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Original Article
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Impact of Early Continuous Kidney Replacement Therapy in Patients With Sepsis-Associated Acute Kidney Injury: An Analysis of the MIMIC-IV Database

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ABSTRACT

Background: Renal replacement therapy (RRT) is an important treatment option for sepsis-associated acute kidney injury (AKI); however, the optimal timing for its initiation remains controversial. Herein, we investigated the clinical outcomes of early continuous kidney replacement therapy (CKRT), defined as CKRT initiation within 6 hours of sepsis-associated AKI onset, which was earlier than the initiation time defined in previous studies.
Methods: We used clinical data sourced from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. This study included patients aged ≥ 18 years who met the sepsis diagnostic criteria and received CKRT because of stage 2 or 3 AKI. Early and late CKRTs were defined as CKRT initiation within 6 hours and after 6 hours of the development of sepsis-associated AKI, respectively.
Results: Of the 33,236 patients diagnosed with sepsis, 553 underwent CKRT for sepsis-associated AKI. After excluding cases of early mortality and patients with a dialysis history, 45 and 334 patients were included in the early and late CKRT groups, respectively. After propensity score matching, the 28-day mortality rate was significantly lower in the early CKRT group than in the late CKRT group (26.7% vs. 43.9%, $P = 0.035$). The early CKRT group also had a significantly greater number of days free of mechanical ventilation (median, 19; interquartile range [IQR], 3–25) and vasopressor administration (median, 21; IQR, 5–26) than the late CKRT group did (median, 10.5; IQR, 0–23; $P = 0.037$ and median, 13.5; IQR, 0–25; $P = 0.028$, respectively). The Kaplan–Meier curve also showed that early CKRT initiation was associated with an improved 28-day mortality rate (log-rank test, $P = 0.040$). In contrast, there was no significant difference in the 28-day mortality between patients who started CKRT within 12 hours and those who did not (log-rank test, $P = 0.237$).
Conclusion: Early CKRT initiation improved the survival of patients with sepsis-associated AKI. Initiation of CKRT should be considered as early as possible after sepsis-associated AKI onset, preferably within 6 hours.

Keywords: Renal Replacement Therapy; Acute Kidney Injury; Sepsis; Mortality

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Disclosure

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Author Contributions

Conceptualization: Oh HJ, Ku NS. Data curation: Lee Y. Formal analysis: Lee Y. Supervision: Oh HJ, Ku NS. Visualization: Lee Y. Writing - original draft: Lee Y. Writing - review & editing: Lee Y, Seo JH, Seong J, Ahn SM, Han M, Lee JA, Kim JH, Ahn JY, Jeong SJ, Choi JY, Yeom JS, Oh HJ, Ku NS.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection; it remains a global concern because of its high incidence and risk of death.[1,2] Acute kidney injury (AKI) is a common complication of sepsis that occurs in 51% of patients with septic shock.[3] Despite advances in sepsis treatment, the mortality rate of sepsis-associated AKI is substantial, at 30–60%.[4-7] Moreover, sepsis-associated AKI has high morbidity rates, with 10–30% of survivors depending on dialysis at hospital discharge and 80% progressing to chronic kidney disease stage 3 or higher.[8]

Renal replacement therapy (RRT) is an important treatment option for sepsis-associated AKI; however, the optimal timing of initiation remains controversial. Several randomized controlled trials have been conducted to compare an early strategy with a delayed strategy for the initiation of RRT but have produced conflicting results.[9-12] In the Early vs Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury (ELAIN) trial, early RRT initiation reduced 90-day mortality, compared with delayed RRT, with an absolute risk reduction of 15.4%.[10] In contrast, the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial found no significant difference in mortality between the early and delayed RRT initiation groups.[11] However, all randomized controlled trials used different criteria for early and delayed RRT, making it difficult to reach a robust conclusion.

In patients with sepsis-associated AKI, RRT can theoretically alleviate the dysregulated host response by removing inflammatory cytokines.[13] Sepsis is characterized by an initial pro-inflammatory response followed by an anti-inflammatory reaction.[14] The removal of inflammatory cytokines during the proinflammatory phase, which is the initial stage of sepsis, can potentially alter the clinical course.[15] However, the effectiveness of early RRT in sepsis-associated AKI remains unclear. Therefore, this study investigated the clinical outcomes of early continuous kidney replacement therapy (CKRT).

METHODS

Study design and study population

This single-center retrospective large cohort study was based on data from 2008 to 2019 from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database version 2.2.[16,17] The MIMIC-IV is a publicly available de-identified electronic health record database that encompasses comprehensive clinical information of patients admitted to the intensive care unit (ICU) of the Beth Israel Deaconess Medical Center in Boston, Massachusetts, between 2008 and 2019. Available information includes patient measurements, orders, diagnoses, procedures, treatments, and de-identified free-text clinical notes. The most recent version of this dataset includes information on 299,712 patients, 431,231 admissions, and 73,181 ICU stays. The study hospital is a university-affiliated hospital with 743 beds.

This study included patients aged ≥ 18 years who met the sepsis diagnostic criteria and had sepsis-associated AKI. Sepsis was diagnosed according to the Sepsis-3 definition, which involves a change in the total sequential organ failure assessment (SOFA) score of ≥ 2 points because of infection.[1] AKI was defined as stage 2 or 3 AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification.[18] The diagnosis of sepsis and AKI was based on the first day of ICU admission. Patients who were initiated on CKRT within 48 hours of sepsis-

associated AKI were included. Cases of early mortality within 48 hours were excluded to address immortality time bias, and patients with a history of any type of dialysis were excluded.

Variables and outcome measures

The following variables were extracted using a structured query language on the BigQuery platform: demographic characteristics (age, sex, and race), comorbidities, SOFA score, laboratory findings, administration of vasopressors (dopamine, dobutamine, norepinephrine, epinephrine, and vasopressin), mechanical ventilation and RRT, chest radiography findings, and cardiac rhythm. The Charlson comorbidity index was calculated using coding algorithms using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and the International Classification of Diseases, 10th Revision (ICD-10) codes.[19] These variables were extracted based on the criteria used during ICU admission. The most abnormal values of laboratory investigations on the first day of the ICU stay were considered. The SOFA score was calculated using the most abnormal values on the first day of the ICU stay.

Early CKRT was defined as CKRT initiation within 6 hours of sepsis-associated AKI development, and late CKRT was defined as CKRT initiated after 6 hours of sepsis-associated AKI development.[9] Septic shock was defined by the administration of vasopressors and lactate levels > 2 mmol/L.[1] Metabolic acidosis was defined as pH < 7.15 and a base deficit < −5 mEq/L or a bicarbonate level ≤ 18 mEq/L, and hyperkalemia was defined as a potassium level > 6.5 mEq/L.[11] Pleural effusion and pulmonary edema were identified based on chest radiographs. The variables were determined based on the most abnormal values on the first day of the ICU stay.

The primary outcome was 28-day mortality. In addition to hospital death records, data related to mortality were referenced using state death records to assess out-of-hospital mortality.[17] State and hospital records regarding the date of death were collected 2 years after the discharge of the last patient from the MIMIC-IV database. Secondary outcomes included 90-day mortality, length of ICU and hospital stay, and the number of days free of mechanical ventilation, RRT, and vasopressors. The number of free days was calculated according to the number of days the patient was alive without intervention on day 28. The structured query language code for data extraction is available on GitHub (https://github.com/MIT-LCP/mimic-iv).

Statistical analyses

Propensity score matching was performed to address potential biases and confounding factors. Propensity scores were estimated for each patient using logistic regression, with early CKRT as the dependent variable and relevant covariates and potential confounders (age, sex, race, comorbidities, Charlson Comorbidity Index, SOFA score, KDIGO AKI stage, blood urea nitrate and creatinine levels, and the presence of septic shock, metabolic acidosis, hyperkalemia, atrial fibrillation, pleural effusion, and pulmonary edema) as independent variables. Patients in the early CKRT group were matched on a 1:4 basis with patients in the late CKRT group, using individual propensity scores.

Two-tailed independent *t*-tests or Mann–Whitney *U* tests were used for continuous variables to compare the clinical characteristics and outcomes. The Shapiro–Wilk test was performed to determine normality, and non-parametric tests were used for non-normally distributed data. Pearson's χ^2 or Fisher's exact test was used to analyze categorical variables. A survival analysis was conducted using the log-rank test to compare the groups.

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Continuous variables were presented as means ± standard deviations if normally distributed or medians (interquartile ranges; IQRs) if non-normally distributed. No adjustments were made for multiple comparisons. For the primary outcome (28-day mortality), the statistical power after propensity score matching was calculated to be 32.3% for an effect size of 0.1 and 99.4% for 0.3 with a significance level of 0.05. Differences were considered statistically significant at $P < 0.05$. All statistical analyses were performed using R, V.4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

We completed a web-based training course on human research and signed a data use agreement to access the database. The Institutional Review Board of the Beth Israel Deaconess Medical Center waived the requirement for informed consent (approval number: 2001P001699).

RESULTS

Patient characteristics

In total, 33,236 patients were diagnosed with sepsis (**Fig. 1**). Of these, 11,574 had sepsis-associated AKIs, and 553 received CKRT within 48 hours. After excluding cases of early mortality (n = 61) and patients with a history of dialysis (n = 93), 379 patients were included in the analysis. In this cohort, 45 (11.9%) patients were classified into the early CKRT group, 12 (26.7%) of whom died within 28 days. In the late CKRT group, 167 patients (50.0%) died within 28 days.

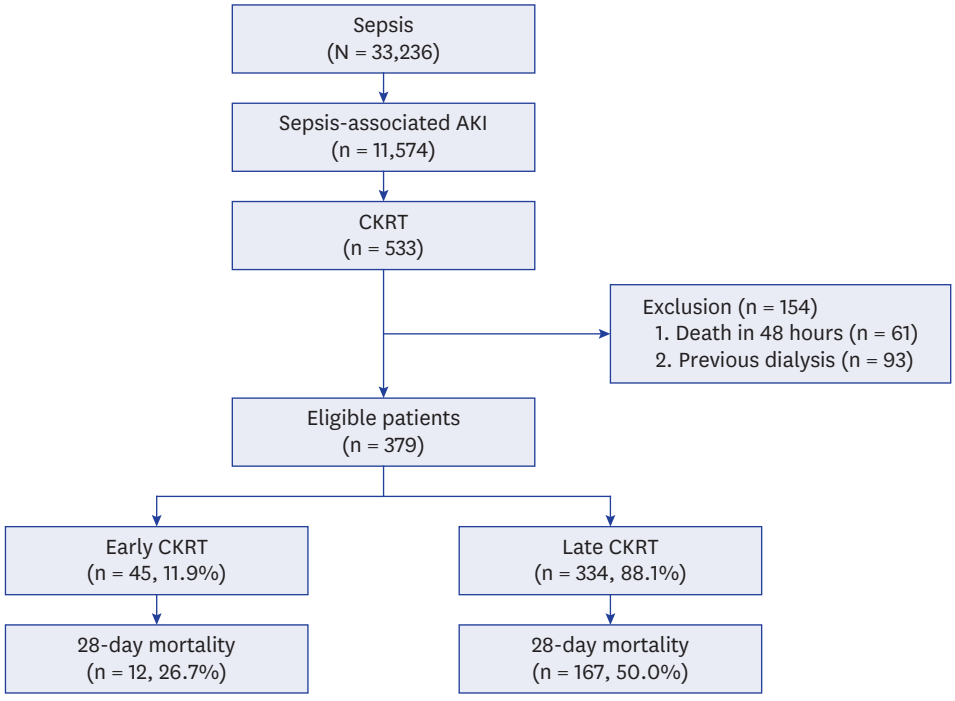

Fig. 1. Study flowchart.
AKI = acute kidney injury, CKRT = continuous kidney replacement therapy.

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The median age of the early CKRT group was 62 (IQR, 46–70) years, which was significantly lower than that of the late CKRT group (63.5 [IQR, 55–73] years; $P = 0.029$) (**Table 1**). There were no significant differences between the two groups in the baseline characteristics, including sex, race, or comorbidities, except cerebrovascular disease, which were significantly more prevalent in the early CKRT group than in the late CKRT group. In the early CKRT group, the SOFA scores and creatinine levels were higher, and metabolic acidosis, hyperkalemia, and pulmonary edema were more prevalent, compared with the late CKRT group.

Table 1. Clinical characteristics of patients with sepsis-associated acute kidney injury before propensity matching

Characteristics	Total (N = 379)	Early CKRT (n = 45)	Late CKRT (n = 334)	*P* value
Age, yr	63.0 (53.5–72.0)	62.0 (46.0–70.0)	63.5 (55.0–73.0)	0.029
Male sex	231 (60.9)	30 (66.7)	201 (60.2)	0.402
Race				
White	235 (62.0)	31 (68.9)	204 (61.1)	0.311
Black	27 (7.1)	5 (11.1)	22 (6.6)	0.347
Others	27 (7.1)	3 (6.7)	24 (7.2)	1.000
Unknown	90 (23.7)	6 (13.3)	84 (25.1)	0.080
Comorbidities				
Diabetes mellitus	142 (37.5)	18 (40.0)	124 (37.1)	0.708
CHF	149 (39.3)	18 (40.0)	131 (39.2)	0.920
Myocardial infarction	94 (24.8)	7 (15.6)	87 (26.0)	0.126
Chronic renal disease	114 (30.1)	13 (28.9)	101 (30.2)	0.853
Chronic liver disease	154 (40.6)	17 (37.8)	137 (41.0)	0.678
COPD	100 (26.4)	10 (22.2)	90 (26.9)	0.500
Cancer	57 (15.0)	7 (15.6)	50 (15.0)	0.918
CVD	43 (11.3)	1 (2.2)	42 (12.6)	0.040
CCI score	6.0 (4.0–9.0)	5.0 (3.0–8.0)	6.0 (5.0–9.0)	0.071
Septic shock	145 (38.3)	22 (48.9)	123 (36.8)	0.118
Vasopressor use	164 (43.3)	23 (51.1)	141 (42.2)	0.258
Mechanical ventilator	57 (15.0)	10 (22.2)	47 (14.1)	0.151
SOFA score	6.0 (3.0–8.0)	7.0 (5.0–9.0)	5.0 (3.0–8.0)	0.013
AKI stage				0.301
2	100 (26.4)	9 (20.0)	91 (27.2)	
3	279 (73.6)	36 (80.0)	243 (72.8)	
AKI diagnosis criteria				0.772
Urine output	301 (79.4)	35 (77.8)	266 (79.6)	
Serum creatinine	78 (20.6)	10 (22.2)	68 (20.4)	
BUN, mg/dL	45.0 (29.0–70.0)	55.0 (35.0–72.0)	45.0 (27.0–70.0)	0.069
Creatinine, mg/dL	3.0 (2.1–4.1)	3.7 (2.6–4.9)	2.9 (2.1–4.0)	0.001
Metabolic acidosis	154 (40.6)	25 (55.6)	129 (38.6)	0.033
Hyperkalemia	44 (11.6)	11 (24.4)	33 (9.9)	0.004
Lactate, mmol/L	5.4 (3.0–9.3)	5.3 (2.8–9.7)	5.4 (3.0–9.3)	0.991
Atrial fibrillation	102 (26.9)	10 (22.2)	92 (27.5)	0.450
Pleural effusion	52 (13.7)	6 (13.3)	46 (13.8)	0.936
Pulmonary edema	45 (11.9)	10 (22.2)	35 (10.5)	0.022
CKRT setting				
CVVHDF	357 (94.2)	42 (93.3)	315 (94.3)	0.792
CVVHD	10 (2.6)	1 (2.2)	9 (2.7)	0.853
CVVH	8 (2.1)	1 (2.2)	7 (2.1)	0.956
Target clearance, mL/kg/h	29.6 (25.6–34.1)	29.6 (25.6–33.7)	31.6 (27.1–37.3)	0.111
Blood flow rate, mL/min	150.0 (120.0–200.0)	150.0 (120.0–200.0)	150.0 (120.0–200.0)	0.444
Dialysate, mL/h	800 (500–1,000)	750 (500–1,000)	800 (500–1,000)	0.324
Replacement, mL/h	1,800 (1,400–2,000)	1,800 (1,475–2,000)	1,800 (1,400–2,200)	0.716

Values are presented as median (interquartile range) or number (%).
CKRT = continuous kidney replacement therapy, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, CCI = Charlson Comorbidity Index, SOFA = sequential organ failure assessment, AKI = acute kidney injury, BUN = blood urea nitrogen, CVVHDF = continuous venovenous hemodiafiltration, CVVHD = continuous venovenous hemodialysis, CVVH = continuous venous hemofiltration.

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The characteristics of the two groups were compared after propensity score matching (**Table 2**). None of the included variables, including age, sex, race, comorbidities, severity index (septic shock, SOFA score, and KDIGO AKI stage), laboratory findings, metabolic acidosis, hyperkalemia, or pulmonary edema, differed significantly after matching. The proportion of CKRT settings in the two groups did not differ significantly, and 93.3% of the CKRT modalities involved continuous venovenous hemodiafiltration (CVVHDF). The covariate balance after propensity score matching is presented as a standardized mean difference in **Table 2**.

Table 2. Clinical characteristics of patients with sepsis-associated acute kidney injury after propensity matching

Characteristics	Total (N = 225)	Early CKRT (n = 45)	Late CKRT (n = 180)	SMD	*P* value
Age, yr	61.0 (50.0–69.0)	62.0 (46.0–70.0)	61.0 (51.0–69.0)	0.155	0.505
Male sex	145 (64.4)	30 (66.7)	115 (63.9)	0.058	0.728
Race					
White	153 (68.0)	31 (68.9)	122 (67.8)	0.024	0.886
Black	17 (7.6)	5 (11.1)	12 (6.7)	0.157	0.344
Others	17 (7.6)	3 (6.7)	14 (7.8)	0.043	1.000
Unknown	38 (16.9)	6 (13.3)	32 (17.8)	0.123	0.477
Comorbidities					
Diabetes mellitus	91 (40.4)	18 (40.0)	73 (40.6)	0.011	0.946
CHF	87 (38.7)	18 (40.0)	69 (38.3)	0.034	0.837
Myocardial infarction	38 (16.9)	7 (15.6)	31 (17.2)	0.045	0.790
Chronic renal disease	62 (27.6)	13 (28.9)	49 (27.2)	0.037	0.823
Chronic liver disease	91 (40.4)	17 (37.8)	74 (41.1)	0.068	0.684
COPD	56 (24.9)	10 (22.2)	46 (25.6)	0.078	0.644
Cancer	36 (16.0)	7 (15.6)	29 (16.1)	0.015	0.928
CVD	4 (1.8)	1 (2.2)	3 (1.7)	0.040	1.000
CCI score	6.0 (4.0–8.0)	5.0 (3.0–8.0)	6.0 (4.0–8.0)	0.120	0.451
Septic shock	99 (44.0)	22 (48.9)	77 (42.8)	0.123	0.460
Vasopressor use	108 (48.0)	23 (51.1)	85 (47.2)	0.078	0.640
Mechanical ventilator	41 (18.2)	10 (22.2)	31 (17.2)	0.126	0.437
SOFA score	6.0 (4.0–9.0)	7.0 (5.0–9.0)	6.0 (4.0–9.0)	0.148	0.403
AKI stage				0.041	0.807
2	48 (21.3)	9 (20.0)	39 (21.7)		
3	177 (78.7)	36 (80.0)	141 (78.3)		
AKI diagnosis criteria				0.053	0.755
Urine output	171 (76.0)	35 (77.8)	136 (75.6)		
Serum creatinine	54 (24.0)	10 (22.2)	44 (24.4)		
BUN, mg/dL	49.0 (30.0–74.0)	55.0 (35.0–72.0)	48.0 (29.0–74.5)	0.072	0.338
Creatinine, mg/dL	3.5 (2.4–4.4)	3.7 (2.6–4.9)	3.3 (2.4–4.3)	0.295	0.122
Metabolic acidosis	110 (48.9)	25 (55.6)	85 (47.2)	0.167	0.317
Hyperkalemia	37 (16.4)	11 (24.4)	26 (14.4)	0.255	0.106
Lactate, mmol/L	5.9 (3.1–9.6)	5.3 (2.8–9.7)	6.1 (3.1–9.5)	0.086	0.829
Atrial fibrillation	54 (24.0)	10 (22.2)	44 (24.4)	0.053	0.755
Pleural effusion	25 (11.1)	6 (13.3)	19 (10.6)	0.086	0.596
Pulmonary edema	37 (16.4)	10 (22.2)	27 (15.0)	0.186	0.242
CKRT setting					
CVVHDF	210 (93.3)	42 (93.3)	168 (93.3)	< 0.001	1.000
CVVHD	6 (2.7)	1 (2.2)	5 (2.8)	0.036	0.836
CVVH	5 (2.2)	1 (2.2)	4 (2.2)	< 0.001	1.000
Target clearance, mL/kg/h	30.0 (25.8–34.1)	29.7 (25.8–33.2)	31.6 (27.1–37.3)	0.218	0.120
Blood flow rate, mL/min	150.0 (120.0–200.0)	150.0 (120.0–200.0)	150.0 (120.0–200.0)	0.221	0.317
Dialysate, mL/h	800 (500–1,000)	800 (500–1,000)	800 (500–1,000)	0.219	0.781
Replacement, mL/h	1,800 (1,500–2,000)	1,800 (1,500–2,000)	1,800 (1,400–2,200)	0.113	0.834

Values are presented as median (interquartile range) or number (%).
CKRT = continuous kidney replacement therapy, SMD = standardized mean difference, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, CCI = Charlson Comorbidity Index, SOFA = sequential organ failure assessment, AKI = acute kidney injury, BUN = blood urea nitrogen, CVVHDF = continuous venovenous hemodiafiltration, CVVHD = continuous venovenous hemodialysis, CVVH = continuous venous hemofiltration.

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Outcomes

Regarding the primary outcome, the 28-day mortality rate was significantly lower in the early CKRT group than in the late CKRT group (26.7% vs. 43.9%, respectively; $P = 0.035$) (**Table 3**). The Kaplan–Meier curve also showed that early CKRT within 6 hours was associated with an improved 28-day mortality rate (log-rank test $P = 0.040$) (**Fig. 2A**). In contrast, the 28-day mortality did not differ between patients who started CKRT within 12 hours and those who did not (log-rank test $P = 0.237$) (**Fig. 2B**).

Regarding the secondary outcomes, the early CKRT group had a significantly greater number of days free of mechanical ventilation (median, 19; IQR, 3–25) and vasopressor administration (median, 21; IQR, 5–26) than the late CKRT group did (median, 10.5; IQR, 0–23; $P = 0.037$ and median, 13.5; IQR, 0–25; $P = 0.028$, respectively). There were no significant differences between the groups in other secondary outcomes such as 90-day mortality, length of ICU and hospital stay, and number of days free from RRT. Kaplan–Meier curves also revealed that early CKRT (both within 6 and 12 hours) was not associated with improved 90-day mortality in patients with sepsis-associated AKI (log-rank test $P = 0.088$ and $P = 0.483$, respectively; **Fig. 2C and D**). In addition, the Kaplan–Meier curves comparing survival between groups receiving CKRT within 6 hours, from 6 to 12 hours, and after 12 hours showed that the within-6-hour group had better survival outcomes than the other groups did; however, this result was not statistically significant (**Supplementary Fig. 1**).

DISCUSSION

We found a significant association between early CKRT and survival benefits in patients with sepsis-associated AKI. Additionally, the number of days free from mechanical ventilation and vasopressor administration was higher in the early CKRT group than in the late CKRT group. This study defined early CKRT as CKRT initiation within 6 hours of the onset of KDIGO stage 2 or 3 AKI, which was earlier than that defined in previous studies, suggesting that earlier initiation of CKRT may help improve patient outcomes.

Sepsis is a biphasic disease in which the initial phase is characterized by overwhelming inflammation, followed by a phase of immune suppression.[20] In the pro-inflammatory phase, pathogen-associated molecular patterns such as lipopolysaccharides are recognized by Toll-like receptors expressed on antigen-presenting cells.[21] Activated Toll-like receptors increase the production of inflammatory cytokines, including tumor necrosis factor-α and interleukin-1, and trigger dysregulated hyperinflammation, which leads to disseminated intravascular coagulation, peripheral vasodilation, and multiorgan dysfunction.[20] Until

Table 3. Clinical outcomes of patients with sepsis-associated acute kidney injury after propensity score matching

Clinical outcomes	Total (N = 225)	Early CKRT (n = 45)	Late CKRT (n = 180)	*P* value
Primary outcome				
28-day mortality	91 (40.4)	12 (26.7)	79 (43.9)	0.035
Secondary outcomes				
90-day mortality	114 (50.7)	18 (40.0)	96 (53.3)	0.110
Length of ICU stay (days)	9.3 (4.6–16.7)	11.4 (5.1–15.4)	9.1 (4.4–16.7)	0.602
Length of hospital stay (days)	17.0 (8.0–31.0)	20.0 (12.0–37.0)	16.0 (7.0–30.0)	0.293
Ventilator-free days	13.0 (0.0–23.0)	19.0 (3.0–25.0)	10.5 (0.0–23.0)	0.037
RRT free days	12.0 (1.0–23.0)	18.0 (2.0–24.0)	8.0 (1.0–22.0)	0.083
Vasopressors free days	16.0 (0.0–25.0)	21.0 (5.0–26.0)	13.5 (0.0–25.0)	0.028

Values are presented as median (interquartile range) or number (%).
CKRT = continuous kidney replacement therapy, ICU = intensive care unit, RRT = renal replacement therapy.

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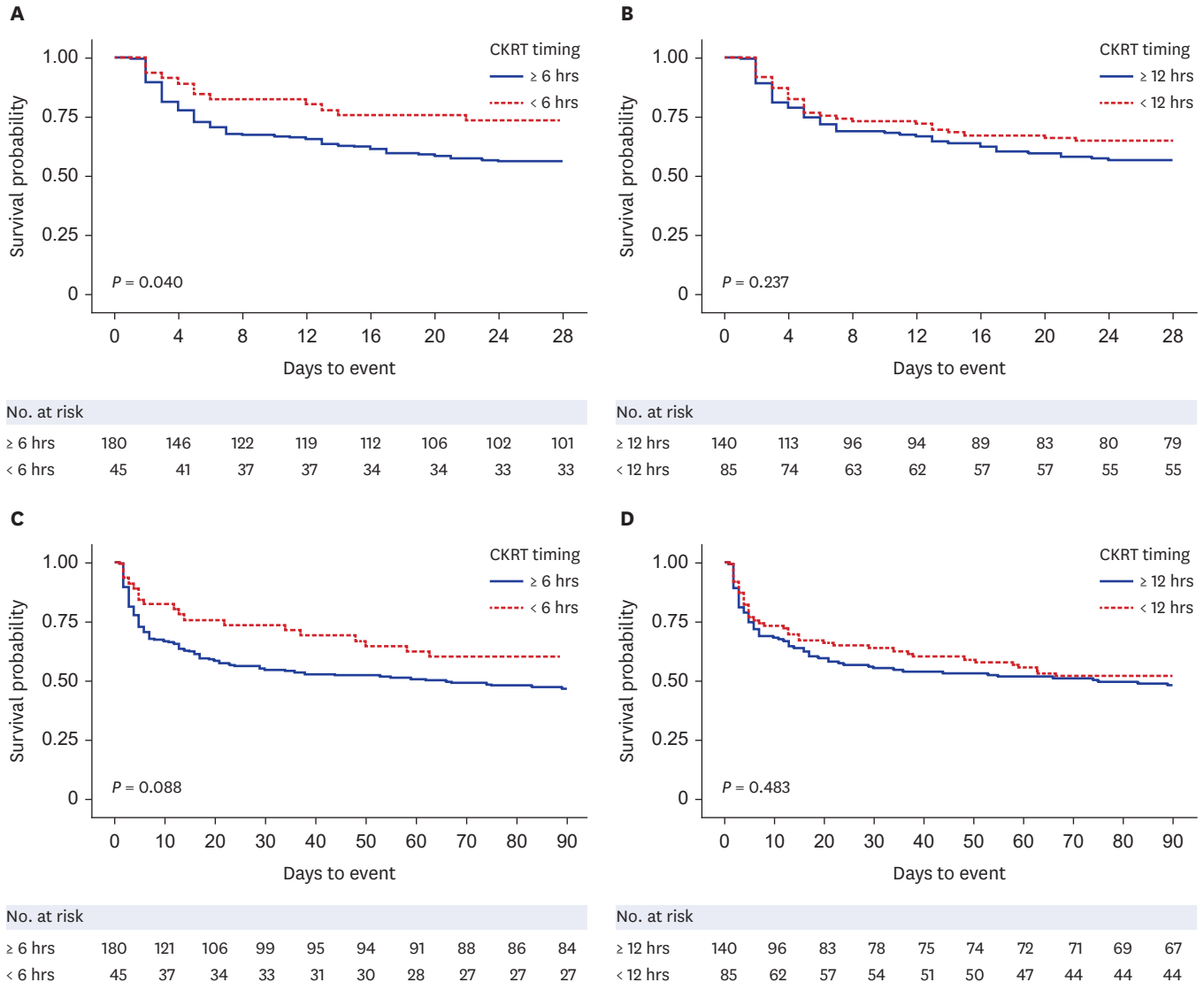

Fig. 2. Kaplan–Meier survival curves of patients with sepsis-associated acute kidney injury after propensity score matching. (**A**) Comparison of 28-day survival with CKRT initiated within 6 hours and after 6 hours and (**B**) within 12 hours and after 12 hours. (**C**) Ninety-day mortality among patients with sepsis and those with CKRT initiated within 6 hours and after 6 hours and (**D**) within 12 hours and after 12 hours.
CKRT = continuous kidney replacement therapy.

recently, kidney hypoperfusion was believed to be a major contributor to sepsis-associated AKI.[22] However, recent evidence suggests that multifactorial mechanisms, including macro- and microcirculatory disturbances, oxidative stress caused by inflammatory cytokines, and microvascular thrombosis, contribute to AKI development.[22]

Considering the pathophysiology of sepsis-associated AKI, initiating CKRT as early as possible may help stabilize patients with sepsis-associated AKI by removing inflammatory mediators from the circulation. Previous randomized controlled trials of early RRT used different definitions of early RRT, and the ELAIN study, the only study that showed a survival benefit of early RRT, used the earliest definition of early RRT.[9-12] In the ELAIN trial, early RRT was defined as the initiation of RRT within 8 hours of KDIGO stage 2 AKI diagnosis, and delayed RRT was defined as RRT initiation within 12 hours of KDIGO stage 3 AKI diagnosis.[10] In contrast, early RRT in the IDEAL-ICU trial was initiated within 12 hours of

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the failure stage of the risk, injury, failure, loss, and end-stage kidney disease classification (equivalent to KDIGO stage 3).[11] In other words, the definitions of the delayed group in the ELAIN trial and the early group in the IDEAL-ICU trial were similar. Our study also showed an improvement in mortality when CKRT was initiated within 6 hours of KDIGO AKI stage 2 or 3 diagnosis, which is consistent with the results of the ELAIN trial. These results suggest that the early initiation of RRT may improve the clinical outcomes of sepsis-associated AKI by removing inflammatory cytokines during the early proinflammatory phase of the disease.

RRT modality may also affect the outcomes of patients with sepsis-associated AKI. Inflammatory cytokines are mainly medium-sized molecules that exist in a protein-bound form. RRT modalities that are better at removing medium-sized molecules may be beneficial (CKRT rather than intermittent hemodialysis and hemodiafiltration rather than hemodialysis).[23,24] The ELAIN trial, which showed the survival benefit of early RRT, exclusively administered CVVHDF, whereas other randomized controlled trials included intermittent hemodialysis and CKRT.[9-12] In the AKIKI trial, which demonstrated no survival benefit from early RRT, > 50% of patients started RRT with intermittent hemodialysis.[9] Our study, as well as the ELAIN study, included only CKRT as an RRT modality, most of which involved CVVHDF. The use of CKRT may have contributed to the reduced risk of death because it is favorable for removing inflammatory cytokines. Therefore, CVVHDF may be preferred for RRT in patients with sepsis-associated AKI; however, this warrants further research.

In applying an early CKRT strategy for sepsis-associated AKI, there are concerns regarding the unnecessary exposure of patients whose renal dysfunction would recover spontaneously to the risks associated with CKRT. Unnecessary CKRT can lead to adverse events because of extracorporeal circulation, increased healthcare costs, and exhaustion of healthcare resources. In the IDEAL-ICU trial, 38% of the delayed-strategy group that did not receive RRT had favorable outcomes.[11] However, among patients in the delayed-strategy group who met the criteria for emergency dialysis and received RRT, the mortality rate was 68%, which was significantly higher than that in patients who did not meet the criteria for emergency dialysis. Therefore, despite the risk of unnecessary CKRT, the risk of not performing CKRT was greater.

Our study only included patients who started CKRT within 48 hours of sepsis-associated AKI and did not include patients whose renal functions recovered spontaneously, showing the significant survival benefit of early CKRT initiation. However, of the 11,574 patients with sepsis-associated AKI, only 533 received CKRT within 48 hours. The remaining patients who did not receive CKRT were not included in our study; however, the condition of many improved with conservative treatment without RRT. Therefore, identifying the subpopulation of patients with sepsis-associated AKI who may benefit most from early CKRT is a very important goal.

Comparing our results with those of previous studies, we would like to emphasize the need for earlier initiation of CKRT in patients with decreased urine output. The ELAIN trial, the only randomized controlled trial that showed a survival benefit with early CKRT, included a higher proportion of patients with decreased urine output and started CKRT at an earlier time point than other trials.[10-12] Similar to the ELAIN trial, our study defined early CKRT as within 6 hours of stage 2 or 3 AKI, and oliguria/anuria was highly prevalent (79.4% of AKI diagnoses). Based on the results of this study and the previous trials, early CKRT could be considered especially in patients with decreased urine output.[10-12] In addition, further studies are needed to identify and predict the characteristics of patients who will eventually require dialysis when a delayed CKRT strategy is applied and apply a more selective early CKRT strategy.

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The strength of our study is that it investigated an earlier point of initiation of CKRT compared with other studies, and the results emphasize the importance of the timing of decreased urine output. Although there have been several studies on the timing of CKRT initiation, there is still no consensus on the optimal timing. Most of the studies included different population cohorts with clinical heterogeneity and mixed causes of AKI.[25] In addition, the criteria for early initiation varied and not all studies included urine output to define AKI.[25] Our study exclusively included patients with sepsis-associated AKI, and approximately 80% of patients were diagnosed with AKI by decreased urine output. In addition, we defined early CKRT as within 6 hours of the onset of AKI, which is earlier than the previous studies, and demonstrated that early CKRT significantly reduced the risk of death. Therefore, future discussions on the optimal timing of CKRT should include urine output to determine timing, and consider earlier initiation, possibly as soon as possible after the onset of AKI of stage 2 or greater.

Our study has some limitations. First, this is a single-center retrospective cohort study based on the MIMIC-IV database, which primarily comprised Western populations. Additionally, the KDIGO criteria for AKI, which we used to define sepsis-associated AKI, do not always adequately reflect renal function deterioration. The KDIGO criteria define AKI as an increase in creatinine levels and a decrease in urine output; therefore, the diagnosis of sepsis-associated AKI may be delayed from the onset of sepsis-associated AKI, depending on the timing of the creatinine test. In addition, the assessment of the glomerular filtration rate using creatinine level analysis may be overestimated or underestimated depending on the patient's body composition. Other important confounding factors, including site and type of infectious diseases, causative microorganisms, treatment, and potential risk factors of AKI (use of contrast media and nephrotoxic agents), were not considered in the analysis. In addition, the mortality rate was an all-cause mortality, which did not account for the cause of death, therefore, comparisons of long-term mortality require particular caution. Finally, we evaluated the number of days free of RRT as a renal outcome; however, owing to the limitations of the database, we could not evaluate other renal outcomes, such as long-term dependency on RRT.

In conclusion, early initiation of CKRT improved survival in patients with sepsis-associated AKI. Initiation of CKRT should be considered as early as possible after the onset of sepsis-associated AKI, preferably within 6 hours.

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SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Kaplan–Meier survival curves of patients with sepsis-associated acute kidney injury after propensity score matching. (**A**) Comparison of 28-day survival and (**B**) 90-day mortality among patients with sepsis between those with CKRT initiated within 6 hours, from 6–12 hours, and after 12 hours.

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