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CLINICAL STUDY

Prognosis of critically ill patients with early and late sepsis-associated acute kidney injury: an observational study based on the MIMIC-IV

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ABSTRACT

Objective: The Acute Disease Quality Initiative (ADQI) working group recently released a consensus definition of sepsis-associated acute kidney injury (SA-AKI), but the prognosis and risk factors for early and late SA-AKI have not been studied.

Methods: This was a retrospective cohort study based on the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (v2.2). First, SA-AKI patients that met the new definition from the ADQI were screened, and then, the relationships between SA-AKI occurrence time and relevant clinical parameters were analyzed.

Results: After propensity score matching, 1,090 early SA-AKI (AKI occurring within 48 h of sepsis diagnosis) cases and late SA-AKI (AKI occurring between 48 h and 7 days after sepsis diagnosis) cases were identified. Compared with late SA-AKI patients, early SA-AKI patients had no significant differences in all-cause mortality at 28 days, 60 days or 180 days, renal replacement therapy (RRT) rates; or major adverse kidney events at 30 days (MAKE-30). However, the renal recovery of early SA-AKI patients was significantly better than that of late SA-AKI patients, their lengths of hospital stay and intensive care unit stay were significantly shorter, and the number of patients with positive fluid balance was lower, but the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and nephrotoxic antibiotics and the incidence of septic shock were higher. In addition, there was a difference in the number of patients with early and late SA-AKI at highest AKI stages 1 and 3. Data analysis also revealed that liver disease, cancer, highest AKI stage 3 and septic shock were associated with renal nonrecovery.

Conclusions: Although there was no significant difference in mortality between early and late SA-AKI patients, there were significant differences in renal recovery, positive fluid balance, nephrotoxic antibiotic use, septic shock and AKI stage. Therefore, the classification of early and late SA-AKI has certain scientific and rational validity, but whether the two have different clinical outcomes and pathogeneses requires further study.

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Intensive care; acute kidney injury; sepsis; SA-AKI; MMIC-IV database

Introduction

Sepsis is a life-threatening organ dysfunction caused by the body's dysfunctional inflammatory response to infection [1]. Acute kidney injury (AKI) is the most common complication of sepsis and is known as sepsis-associated acute kidney injury (SA-AKI) [2,3]. SA-AKI accounts for approximately 50% of all AKI cases and is associated with longer intensive care unit (ICU) and hospital stays, and higher mortality, posing a serious threat to human health [2,4].

SA-AKI is common in the ICU and is closely associated with adverse outcomes, including chronic kidney disease, cardiovascular events and increased risk of death [2]. The pathophysiology of SA-AKI is complex and currently not fully understood, and improving the outcome of SA-AKI remains a challenge [5]. Early identification of patients at risk of AKI or those at risk of progressing to severe and/or persistent AKI may improve outcomes *via* timely initiation of appropriate support measures. However, many aspects of SA-AKI have been poorly described and there has been no standardized

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consensus or definition. To this end, the 28th Acute Disease Quality Initiative (ADQI) working group discussed this issue and formulated the world's first expert consensus on SA-AKI in 2022 [6]. The consensus clearly defines SA-AKI as AKI occurring within 7 days after sepsis diagnosis on the basis of the criteria of Sepsis 3 and Kidney Disease Improving Global Outcome (KDIGO); the group also proposed defining AKI occurring within 48 h after sepsis diagnosis as early SA-AKI and AKI occurring between 48 h and 7 days as late SA-AKI [6].

Expert consensus assumes that early and late SA-AKI may have different mechanisms of occurrence, corresponding to different phenotypes and prognoses, and may even have different treatment responses to interventions. Similar time differences have been observed in critically ill patients with septic shock and acute respiratory distress syndrome (ARDS), where the prognosis appears to be poorer in patients with late-onset disease, possibly related to reduced tolerance to injury in patients with organ failure [7,8]. Previous studies have shown that early AKI may have lower mortality and may be related to physiological and pathological mechanisms that differ from those of late-onset AKI [9,10]. However, these studies used outdated definitions of sepsis and AKI. Therefore, this study extracted and compared the relevant clinical information of SA-AKI patients from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, and explored the relationship between the occurrence time of SA-AKI and clinical outcomes to better guide clinical intervention for SA-AKI patients.

Materials and methods

Data source

A retrospective observational study was conducted using the MIMIC-IV database, which is a freely available open database containing real hospitalization information for patients admitted to a tertiary academic medical center in Boston, Massachusetts, USA between 2008 and 2019. The MIMIC-IV database is specifically designed to facilitate different healthcare research projects and contains comprehensive information on each patient's stay, including laboratory measurements, medication use, and recorded vital signs. One of the authors (Bo-wen Shi) obtained access to the database (certificate number 54891297). The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [11].

Study population

This study included SA-AKI patients in the MIMIC-IV database who met the latest definition from the ADQI. The diagnosis of AKI was in accordance with KDIGO guidelines: serum creatinine (Scr) was increased by more than 50% relative to baseline and/or the Scr level was increased to 26.5 mol/L within 48 h and/or the urine output was less than 0.5 mL/kg/h within the shortest 6 h. The exclusion criteria were as follows: (1) patients under 18 years old; (2) patients who were repeatedly admitted to the ICU; (3) patients who were discharged from a hospital less than 24 h after admission to the ICU; (4) patients with incorrect information regarding death; (5) patients with end-stage renal disease; (6) patients lacking data on the timing of ICU entry and exit; (7) patients with AKI that was diagnosed before the diagnosis of sepsis; and (8) patients with AKI diagnosed 7 days or later after the diagnosis of sepsis.

Outcomes

The primary outcome was the 28-day mortality of patients with early or late SA-AKI. The secondary outcomes included prognostic indicators and differences between early and late SA-AKI patients according to the ADQI consensus recommendation, such as all-cause mortality at 60 days or 180 days, renal recovery, renal replacement therapy (RRT) utilization, and major adverse kidney events at 30 days (MAKE-30). Renal recovery was assessed on the basis of the recovery status at discharge or within 28 days, with the complete recovery criteria being survival and the Scr level being restored to within 1.5 times the reference creatinine value [12,13]. Definitions of the relevant parameters are provided in Table S4.

Statistical analysis

Descriptive statistics are expressed as the frequency and proportion of categorical variables, the median of the interquartile range (IQR) or the mean based on the standard deviation of their parametric or nonparametric distributions. Univariate logistic regression analysis was used to examine the relationship between each candidate indicator and the occurrence of renal recovery. After excluding the multicollinearity indicators in the logistic regression model, multivariable logistic regression analysis was used to evaluate the independent variables associated with renal recovery. Multivariable logistic stepwise regression was subsequently used to determine the most effective predictors of renal recovery. The results of the multivariable analysis are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). Kaplan–Meier curves were used to compare the cumulative survival between early and late SA-AKI patients. Considering the large data set, bilateral P values < 0.05 were considered statistically significant.

A preliminary analysis was performed in a matched cohort to investigate the associations of early and late SA-AKI with primary and secondary outcomes. We used propensity score matching to adjust the variables [14]. Logistic regression models were used to obtain the probability that each patient belonged to the 'early SA-AKI' group (i.e. propensity score). Variables in the propensity score matching model were selected on the basis of consensus statements published in the literature and included age, sex, race, anchoring year, first unit of care, Charlson comorbidity index and SOFA score. The nearest neighbor method was used to build a 1:1 scale match, the caliper width was 0.2, and no substitution was made. The standardized mean difference (SMD) was used to

evaluate the balance of variables between groups before and after matching. A value less than 0.10 indicates balance in the matched cohort dataset. Variables with $p < 0.05$ in the univariate analysis were included in the multivariable analysis for adjustment, including age, sex, race, anchoring year, first care unit, ICU type, Charlson comorbidity index, and SOFA score (Figure S3).

Univariate logistic regression analysis was used to examine the relationship between each candidate index and the occurrence of kidney recovery. Indicators of multicollinearity in logistic regression models were excluded. Multivariable logistic regression analysis was used to evaluate independent variables associated with kidney recovery. A significance threshold of $p < 0.05$ was used to select variables for multivariable analysis. Multiple logistic stepwise regression was subsequently used to determine the most effective predictors of kidney recovery. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. Among them, the number of partial recovery patients in the late SA-AKI group was too small, and these patients were merged into the nonrecovery group.

Statistical calculations were performed *via* the R language environment (R Foundation for Statistical Computing, version 4.3.1; Vienna, Austria).

Results

Population characteristics

A total of 11266 early SA-AKI patients and 1091 late SA-AKI patients were screened in the MIMIC-IV database, accounting for 91.2% and 8.8% of total the patients, respectively. After propensity score matching, there were 1090 early and late SA-AKI patients each (Table 1). The study enrollment flow diagram is shown in Figure 1. The handling of missing values is shown in Figures S1 and S2. Propensity score matching is shown in Figure S3.

In the analysis of risk factors, we identified nephrotoxic antibiotics, cerebrovascular disease, and septic shock as risk factors for 28-day mortality (Table S2).

Relationship between SA-AKI occurrence time and survival

SA-AKI can be divided into early SA-AKI and late SA-AKI according to the ADQI definition. Further data analysis revealed that there was no significant difference in all-cause mortality at 28 days, 60 days or 180 days between patients with early SA-AKI and patients with late SA-AKI ($p = 0.95$, $p = 0.81$, $p = 0.98$, respectively, Table 2). The 28-day

Table 1. Baseline analysis of patients before and after propensity score matching.

	Before PSM			After PSM		
Variable	Early SA-AKI($n = 11266$)[a]	Late SA-AKI ($n = 1091$)[a]	SMD	Early SA-AKI($n = 1090$)[a]	Late SA-AKI($n = 1090$)[a]	SMD
Age	69.0 [58.0, 80.0]	67.0 [55.0, 78.0]	0.16	67.0 [55.0, 77.0]	67.0 [55.2, 78.0]	0.02
Sex						
Male	6,624 (58.8%)	638 (58.5%)	0.01	642 (58.9%)	638 (58.5%)	0.01
Female	4,642 (41.2%)	453 (41.5%)		448 (41.1%)	452 (41.5%)	
Race			0.13			0.03
ASIAN	255 (2.3%)	30 (2.7%)		33 (3.0%)	30 (2.8%)	
BLACK	784 (7.0%)	82 (7.5%)		83 (7.6%)	82 (7.5%)	
HISPANIC/LATINO	301 (2.7%)	20 (1.8%)		16 (1.5%)	20 (1.8%)	
OTHER	2,176 (19.3%)	261 (23.9%)		258 (23.7%)	260 (23.9%)	
WHITE	7,750 (68.8%)	698 (64.0%)		700 (64.2%)	698 (64.0%)	
Type of ICU			0.39			0.03
CVICU	3,035 (26.9%)	134 (12.3%)		141 (12.9%)	134 (12.3%)	
CCU	1,005 (8.9%)	116 (10.6%)		120 (11.0%)	116 (10.6%)	
MICU	2,435 (21.6%)	239 (21.9%)		226 (20.7%)	239 (21.9%)	
MICU/SICU	1,905 (16.9%)	219 (20.1%)		218 (20.0%)	219 (20.1%)	
OTHER ICU	2,886 (25.6%)	383 (35.1%)		385 (35.3%)	382 (35.0%)	
Charlson Comorbidity Index	5.0 [3.0, 7.0]	5.0 [3.0, 7.0]	0.05	5.0 [3.0, 7.0]	5.0 [3.0, 7.0]	0.01
SOFA	6.0 [4.0, 8.0]	5.0 [3.0, 7.0]	0.32	5.0 [3.0, 7.0]	5.0 [3.0, 7.0]	0.03
Coronary heart disease	2,081 (18.5%)	181 (16.6%)	0.05	193 (17.7%)	181 (16.6%)	0.03
Congestive heart failure	3,430 (30.4%)	308 (28.2%)	0.05	320 (29.4%)	308 (28.3%)	0.02
Renal disease	2,088 (18.5%)	183 (16.8%)	0.05	186 (17.1%)	183 (16.8%)	0.01
Liver disease	1,758 (15.6%)	148 (13.6%)	0.06	162 (14.9%)	148 (13.6%)	0.04
CKD stage			0.07			0.04
0	9,219 (81.8%)	916 (84.0%)		907 (83.2%)	915 (83.9%)	
1	5 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
2	61 (0.5%)	4 (0.4%)		4 (0.4%)	4 (0.4%)	
3	562 (5.0%)	43 (3.9%)		46 (4.2%)	43 (3.9%)	
4	174 (1.5%)	15 (1.4%)		19 (1.7%)	15 (1.4%)	
5	39 (0.3%)	3 (0.3%)		2 (0.2%)	3 (0.3%)	
Unspecified	1,206 (10.7%)	110 (10.1%)		112 (10.3%)	110 (10.1%)	
Nephrotic syndrome	6 (0.1%)	2 (0.2%)	0.04	0 (0.0%)	2 (0.2%)	0.06

PSM: propensity score matching; SA-AKI: sepsis associated acute kidney injury; ICU: intensive care unit; CVICU: cardiovascular intensive care unit; CCU: cardiac care unit; MICU: medisive care unit; SICU: surgical intensive care unit; SOFA: sequential organ failure assessment; APS: acute physiology score; CKD: Chronic Kidney Disease.

[a]Median [IQR] or frequency (%).

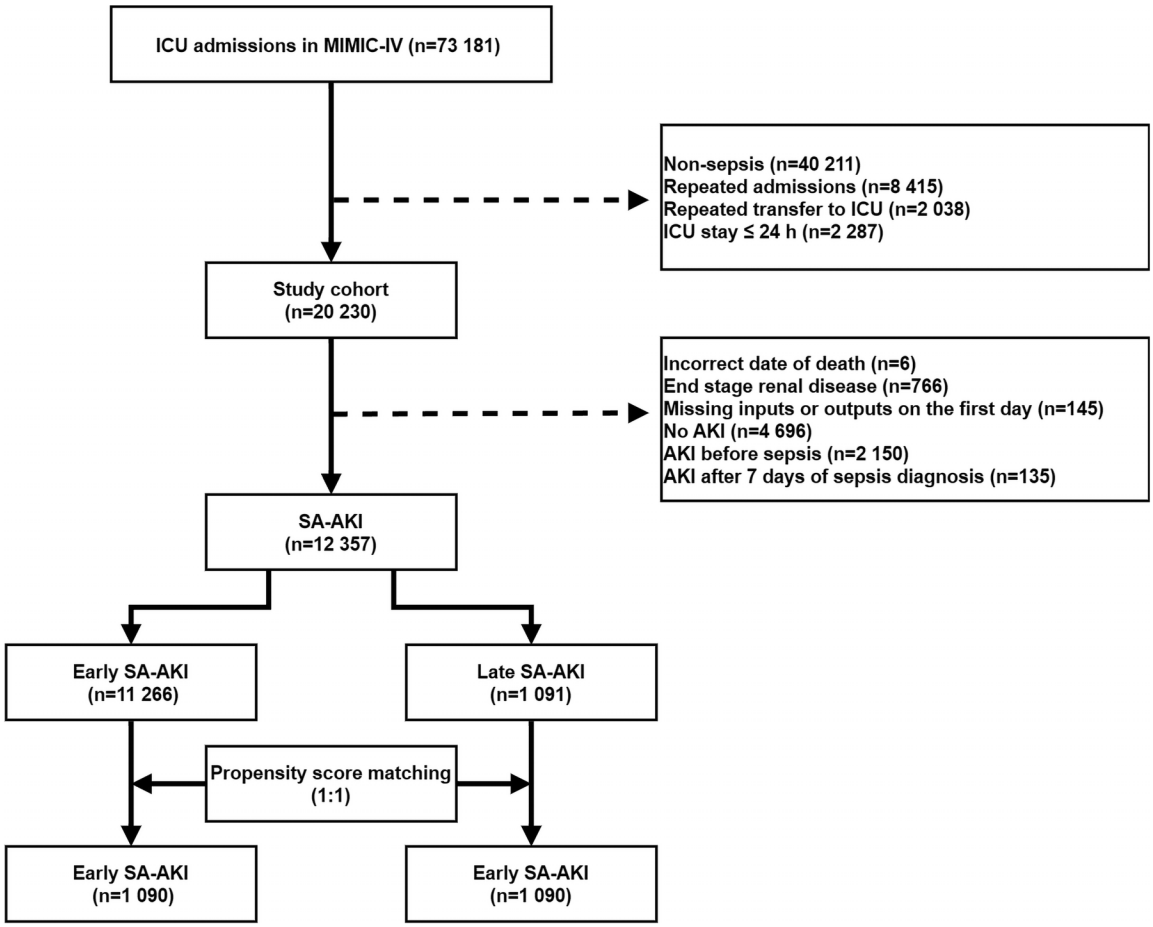

Figure 1. Flow chart of patient selection.
ICU; intensive care unit; MIMIC-IV; Medical Information Mart in Intensive Care-IV; AKI: acute kidney injury; SA-AKI: sepsis-associated acute kidney injury.

Table 2. Survival and prognosis of early and late SA-AKI patients.

	SA-AKI group		
Variable	Early ($n = 1090$)[a]	Late ($n = 1090$)[a]	p-value
Primary outcome			
28-day all-cause mortality	214 (19.6%)	218 (20%)	0.95
Secondary outcomes			
60-day all-cause mortality	257 (23.6%)	265 (24.3%)	0.81
180-day all-cause mortality	323 (29.6%)	329 (30.2)	0.98
ICU all-cause mortality	119 (10.9%)	134 (12.3%)	0.22
In-hospital mortality	170 (15.6%)	180 (16.5%)	0.63
ICU LOS (days)[b]	3.0 [2.0, 6.0]	6.0 [4.0, 10.0]	<0.01
Hospital LOS (days)[b]	9.0 [5.0, 16.0]	12.0 [8.0, 19.0]	<0.01
Maximum (highest) AKI stage in ICU			<0.01
1	219 (20.1%)	451 (41.4%)	
2	569 (52.2%)	502 (46.1%)	
3	302 (27.7%)	137 (12.6%)	
Any RRT	32 (2.9%)	21 (1.9%)	0.21
Renal recovery			<0.01
Complete recovery	638 (58.5%)	593 (54.4%)	
Partial	150 (13.8%)	98 (9.0%)	
None	302 (27.7%)	399 (36.6%)	
MAKE-30	339 (31.1%)	321 (29.4%)	0.21

LOS: length of stay; AKI: acute kidney injury; RRT: renal replacement therapy; MAKE-30: major adverse kidney events at day 30; SA-AKI: sepsis associated acute kidney injury.
[a]Median [IQR] or frequency (%).
[b]Medians Differences with 95% CI was calculated using Wilcoxonrank sum teste.

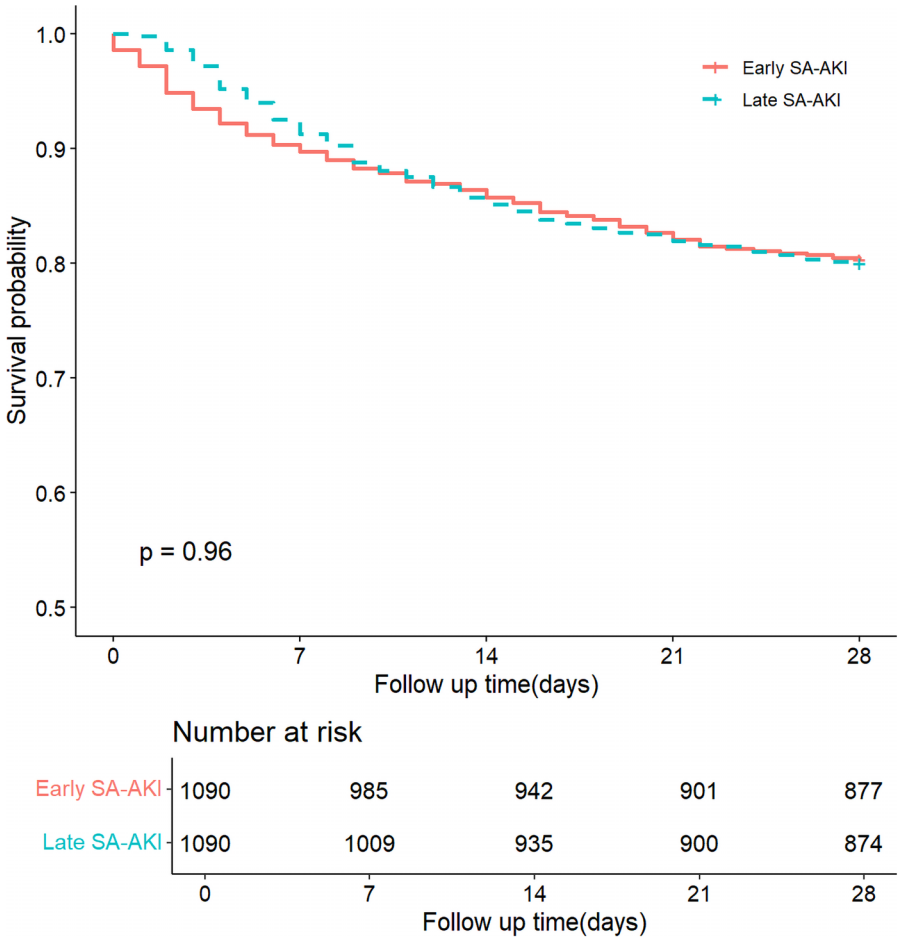

Figure 2. Kaplane-Meier Curve for 28-day all-cause mortality according to early and late SA-AKI in the matched cohort. SA-AKI: sepsis-associated acute kidney injury.

Kaplan–Meier survival curves before and after propensity-score matching were similar (Figure 2 and Figure S4). Definitions of the relevant parameters are provided in Table S4.

Relationships between SA-AKI occurrence time and other clinical parameters

Data analysis also revealed that although there were no significant differences in the RRT or MAKE-30($p = 0.21$) between early and late SA-AKI patients, early SA-AKI patients had significantly better rate of renal recovery than late SA-AKI patients did($p < 0.01$; Table 2). Further analysis revealed that liver disease, malignancy, Max AKI stage 3, and septic shock were detrimental to renal recovery (Table 4). For other data, please refer to Table S3.

In addition, compared with late SA-AKI patients, the lengths of hospital stay and ICU stay of early SA-AKI patients were significantly shorter, and the number of patients with positive fluid balance was lower; however, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), nephrotoxic antibiotics and the incidence of septic shock were higher (Table 3). Moreover, the number of early SA-AKI patients at Max AKI stage 1 was significantly lower than that of late SA-AKI patients, but the number of early SA-AKI patients at Max AKI stage 3 was significantly greater than that of late SA-AKI patients (Table 2).

Table 3. Differences in patients with early and late SA-AKI.

	SA-AKI group		
Variable	Early ($n = 1090$)[a]	Late ($n = 1090$)[a]	*p*-value
NSAIDs	333 (30.6%)	211 (19.4%)	0.01
Nephrotoxic antibiotics	269 (24.7%)	156 (14.3%)	<0.01
Vasoactive agents	444 (40.7%)	466 (42.8%)	0.41
Mechanical ventilation	472 (43.3%)	477 (43.8%)	0.43
Positive fluid balance, mL	717 (65.8%)	852 (78.2%)	<0.01
Heart Rate, bpm	87.4 ± 16.5	86.8 ± 16.5	0.40
MAP, mmHg	78.6 ± 10.3	77.8 ± 10.2	0.07
Resp Rate, /min	20.1 ± 4.2	19.6 ± 4.0	0.28
Temperature, C°	37.0 ± 0.6	36.9 ± 0.6	<0.01
Lactate level Max (mmol/L)	2.6 ± 2.0	2.8 ± 2.4	0.10
Septic shock	199 (18.3%)	157 (14.4%)	0.02

SA-AKI: sepsis associated acute kidney injury; NSAIDs: non-steroidal anti-inflammatory drugs; MAP: Mean Arterial Pressure.
[a]Average (±SD) or frequency (%).

Univariable and multivariable analysis of risk factors associated with kidney recovery

In our study, a comprehensive univariate and multivariable analyses were performed to delineate the risk factors linked

Table 4. Factors and extent associated with renal recovery.

Variable	Complete recovery ($n=6976$)[a]	Partial or None ($n=5381$)[a]	OR (univariable)[b]	OR (multivariable)[b]	p-value
Sex					
Male	4,224 (60.6%)	3,037 (56.4%)			
Female	2,750 (39.4%)	2,344 (43.6%)	1.19 (1.10-1.27)	1.12 (1.03-1.22)	0.01
Cerebrovascular disease	913 (13.1%)	802 (14.9%)	1.16 (1.05-1.29)	1.33 (1.19-1.48)	<0.01
NSAIDs	1,503 (21.5%)	931 (17.3%)	0.76 (0.70-0.83)	0.99 (0.88-1.12)	0.87
Liver disease	813 (11.7%)	1,093 (20.3%)	1.93 (1.75-2.13)	1.43 (1.26-1.61)	<0.01
Nephrotoxic antibiotics	935 (13.4%)	812 (15.1%)	1.15 (1.04-1.27)	1.23 (1.08-1.40)	<0.01
Cancer	710 (10.2%)	863 (16%)	1.69 (1.52-1.88)	1.55 (1.38-1.74)	<0.01
AKI stage maximum (highest stage reached)					
1	1,716 (24.6%)	1,072 (19.9%)			
2	4,106 (58.9%)	2,132 (39.6%)	0.83 (0.76-0.91)	0.75 (0.68-0.83)	<0.01
3	1,154 (16.5%)	2,177 (40.5%)	3.02 (2.72-3.35)	1.54 (1.36-1.75)	<0.01
Septic shock	879 (12.6%)	1,346 (25%)	2.31 (2.11-2.54)	1.26 (1.12-1.41)	<0.01

APS: acute physiology score; AKI: acute kidney injury.
[a]Average (±SD) or frequency (%).
[b]Odds ratio for complete renal recovery.

to renal recovery. Given the scarcity of patients with partial renal recovery, this cohort was integrated into the nonrecovery group for analysis. The multivariable analysis identified several influential factors associated with kidney recovery, including age, any renal replacement therapy (any RRT), AKI stage, hemoglobin and lactate levels, sex, diuretic use, exposure to nephrotoxic antibiotics, cerebrovascular disease, hypertension, liver disease, cancer, the maximum AKI stage, and septic shock, as detailed in Table 4. Following multivariable adjustment, sex, nephrotoxic antibiotic exposure, cerebrovascular disease, hypertension, liver disease, cancer, maximum AKI stage, and septic shock emerged as independent risk factors for kidney recovery. Although age and lactate levels were statistically significant ($p<0.05$) in the multivariable logistic regression analysis, the adjusted odds ratios of 1.01 (95% CI, 1.01-1.02), 1.01 (95% CI, 1.00-1.02), and 1.03 (95% CI, 1.01-1.04), respectively, indicate that these factors may not have substantial clinical implications. The analysis of any RRT was limited due to the insufficient sample size, as noted in Table S3.

Discussion

SA-AKI is difficult to identify in its early stage, resulting in high mortality and poor prognosis [15]. Its pathogenesis is complex and involves multiple factors and its clinical phenotype, disease progression and treatment response are heterogeneous [15,16]. At present, there are no exact and effective interventions. Therefore, early detection of SA-AKI and the prediction of its progression may improve the outcomes of SA-AKI through the timely provision of supportive treatment and the prevention of further kidney injury.

Previous studies focusing on SA-AKI have usually used the criteria of Sepsis 3 and KDIGO, which indicate that there may be heterogeneity in the population of SA-AKI patients, as well as differences in morbidity and mortality [17]. Recently, the ADQI redefined SA-AKI and divided it into early SA-AKI and late SA-AKI [6]. However, to date, there has been no research on or exploration of the latest definitions of early and late SA-AKI in large databases. This study retrieved SA-AKI case information from the MIMIC-IV database and reported that there was no significant difference in 28-day all-cause mortality between early and late SA-AKI patients. Monard et al. [18] reported no significant difference in in-hospital mortality between early and late SA-AKI patients. White et al. [19] reported that the hospital mortality of SA-AKI patients was 18%, and SA-AKI was independently associated with an increase in mortality. These findings indicate that the occurrence time of SA-AKI may not be significantly associated with mortality. However, observational studies have shown that late SA-AKI in patients is associated with worse clinical outcomes and higher mortality than early SA-AKI is; however, the number of cases in that study was small, and the classification criteria for early and late SA-AKI were within and outside 24 h after the diagnosis of sepsis [9]. Wang et al. [20] reported that the incidence of MAKE and in-hospital mortality in patients with late SA-AKI were significantly greater than those in patients with early SA-AKI. Therefore, more studies are needed to confirm the association between SA-AKI occurrence time and mortality.

In addition, the increased use of NSAIDs in the early SA-AKI group (better renal recovery) and the lower mortality associated with the use of NSAIDs (Table S2) are not consistent with previous perceptions [21]. This may be the result of confounding factors, such as patients with better renal recovery and/or overall prognosis being more likely to be prescribed NSAIDs in the ICU than patients with persistent renal dysfunction or higher overall disease severity. However, in our multivariate analysis of risk factors for renal recovery in the total population, NSAIDs were not found to be a factor affecting renal recovery (Table 4). Similarly, a positive fluid balance may be a consequence of the difference between patients with early and late SA-AKI, but it does not appear to have an effect on mortality.

This study also revealed that the renal recovery of patients with early SA-AKI was significantly better than that of patients with late SA-AKI, and there may be some associations between diuretic use and renal recovery, whereas liver disease, cancer, Max AKI stage 3 and septic shock were associated with lower rates of renal recovery. Compared with

patients with late SA-AKI, patients with early SA-AKI had shorter hospital stays and ICU stays and fewer patients with a positive fluid balance, but the use of nonsteroidal anti-inflammatory drugs and nephrotoxic antibiotics and the incidence of septic shock were higher. The number of early SA-AKI patients at Max AKI stage 1 was significantly lower than that of late SA-AKI patients, but the number of early SA-AKI patients at Max AKI stage 3 was significantly greater than that of late SA-AKI patients. Compared with patients with late SA-AKI, patients with early SA-AKI develop AKI earlier, and the initiation of AKI treatment was earlier. For those who survived, the proportion with renal recovery was higher, and the length of hospital stay and ICU stay was shorter, but there seemed to be no effect on mortality. However, Monard et al. [18] reported that compared with patients with early SA-AKI, patients with late SA-AKI were younger, had greater renal recovery at ICU discharge, and required less continuous RRT during their ICU stay, which is slightly different from the findings of this study; however, only 50 late SA-AKI patients were included in Monard et al., so its conclusions need to be further verified. This study was conducted in a large cohort of patients from the MIMIC-IV database, which provides comprehensive data over a large time span, a larger sample size, and a greater number and proportion of patients with late SA-AKI; thus, its conclusions may be more reliable. Given the significant differences in the univariate analysis between early and late SA-AKI patients, the distinction between early and late SA-AKI may be useful for the targeted assessment and intervention of SA-AKI patients.

The findings of this study indicate that the classification of early and late SA-AKI by the ADQI has a certain degree of scientific validity, but there is currently no consensus on whether the two are related to different pathophysiological mechanisms. Studies have shown that early renal changes in SA-AKI are functional rather than structural, with microvascular and tubular stress abnormalities being more pronounced than pathological abnormalities within the first 48 h; with the redistribution of renal blood flow perfusion, renal medullary hypoxia can cause oxidative stress and inflammation, which can lead to the injury of renal mesangial cells and the development of SA-AKI [22,23]. The progression of disease may result in renal function recovery or deterioration, and the outcome largely depends on the severity of kidney injury, including the duration and recurrence of SA-AKI [2]. Moreover, several factors may lead to delayed recovery and the progression of kidney injury, resulting in chronic kidney disease [3]. These factors include persistent inflammation, fibrosis and decreased capillary density, resulting in persistent tissue hypoxia and ischemia, which promote interstitial fibrosis [3]. However, pharmacological treatments to alleviate fibrosis and oxidative stress are still in the experimental stage [2]. Therefore, the pathogenesis and clinical outcome of early and late SA-AKI still need more research.

Overall, this study revealed that although there were no significant differences in 28-day mortality, RRT or MAKE-30 between early SA-AKI patients and late SA-AKI patients, patients with early SA-AKI had higher rates of renal recovery and significantly shorter hospital stays and ICU stays. There were significant differences between the early and late SA-AKI patient groups in positive fluid balance, nephrotoxic antibiotic use, septic shock and AKI stage.

However, this study also has several limitations. First, SA-AKI patients screened for sepsis and AKI may be misclassified, and organ dysfunction identified through analysis may not be caused by infection. Second, the classification of the ADQI does not subdivide SA-AKI into various phenotypes, so the studied SA-AKI patient cohort may represent different groups with different risk factors and outcomes. Third, screening for RRT and nephrotoxic antibiotics at ICU discharge alone may introduce deterministic bias. Fourth, this study is based on electronic healthcare records from routine clinical practice, which lack data and outlier adjustment. Finally, the data used in this study are purely observational, and although propensity scores were used to adjust for confounders, the results may still be influenced by residual confounding factors, so the conclusions obtained are only hypothetical; moreover, the data in the MIMIC-IV database come from a single academic medical center in the United States, so the generalizability of the conclusions drawn in this study may be limited.

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Disclosure statement

The authors declare that they have no conflicts of interest.

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References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic

shock (sepsis-3). JAMA. 2016;315(8):801–810. doi: 10.1001/jama.2016.0287.
[2] Peerapornratana S, Manrique-Caballero CL, Gómez H, et al. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int. 2019;96(5):1083–1099. doi: 10.1016/j.kint.2019.05.026.
[3] Legrand M, Bagshaw SM, Bhatraju PK, et al. Sepsis-associated acute kidney injury: recent advances in enrichment strategies, sub-phenotyping and clinical trials. Crit Care. 2024;28(1):92. doi: 10.1186/s13054-024-04877-4.
[4] Pickkers P, Darmon M, Hoste E, et al. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. Intensive Care Med. 2021;47(8):835–850. doi: 10.1007/s00134-021-06454-7.
[5] Zarbock A, Koyner JL, Gomez H, et al. Sepsis-associated acute kidney injury-treatment standard. Nephrol Dial Transplant. 2023;39(1):26–35. doi: 10.1093/ndt/gfad142.
[6] Zarbock A, Nadim MK, Pickkers P, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol. 2023;19(6):401–417. doi: 10.1038/s41581-023-00683-3.
[7] Roman-Marchant O, Orellana-Jimenez CE, De Backer D, et al. Septic shock of early or late onset: does it matter? Chest. 2004;126(1):173–178. doi: 10.1378/chest.126.1.173.
[8] Vincent JL, Sakr Y, Groeneveld J, et al. ARDS of early or late onset: does it make a difference? Chest. 2010;137(1):81–87. doi: 10.1378/chest.09-0714.
[9] Lima RS, Marques CN, Silva Júnior GB, et al. Comparison between early and delayed acute kidney injury secondary to infectious disease in the intensive care unit. Int Urol Nephrol. 2008;40(3):731–739. doi: 10.1007/s11255-008-9352-9.
[10] Guerin C, Girard R, Selli JM, et al. Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhône-Alpes area study group on acute renal failure. Am J Respir Crit Care Med. 2000;161(3 Pt 1):872–879. doi: 10.1164/ajrccm.161.3.9809066.
[11] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–1499. doi: 10.1016/j.ijsu.2014.07.013.
[12] Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol. 2017;13(4):241–257. doi: 10.1038/nrneph.2017.2.
[13] Kellum JA, Chawla LS, Keener C, et al. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med. 2016;193(3):281–287. doi: 10.1164/rccm.201505-0995OC.
[14] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41–55. doi: 10.1093/biomet/70.1.41.
[15] Liu J, Xie H, Ye Z, et al. Rates, predictors, and mortality of sepsis-associated acute kidney injury: a systematic review and meta-analysis. BMC Nephrol. 2020;21(1):318. doi: 10.1186/s12882-020-01974-8.
[16] Manrique-Caballero CL, Del Rio-Pertuz G, Gomez H. Sepsis-associated acute kidney injury. Crit Care Clin. 2021;37(2):279–301. doi: 10.1016/j.ccc.2020.11.010.
[17] Qiao J, Cui L. Multi-omics techniques make it possible to analyze sepsis-associated acute kidney injury comprehensively. Front Immunol. 2022;13:905601. doi: 10.3389/fimmu.2022.905601.
[18] Monard C, Bianchi N, Kelevina T, et al. Epidemiology and outcomes of early versus late septic acute kidney injury in critically ill patients: a retrospective cohort study. Anaesth Crit Care Pain Med. 2024;43(1):101332. doi: 10.1016/j.accpm.2023.101332.
[19] White KC, Serpa-Neto A, Hurford R, et al. Sepsis-associated acute kidney injury in the intensive care unit: incidence, patient characteristics, timing, trajectory, treatment, and associated outcomes. A multicenter, observational study. Intensive Care Med. 2023;49(9):1079–1089. doi: 10.1007/s00134-023-07138-0.
[20] Wang N, Wang MP, Jiang L, et al. [Association between onset time of sepsis-associated acute kidney injury and clinical outcome in patients with sepsis]. Zhonghua Yi Xue Za Zhi. 2024;104(21):1972–1978. doi: 10.3760/cma.j.cn112137-20231030-00940.
[21] Baker M, Perazella MA. NSAIDs in CKD: are they safe? Am J Kidney Dis. 2020;76(4):546–557. doi: 10.1053/j.ajkd.2020.03.023.
[22] Ma S, Evans RG, Iguchi N, et al. Sepsis-induced acute kidney injury: a disease of the microcirculation. Microcirculation. 2019;26(2):e12483. doi: 10.1111/micc.12483.
[23] Lankadeva YR, Okazaki N, Evans RG, et al. Renal medullary hypoxia: a new therapeutic target for septic acute kidney injury? Semin Nephrol. 2019;39(6):543–553. doi: 10.1016/j.semnephrol.2019.10.004.