6. Comparison of mortality rates by group

Time Point	ES Group (n = 51)	IS Group (n = 35)	AS Group (n = 27)	χ^2	P
Death within 2 weeks	15 (29.41%)	14 (40.00%)	12 (44.44%)	2.023	0.364
Death within 28 days	18 (35.29%)	16 (45.71%)	13 (48.15%)	1.138	0.566
Death within 60 days	21 (41.18%)	17 (48.57%)	14 (51.85%)	0.588	0.745
Death within 90 days	23 (45.10%)	19 (54.29%)	17 (62.96%)	0.530	0.767

Note: ES Group, Early-stage Group; IS Group, Intermediate-stage Group; AS Group, Advanced-stage Group; χ^2, Chi-square statistic.

ent from either, as shown in **Table 5**. *Post-hoc* pairwise comparisons indicated that for ICU LOS and MV duration, the AS Group was significantly longer than the ES Group ($P < 0.01$), and the IS Group was also longer than the ES Group ($P < 0.05$). For CRRT duration, the ES group received significantly longer therapy than the AS group ($P < 0.05$), while the IS group did not differ significantly from either.

Results of mortality and survival analysis in patients initiating CRRT

A comparison of mortality rates among the three groups revealed that the ES Group consistently had the lowest mortality rates, while the AS Group consistently had the highest mortality rates at all measured time points: within 2 weeks, 28 days, 60 days, and 90 days. However, no significant differences were found between the groups at any of these time points ($P > 0.05$ for all), as shown in **Table 6**.

Survival curve analysis, however, revealed significant differences in survival probability among the three groups ($\chi^2 = 125.853$, df = 2, $P < 0.001$). This indicated that the timing of CRRT initiation significantly affected patient survival. The characteristics of the survival curves (**Figure 1**) demonstrate this: the survival curve for the ES Group was positioned highest and declined most slowly, indicating the best prognosis (highest survival rate) among the three groups. The survival curve for the IS Group was positioned in the middle and declined at a moderate rate, indicating an intermediate prognosis. The survival curve for the AS Group was positioned lowest and declined rapidly early on, indicating the worst prognosis (highest risk of death) among the three groups.

Quantification using Cox proportional hazards regression models confirmed significant differences in survival probability between every pair of groups (**Table 7**). The hazard of death increased stepwise with delayed CRRT treatment initiation time. AS patients carried a 4.83-times higher risk of death compared to ES patients (95% CI: 3.2-7.3; $P < 0.001$). IS patients carried a 2.15-times higher risk of death compared to ES patients (95% CI: 1.5-3.1; $P = 0.003$). AS patients carried a 2.25-times higher risk of death compared to IS patients (95% CI: 1.6-3.2; $P < 0.001$). These results demonstrate that the timing of CRRT initiation served as a crucial prognostic indicator. Later initiation of CRRT therapy was associated with progressively worse survival outcomes.

Discussion

The optimal timing for initiating CRRT in SAKI remains a significant clinical dilemma, primarily due to the lack of a standardized definition for

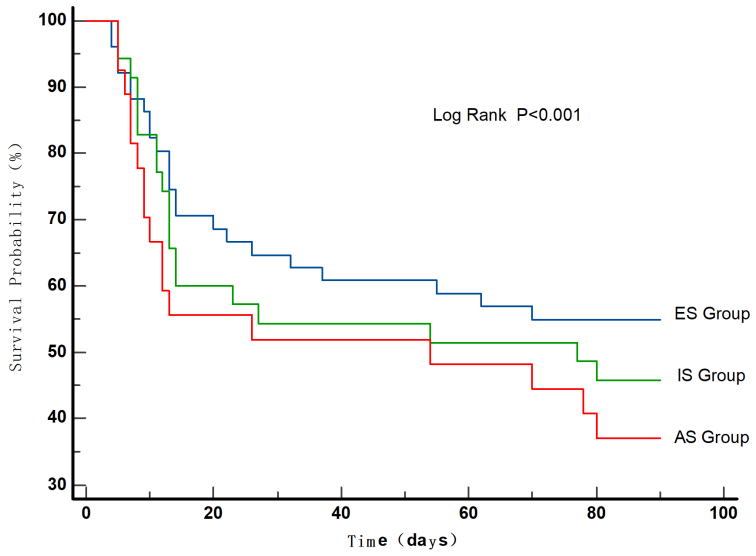

Figure 1. Kaplan-Meier survival curves of the three groups of patients.

Table 7. Quantification of hazard ratios

Comparison	HR (95% CI)	P
AS vs ES	4.83 (3.2-7.3)	< 0.001
IS vs ES	2.15 (1.5-3.1)	0.003
AS vs IS	2.25 (1.6-3.2)	< 0.001

Note: ES, Early-stage Group; IS, Intermediate-stage Group; AS, Advanced-stage Group; HR, Hazard Ratio; CI, Confidence Interval.

"early" versus "late" initiation [11]. Our study aimed to address this gap by evaluating CRRT timing based on the objective metric of hours from ICU admission. The key finding was that delayed CRRT initiation was strongly associated with worsened clinical outcome, including more severe organ dysfunction, impaired inflammatory control, and a substantially increased risk of mortality, compared to early intervention.

Our results both corroborate and refine the existing body of evidence. The finding that earlier CRRT is beneficial aligns with several previous studies. For instance, a large randomized controlled trial by Barbar et al. demonstrated a survival benefit with an "early" strategy, although their definition (initiation within 12 hours of meeting KDIGO stage 3 criteria) differs from our stratification based on ICU admission time at KDIGO stage 2 [8]. This similarity in conclusion despite differing definitions underscores the potential robustness of the "earlier is better" principle. Conversely, other meta-analyses have concluded no significant mortality difference, a discrepancy often attributed to the profound heterogeneity in timing definitions across included trials [12, 13]. Recent studies further suggest that phenotype-driven timing may be more relevant than a fixed time window [14, 15]. Our study helps to cut through this heterogeneity by providing clear, time-stratified data and adds value by detailing the associated differential trajectories in organ function and inflammation, which many previous reports lacked.

This study provides critical evidence supporting earlier intervention. Although the 90-day crude mortality showed no statistical difference, survival analysis demonstrated a significantly and progressively higher mortality risk with delayed CRRT initiation. This suggests that survival analysis may be a more sensitive metric for evaluating the effect of timing in this context, potentially obscured in crude rate comparisons by sample size limitations or competing early risks.

In this study, patients with delayed CRRT exhibited a distinct and severe clinical phenotype by day 3 post-treatment, characterized by a triad of interrelated dysfunctions [16, 17]: 1) Coupled Cardiopulmonary Failure, evidenced by impaired oxygenation alongside elevated cardiac stress markers. 2) Coagulopathy-Hematologic Dysfunction, indicated by concurrent abnormalities in coagulation and platelet counts. 3) Sustained Systemic Inflammation, with persistently high inflammatory markers and SOFA scores. The emergence of this triad likely stems from delayed CRRT missing the critical window for early inflammatory cytokine clearance, resulting in inflammatory mediator accumulation that exacerbates endothelial damage and organ hypoperfusion [18]. This persistent inflammatory milieu not only causes direct tissue injury but may also induce a state of immunoparalysis in later sepsis phases. Recent mechanistic studies have shown that during late-stage sepsis, key immune receptors such as CX3CR1 on monocytes/macrophages undergo TLR4-dependent internalization, leading to im-

paired immune cell responsiveness and a failure to mount an adequate defense against secondary challenges [19]. This immunodeficient state could explain why our delayed CRRT group, burdened with higher inflammatory markers, showed a more fragile recovery and higher mortality risk-they may have been less capable of resolving the ongoing infection due to concurrent immune dysfunction. This aligns with and extends the "SAKI dual-hit" (ischemia + inflammation) pathophysiology by incorporating the dimension of acquired immune suppression [8].

Furthermore, we observed a notable pattern in renal recovery. While serum creatinine levels converged across groups at day 3, patients with delayed CRRT showed a significant rebound in creatinine by day 5, indicating a more fragile and incomplete renal recovery. This phenomenon suggests that delayed initiation may heighten the fragility of renal function recovery. Potential underlying mechanisms include: 1) Re-injury of renal tubular epithelial cells: delayed clearance of inflammatory mediators and uremic toxins may sustain intrarenal oxidative stress and apoptotic signaling, hampering tubular repair and promoting secondary injury; 2) Occult volume overload: reflected by elevated cardiac stress markers, delayed CRRT may aggravate renal interstitial edema, thereby compressing the tubular microcirculation and perpetuating an "edema-ischemia" cycle; 3) Inflammation-coagulation vicious cycle: concomitant coagulation abnormalities and thrombocytopenia suggest microthrombus formation and consumptive coagulopathy, which can exacerbate local ischemia and impede renal recovery; therefore, delayed CRRT in SAKI patients not only increases early mortality risk but may also compromise sustainable renal functional recovery, necessitating clinical vigilance for post-treatment creatinine "pseudodecline" followed by rebound alongside dynamic monitoring of volume and inflammatory indicators. Recent experimental studies also highlight the role of mitochondrial dysfunction and endothelial injury in delayed CRRT settings [20, 21].

This study found no significant difference in 90-day mortality among the three patient groups, yet survival analysis revealed significantly stratified survival probabilities, with the highest risk in the delayed-initiation group. This apparent contradiction may stem from short-term events obscuring long-term risk, as suggested by the steeper early decline in the survival curve of the delayed group, with curves converging later; additionally, the limited sample size, especially in the delayed group, may have reduced statistical power to detect differences, underscoring the need for validation in larger cohorts. The study further observed that the AS Group had significantly longer ICU stays and mechanical ventilation durations, yet paradoxically the shortest CRRT duration. This phenomenon may reflect premature death or treatment discontinuation due to multi-organ failure in these patients, which shortens the actual course of CRRT. Alternatively, earlier initiation may allow for longer transitional support due to better renal recovery. These results suggest that comparing CRRT duration alone may be misleading and should be interpreted alongside clinical outcomes.

This study has several limitations. Its retrospective single-center design may have introduced selection bias; and the relatively small sample size, particularly in the delayed-initiation group, may have limited the generalizability and precision of the findings. Collectively, these findings suggest that CRRT should be initiated within 12 hours after stage 2 AKI diagnosis in SAKI patients, especially in those with high inflammatory burden, cardiac dysfunction or coagulopathy. Dynamic monitoring of biomarkers such as BNP, INR, and CRP is recommended, with consideration for CRRT initiation if any show deterioration within 12 hours. Future studies should validate this biomarker triad as an indicator for timely intervention and explore the potential of combined extracorporeal support strategies in high-risk patients.

This study provides important evidence for individualized decision-making regarding CRRT timing in SAKI patients, yet future research should deepen exploration in multiple dimensions: First, developing integrated predictive models that combine dynamic biomarkers, genomic profiles, and real-time physiological data to guide CRRT initiation in a more phenotype-driven rather than empirical manner; Second, elucidating the mechanisms through which delayed CRRT aggravates renal tubular injury and mitochondrial dysfunction, and exploring targeted pharmacotherapies that could be combined with CRRT to interrupt the vicious cycle of kidney damage; Third, assessing the rescue

potential of advanced extracorporeal support modalities [22] in high-risk patients with delayed treatment; Fourth, conducting large, multicenter prospective studies and dedicated randomized trials to compare early-goal-directed with monitoring-guided CRRT strategies, thereby generating high-level evidence for guideline refinement. Only through this integrated approach-mechanistic exploration, technological innovation, and clinical validation-can we ultimately optimize CRRT decision pathways for SAKI patients and improve their long-term survival and renal functional recovery outcome.

Conclusion

The timing of CRRT initiation was significantly associated with outcome in SAKI patients. Early CRRT intervention (≤ 12 h) was associated with improved organ function, better inflammation control, shorter ICU and mechanical ventilation duration, and significantly reduces mortality risk. Conversely, delayed treatment (> 24 h) correlated with persistent multi- organ dysfunction- including cardiopulmonary coupling failure, coagulopathy- hematologic disturbances, and systemic inflammation- and worse survival.

Disclosure of conflict of interest

None.

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