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Epidemiology of sepsis-associated acute kidney injury in the ICU with contemporary consensus definitions

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Abstract

Background The definition of sepsis-associated acute kidney injury (SA-AKI) was updated in 2023. This study aims to describe the epidemiology of SA-AKI using updated consensus definition and to evaluate clinical outcomes.

Methods The study was a retrospective cohort analysis conducted at two academic medical centers. Adult patients admitted to intensive care units (ICU) between 2010 and 2022 were included and categorized as SA-AKI, sepsis alone, or AKI alone. SA-AKI was further classified by time of onset (early < 2 days from sepsis diagnosis vs. late 2–7 days following sepsis diagnosis) and presence of septic shock. Clinical outcomes included hospital mortality and major adverse kidney events (MAKE = death, kidney replacement therapy, or reduced kidney function from baseline) at discharge.

Results 187,888 adult ICU patients were included, and SA-AKI was found in nearly half of sepsis patients and about 1 in 6 ICU admissions. 1 in 4 patients with SA-AKI died during hospitalization and 37.7% experienced at least one MAKE by hospital discharge. Compared to sepsis or AKI alone, SA-AKI was associated with higher mortality (adjusted HR 1.59; 95% CI 1.51–1.66) and higher odds of MAKE (adjusted OR 3.35; 95% CI 3.19–3.51). The early clinical phenotype of SA-AKI was most common, with incident AKI decreasing daily from sepsis onset. The presence of septic shock significantly worsened outcomes.

Conclusions Applying updated consensus definitions highlights the high prevalence of SA-AKI in the ICU and its significant associated morbidity and mortality. Outcomes differ based on clinical phenotypes, including the timing of SA-AKI onset and the presence of shock.

Keywords Sepsis-associated acute kidney injury (SA-AKI), Acute kidney injury (AKI), Sepsis, Epidemiology

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Introduction

Sepsis and acute kidney injury (AKI) are complex heterogeneous syndromes whose definitions have evolved over the years [1, 2]. Sepsis-associated acute kidney injury (SA-AKI) is associated with substantial morbidity and mortality [3]. Patients with SA-AKI are at risk of prolonged kidney injury during hospitalization, which can lead to long-term complications such as chronic kidney disease (CKD), the need for kidney replacement therapy (KRT), or death [4]. Sepsis is the most frequently identified risk factor in 26–50% of all hospitalized AKI cases. SA-AKI often presents with more severe forms of AKI and a higher risk of mortality compared to non-septic AKI, with a global incidence estimated at 6 to 10 million cases per year [3, 5–8]. Until recently, the lack of a standardized definition for SA-AKI has hampered its epidemiological study, leading to variations in reported incidence and outcomes [8, 9].

A consensus report from the 28th Acute Disease Quality Initiative (ADQI) Workgroup has now defined SA-AKI as the concurrence of sepsis (as per Sepsis-3 criteria) and AKI (as per Kidney Disease: Improving Global Outcomes [KDIGO] criteria) occurring within 7 days of sepsis diagnosis [1, 10, 11]. Further, SA-AKI is categorized into early (within 48 h of sepsis diagnosis) and late (48 h to 7 days after sepsis diagnosis) [10].

While this harmonized definition of SA-AKI is a significant step forward, further research is needed to better understand its epidemiology based on the new criteria. Although several studies have explored SA-AKI epidemiology, the reports originate from regions outside North America, leaving a gap in understanding the epidemiology specific to this region [12–14]. Additionally, there is limited research that provides a comprehensive analysis of SA-AKI subtypes, such as differentiating between early and late SA-AKI. Addressing these gaps through more detailed and region-specific investigations will not only enhance our understanding of SA-AKI but also provide insights that may inform clinical practice globally.

Methods

Cohort

We performed a retrospective cohort study using electronic health record (EHR) data of two large, tertiary care academic medical centers: the University of Alabama at Birmingham (UAB) including patients admitted between February 2010 and June 2022 and the University of Kentucky (UK) including patients admitted between January 2009 and March 2020. All ICU admissions during the studied time periods were included. If patients had multiple ICU admissions over this time, only the first ICU admission was analyzed. Patients discharged from the ICU and re-admitted to the ICU within 36 h or sooner were assessed as a single ICU encounter. Patients with End-Stage Kidney Disease (ESKD) or kidney transplant were excluded from the cohort. The study was approved by the Institutional Review Boards of both institutions, which granted a waiver of informed consent given its minimal risk and retrospective nature.

Definitions

Sepsis was defined using Sepsis-3 criteria: suspected infection with organ dysfunction characterized as a Sequential Organ Failure Assessment (SOFA) score ≥ 2 [1, 15, 16]. In order to identify the timestamp of infection, the combination of culture and antibiotic start times were used [17] (Figure S1). If antibiotics were administered first, culture sampling must have been obtained during the subsequent 24 h. If cultures were obtained first, antibiotics must have been ordered within the subsequent 72 h. The earlier of these two was adopted as the reference time point for suspected infection. All cultures related to bacterial, fungal, or viral infections were considered, while cultures obtained for clear surveillance purposes were excluded when identified. The onset of sepsis was defined as the day when the maximum SOFA score reached 2 points or higher within a time window from 48 h before to 24 h after the reference time point of infection, as organ dysfunction in sepsis can arise even before infection is clinically recognized by health professionals [17]. This approach assumes a baseline SOFA score of 0 before the reference time point, as the Sepsis-3 definition of sepsis is based on an increase of 2 points or more in the score. A separate timestamp for the onset of AKI was created based on KDIGO definitions using serum creatinine and urine output components (in patients with a urinary catheter present), and KDIGO AKI stage was classified accordingly [11]. Details of urine output data utilized to define AKI are presented in Figure S2. Notably, to ensure accurate identification of both sepsis and AKI, clinical data—including infection markers, laboratory values, and organ dysfunction parameters—were examined from up to three days prior to ICU admission.

Using the established timestamps and based on the ADQI definition, SA-AKI was documented when AKI occurred within 7 days of the onset of sepsis [10]. Using this definition, patients with SA-AKI were further classified into early (AKI occurring on the same day or following day of sepsis diagnosis) or late (AKI occurring between 2 and 7 days following sepsis diagnosis) [10]. SA-AKI was characterized as either concurrent with septic shock or not, occurring within 48 h (early) or 2–7 days (late) of the sepsis diagnosis. Septic shock was defined as the intravenous administration

of norepinephrine, vasopressin, epinephrine, phenylephrine, or dopamine during these time frames, in conjunction with a lactate level of ≥ 2.0 mmol/L [1].

To assess the attributable harm of SA-AKI, patients were categorized as follows: those with SA-AKI (including early and late onset), those with sepsis only (no AKI), those with AKI only (no sepsis), and those with both sepsis and AKI but not meeting the criteria for SA-AKI. Recognizing that definitions used for diagnosing sepsis from EHR (such as antibiotic and culture ordering) are clinician-driven, and that organ injury from sepsis may occur before sepsis is clinically recognized, we also investigated the impact of a modified ADQI SA-AKI definition on the prevalence of this condition as a sensitivity analysis. In this revised definition, the timestamp for AKI could occur up to 2 days prior to the sepsis diagnosis onset.

Demographics and outcomes

Baseline demographic and clinical characteristics were documented including comorbidities (Charlson Comorbidity Index [CCI]) and acuity of illness (SOFA) [16, 18, 19]. Baseline creatinine was defined as the closest outpatient creatinine measurement within 7 to 365 days before admission. If unavailable, prior inpatient serum creatinine measurements meeting the same condition were used. If still unidentifiable, the lowest serum creatinine measurement from 7 days before admission to discharge (of the index hospitalization) was considered. Estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD-EPI race-free creatinine equation [20]. Receipt of concurrent nephrotoxins, defined as vancomycin, aminoglycosides, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers, were documented in relation to sepsis onset.

The primary outcomes of interest were hospital mortality and the occurrence of major adverse kidney events (MAKE) at hospital discharge, a composite of death, KRT, or reduced kidney function [21]. KRT dependence was defined as any type of dialysis modality received within 3 days of hospital discharge. Reduced kidney function was defined as a discharge serum creatinine ≥ 1.5 times baseline or eGFR ≤ 50% of baseline for those not dependent on KRT at the time of discharge. Additional study outcomes included persistent AKI (≥ 7 days as any level of AKI by KDIGO), serum creatinine and blood urea nitrogen up to 7 days following AKI, need for any KRT during ICU admission, duration of mechanical ventilation, and ICU and hospital length of stay. For patients who developed AKI, ICU-, KRT-, and mechanical ventilator-free days were defined as the number of days within a 28-day period following the onset of AKI during which the patient did not require each resource. For patients who died within this 28-day timeframe, the count of free days was set to zero. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cohort studies [22].

Statistical analysis

Summary statistics were used to describe cohorts. Continuous variables were expressed as median (interquartile range). For two-group comparisons of continuous variables, the Wilcoxon rank-sum test was used. Categorical variables were analyzed using the Chi-square test. Multivariable models included Cox proportional hazards model (illustrated with adjusted survival curves) and logistic regression. Time-to-event models were selected for mortality while logistic regression models were used for the MAKE outcome since hospital length of stay would confound a time-to-event assessment of MAKE at hospital discharge. In order to adjust for potential differences in baseline characteristics, all models were adjusted for the following variables selected by the investigators: study site, age, sex, race, body mass index (BMI), diabetes, hypertension, cardiovascular disease, coronary artery disease, CKD, liver cirrhosis, CCI, and SOFA score at ICU admission. As an additional analysis, a logistic regression model was constructed to investigate risk factors for SA-AKI development among patients with sepsis, incorporating the adjustment variables mentioned above as independent variables while using the non-renal SOFA score at sepsis onset, which excludes the renal component. Due to missing BMI values at admission in 21.2% of patients, we used Multivariate Imputation by Chained Equations (MICE) [23]. The predictive variables for BMI used in MICE used were age, sex, race, presence of diabetes, CCI, SOFA score at ICU admission, and study site. All statistical analyses were performed using R (Version 4.22, Vienna Austria).

Results

Cohort derivation

From the two included centers, 203,412 adult ICU patients were identified. Applying the exclusion criteria resulted in 187,888 patients for further evaluation (Fig. 1). Of these, 63,536 (33.8%) met criteria for sepsis as defined using Sepsis-3 [1]. The median onset of sepsis was ICU day 0 (IQR 0–0), with 51,815 patients (81.6% of septic patients) already meeting sepsis criteria by the day of ICU admission. SA-AKI, using the ADQI definition, was present in 29,615 individuals, representing 46.6% of

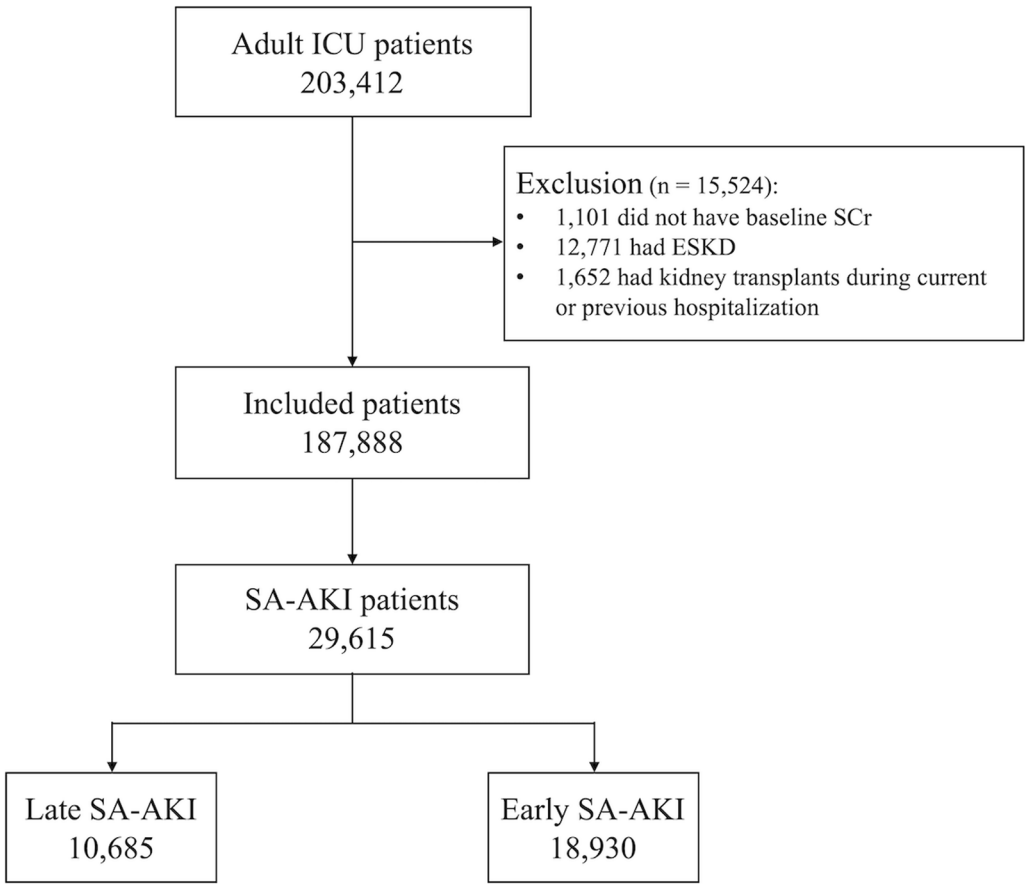

Fig. 1 Cohort derivation. *ICU* intensive care unit; *ESKD* end-stage kidney disease; *SA-AKI* sepsis-associated acute kidney injury

all sepsis patients and 15.8% of all adult ICU admissions [10]. The median onset of SA-AKI was ICU day 1 (IQR 0–2), which corresponded to a median of 1 day (IQR 0–2) from sepsis onset.

Patients with SA-AKI were 43.9% women, 21.7% black and had a median age of 60 years (IQR 48–70) (Table 1). The overall hospital mortality of patients with SA-AKI was 25%, and the incidence of MAKE was 37.7% at hospital discharge (Table 2). Among patients with SA-AKI, 18,930/29,615 (63.9%) were classified as the early SA-AKI phenotype while 10,685/29,615 (36.1%) were classified as late SA-AKI [10]. From this cohort derivation, distinct groups of patients are identified as shown in Fig. 2 and henceforth referred to as: sepsis only (A), AKI only (B), SA-AKI (C) (split into early (D) and late (E) SA-AKI), and sepsis and AKI occurring during hospitalization without SA-AKI criteria (F). The latter group is displayed in Fig. 3, as is the incidence of AKI in relation to sepsis onset for SA-AKI patients. The incidence of AKI in SA-AKI patients was highest the day of sepsis onset and decreased daily over the subsequent week.

Using a modified ADQI SA-AKI definition allowing for AKI to occur prior to sepsis onset/recognition, an additional 2082 patients were identified, increasing the total number by 7% to 31,697 (49.9% of all sepsis cases; 16.9% of all adult ICU admissions). This group is partly represented by F in Fig. 2.

SA-AKI vs. sepsis only

Baseline demographics comparing patients with and without sepsis, as well as SA-AKI vs. sepsis only are shown in Table S1. Compared to patients with sepsis only (A), SA-AKI (C) patients tended to be slightly older, have more comorbidities (including CKD), and have lower baseline eGFR. SA-AKI patients also demonstrated worse outcomes than sepsis only patients, including a more than twofold increase in mortality (25.0% vs. 11.2%; $p < 0.001$) and nearly threefold increase in MAKE (37.7% vs. 12.9%; $p < 0.001$) (Table S2).

Table 1 Baseline demographics: early vs. late sepsis-associated acute kidney injury

	Overall SA-AKI (n = 29,615)	Early SA-AKI (n = 18,930)	Late SA-AKI (n = 10,685)	p^*
Location (%)				
UAB	15,678 (52.9)	9873 (52.2)	5805 (54.3)	< 0.001
UK	13,937 (47.1)	9057 (47.8)	4880 (45.7)	
Age (median [IQR])	60 [48,70]	59 [47,69]	61 [50,71]	< 0.001
Sex (%)				
Female	13,012 (43.9)	8398 (44.4)	4614 (43.2)	0.051
Male	16,603 (56.1)	10,532 (55.6)	6071 (56.8)	
Race (%)				
White	21,945 (74.1)	14,028 (74.1)	7917 (74.1)	0.769
Black	6421 (21.7)	4115 (21.7)	2306 (21.6)	
Other/Unknown	1249 (4.2)	787 (4.2)	462 (4.3)	
BMI (median [IQR])	28.80 [24.45,33.46]	28.73 [24.41,33.38]	28.94 [24.58,33.64]	0.007
Diabetes (%)	7502 (25.3)	4665 (24.6)	2837 (26.6)	< 0.001
Hypertension (%)	11,606 (39.2)	7402 (39.1)	4204 (39.3)	0.690
Cardiovascular Disease (%)	9594 (32.4)	5816 (30.7)	3778 (35.4)	< 0.001
Coronary Artery Disease (%)	7163 (24.2)	4444 (23.5)	2719 (25.4)	< 0.001
Chronic Kidney Disease (%)	5292 (17.9)	2992 (15.8)	2300 (21.5)	< 0.001
Liver cirrhosis (%)	2693 (9.1)	1628 (8.6)	1065 (10.0)	< 0.001
Charlson comorbidity index (median [IQR])	4 [2, 6]	4 [2, 6]	4 [2, 7]	< 0.001
Type of ICU admission (%)				
Medicine	19,328 (65.3)	12,505 (66.1)	6823 (63.9)	< 0.001
Surgical	10,287 (34.7)	6425 (33.9)	3862 (36.1)	
COVID-19 during hospitalization (%)	1940 (6.6)	1182 (6.2)	758 (7.1)	0.005
Baseline SCr (median [IQR]) (mg/dl)	0.96 [0.69,1.40]	0.93 [0.67,1.40]	1.00 [0.70,1.40]	< 0.001
Baseline eGFR (median [IQR]) (mL/min/1.73m^2)	81.40 [50.23, 105.80]	83.01 [50.58,106.64]	78.44 [49.61,103.85]	< 0.001
Nephrotoxin exposure days -7 to + 6 from sepsis onset (%)	21,547 (72.8)	13,505 (71.3)	8042 (75.3)	< 0.001
SOFA score at ICU admission onset (median [IQR])	6 [3, 9]	6 [3, 9]	5 [3, 8]	< 0.001
Renal SOFA score at ICU admission (median [IQR])	1 [0, 2]	1 [0, 2]	1 [0, 1]	< 0.001
SOFA score at sepsis onset (median [IQR])	5 [3, 8]	5 [3, 8]	4 [3, 7]	< 0.001
Renal SOFA score at sepsis onset (median [IQR])	1 [0, 2]	1 [0, 2]	1 [0, 1]	< 0.001
Septic shock within 7 days of sepsis onset (%)	7831 (26.4)	5026 (26.6)	2805 (26.3)	0.585
KDIGO AKI stage at AKI onset (%)				
Stage 1	17,921 (60.5)	10,839 (57.3)	7082 (66.3)	< 0.001
2	5435 (18.4)	3620 (19.1)	1815 (17.0)	
3	4197 (14.2)	2894 (15.3)	1303 (12.2)	
3D	2062 (7.0)	1577 (8.3)	485 (4.5)	
AKI diagnostic criteria				
SCr and KRT only	25,025 (84.5)	16,669 (88.1)	8356 (78.2)	< 0.001
UOP only	4425 (14.9)	2165 (11.4)	2260 (21.2)	
Both	165 (0.6)	96 (0.5)	69 (0.6)	

SA-AKI sepsis-associated acute kidney injury; *UAB* University of Alabama at Birmingham; *UK* University of Kentucky; *IQR* interquartile range; *BMI* body mass index; *SCr* serum creatinine; *eGFR* estimated glomerular filtration rate; *UOP* urine output; *SOFA* sequential organ failure assessment; *KDIGO* kidney disease; improving global outcomes; *AKI* acute kidney injury; *3D* stage 3 with KRT; *KRT* kidney replacement therapy

* This represents comparison between Early and Late SA-AKI

AKI only vs. SA-AKI

When evaluating AKI only (B) vs. SA-AKI (C), demographics were overall similar, however, patients with SA-AKI tended to present with a slightly higher comorbidity burden and had lower baseline eGFR (Table S3). SA-AKI patients were more likely to require dialysis at the time of AKI onset (Table S3), as well as

Table 2 Outcomes: early vs. late sepsis-associated acute kidney injury

	Overall SA-AKI (n = 29,615)	Early SA-AKI (n = 18,930)	Late SA-AKI (n = 10,685)	*p**
Mortality (%)	7418 (25.0)	4538 (24.0)	2880 (27.0)	< 0.001
Major adverse kidney event (%)	11,162 (37.7)	7013 (37.0)	4149 (38.8)	0.002
Maximum creatinine within 7 days of AKI onset (median [IQR]), mg/dl	1.80 [1.20,2.88]	1.85 [1.22, 3.00]	1.70 [1.12, 2.60]	< 0.001
Maximum blood urea nitrogen within 7 days of AKI onset (median [IQR]), mg/dl	36 [23,57]	36 [22,57]	38 [24,58]	< 0.001
Maximum KDIGO stage within 7 days of AKI onset (%)				< 0.001
Stage 1	12,657 (42.7)	7512 (39.7)	5145 (48.2)	
2	6388 (21.6)	4222 (22.3)	2166 (20.3)	
3	6869 (23.2)	4545 (24.0)	2324 (21.8)	
3D	3701 (12.5)	2651 (14.0)	1050 (9.8)	
Persistent AKI (%)	5359 (18.1)	3291 (17.4)	2068 (19.4)	< 0.001
Hospital length of stay (median [IQR]), days	10 [6, 19]	9 [5, 18]	12 [7, 21]	< 0.001
ICU length of stay (median [IQR]), days	5 [2, 10]	4 [2, 8]	7 [4, 12]	< 0.001
ICU-free days (median [IQR]), days	22 [0,26]	22 [0,26]	21 [0,26]	< 0.001
KRT-free days (median [IQR]), days	28 [0,28]	28 [5, 28]	28 [0,28]	0.001
Mechanical ventilation-free days (median [IQR]), days	26 [0,28]	26 [0,28]	26 [0,28]	0.894

SA-AKI sepsis-associated acute kidney injury; *AKI* acute kidney injury; *IQR* interquartile range; *KDIGO* kidney disease: improving global outcomes; *3D* stage 3 with KRT; *ICU* intensive care unit; *KRT* kidney replacement therapy

* This represents comparison between Early and Late SA-AKI

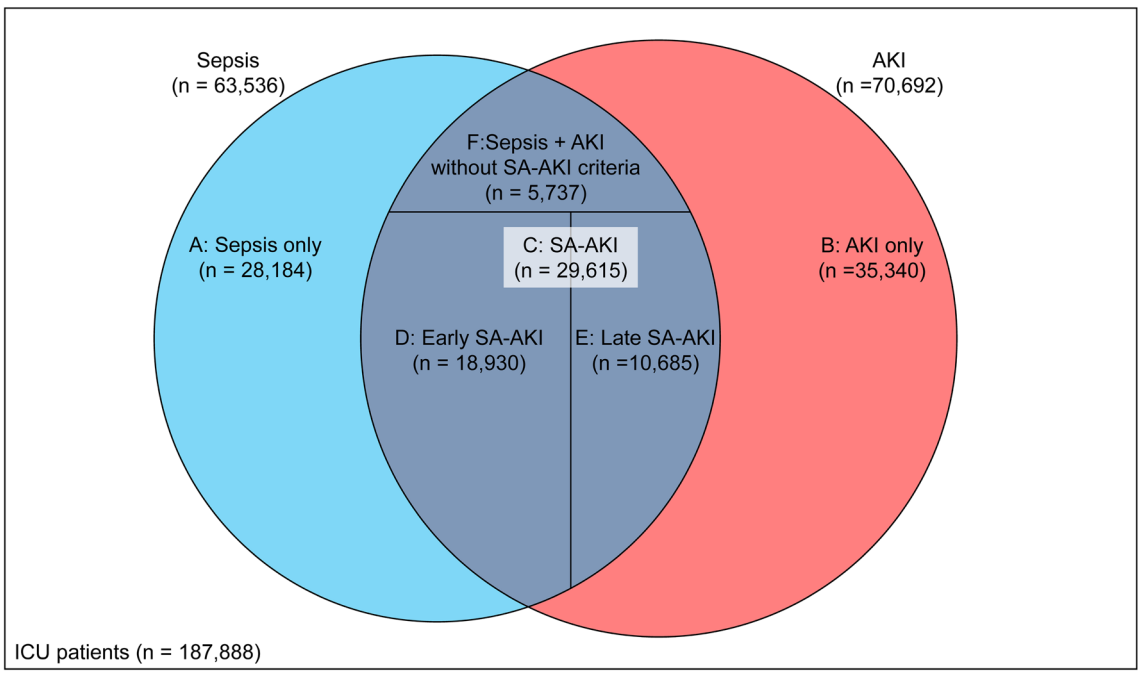

Fig. 2 Venn diagram of patient categorization for analysis. Displayed areas are representative of relative proportions. Letters **A**–**F** are for reference of specific patient cohorts. *AKI* acute kidney injury; *ICU* intensive care unit; *SA-AKI* sepsis-associated acute kidney injury

more likely to die and experience a MAKE at hospital discharge (Table S4).

SA-AKI: adjusted analyses and phenotypes

In the adjusted Cox proportional hazards model, SA-AKI (C) was associated with the highest hospital mortality (HR 1.59; 95% CI 1.51–1.66) compared to sepsis only

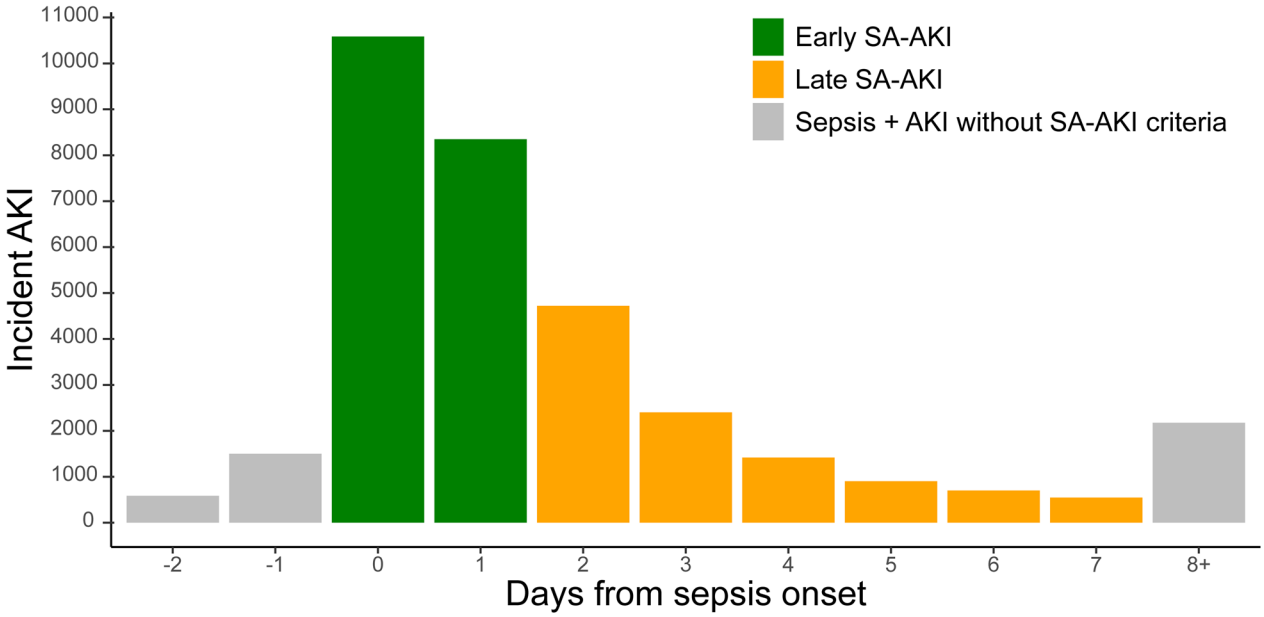

Fig. 3 Incident AKI in relation to sepsis onset. *AKI* acute kidney injury; *SA-AKI* sepsis-associated acute kidney injury

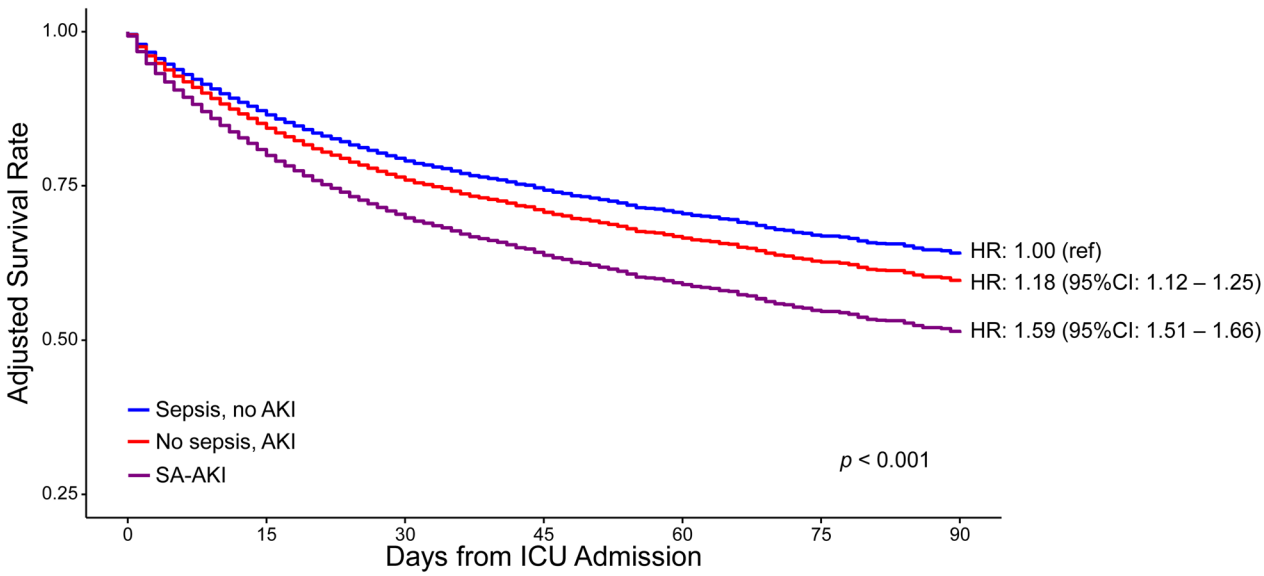

Fig. 4 Adjusted survival curves from cox proportional hazards model. *AKI* acute kidney injury; *SA-AKI* sepsis-associated acute kidney injury

patients (A) and AKI only patients (B) (Fig. 4, Table S5). The risk of death is 59% higher in SA-AKI vs. sepsis alone (without AKI). This risk is similar whether SA-AKI is phenotypically classified as early or late (Figure S3). Similarly, SA-AKI carried the highest risk of MAKE at discharge compared to the other groups when controlling for baseline variables in the adjusted model (Table S5), with SA-AKI conferring 3.35 times higher odds of MAKE (OR 3.35; 95% CI 3.19–3.51).

Demographic data for SA-AKI patients stratified by early vs. late phenotype are shown in Table 1. KDIGO stage 1 AKI was the most common classification at AKI onset. Within 7 days from AKI onset, 29.4% of SA-AKI patients who initially presented with stage 1 and 57.3% of overall SA-AKI patients progressed to AKI stages 2 or 3. Risk factors for SA-AKI among all patients with sepsis included: site, older age, black race, higher BMI, coronary

artery disease, CKD, liver cirrhosis, higher CCI, and higher non-renal SOFA score at sepsis onset (Table S6).

Early (vs. late) SA-AKI was associated with a higher prevalence of comorbid conditions such as diabetes, hypertension, and coronary artery disease; however, the overall comorbidity index was lower (Table 1 and Table S7). The severity of acute illness was higher in this group in terms of both total SOFA and non-renal SOFA scores. In contrast, late SA-AKI was more frequently associated with comorbidities such as cardiovascular disease, chronic kidney disease, and liver cirrhosis. This group exhibited lower overall acute illness severity but had a higher likelihood of nephrotoxin exposure before and after sepsis onset. Clinical outcomes are shown in Table 2.

Overall, SA-AKI defined with consensus definitions is associated with significant morbidity and mortality as reflected by a 25% hospital mortality rate and a 37.7% MAKE rate by hospital discharge. Approximately 1 in 8 SA-AKI patients required KRT during the first week of AKI onset. When compared to early SA-AKI, patients with late SA-AKI tended to have distinct clinical outcomes from early SA-AKI, including a higher hospital mortality and increased frequency of MAKE at hospital discharge. Additional comparisons of characteristics and outcomes between patients with early and late SA-AKI excluding those who died within two days of sepsis onset are consistent with the findings described above (Tables S8, S9).

Patients with septic shock and SA-AKI tended to present with a higher comorbidity burden based on CCI (not necessarily each comorbidity assessed by the study team in isolation) and more severe AKI presentation (Table S10) and were at a distinctly higher risk for poor outcomes compared to SA-AKI patients without septic shock (Table S11). The presence of septic shock was associated with a doubling of hospital mortality. Approximately 1 out of every 2 patients with septic shock and SA-AKI experienced MAKE by hospital discharge.

Discussion

By applying the ADQI consensus definition for SA-AKI in ICU patients from two different centers, we observed that SA-AKI is present in nearly 50% of sepsis cases and nearly 1 in every 6 ICU admissions [10]. SA-AKI is associated with significantly higher hospital mortality and MAKE at hospital discharge when compared to patients with sepsis or AKI alone, and the presence of septic shock worsens outcomes in SA-AKI. The early phenotype predominates in approximately two-thirds of SA-AKI cases, with incident AKI decreasing daily from the onset of sepsis. Despite occurring less commonly, the late SA-AKI phenotype is associated with higher MAKE. Using the largest cohort of SA-AKI patients with contemporary definitions, this work captures the significant degree of morbidity and mortality attributable to SA-AKI among ICU adult patients.

The challenges created by the heterogeneity of definitions used for sepsis and AKI in SA-AKI research is highlighted in a recent systematic review [10, 24]. Of 47 included studies, four different definitions were observed for sepsis and three for AKI. Incomplete details, including specific sepsis criteria or timing of AKI relative to sepsis, were noted [10, 24]. This non-standardized reporting around SA-AKI has created challenges for clinical research, and for this reason, the formalization of an SA-AKI definition is a step forward for the field. Definitions and sub-classification of syndromes must be validated, hence we sought to characterize SA-AKI epidemiology and outcomes with the newly proposed ADQI SA-AKI definition [10]. Interestingly, we observed a small but notable increase in SA-AKI frequency when applying a modified ADQI definition that allowed for AKI prior to sepsis onset/recognition that deserves future investigation as AKI could be an early sign of sepsis in select cases [10].

A similar approach to describe the epidemiology was undertaken in a multicenter study of Australian ICUs using the ADQI SA-AKI definition [10, 12]. Of 84,528 patients identified, 13,451 met criteria for SA-AKI, or approximately 1 out of 6 ICU patients which is similar to our findings [12]. SA-AKI patients had more comorbidities and a higher acuity of illness compared to patients not meeting SA-AKI criteria, including 40% of SA-AKI patients classified as in septic shock at the time of sepsis diagnosis which is a somewhat higher proportion of septic shock than the one observed in our study. Similar to our findings, in this cohort more than half of SA-AKI patients were classified as stage 1 AKI, and the diagnosis of sepsis and AKI tended to be on the same day. The study also reported that the time from sepsis onset to AKI development in SA-AKI patients was a median of 0 days (IQR 0-1), which was shorter than our study (median of 1 day [IQR 0-2]), suggesting that the proportion of late SA-AKI cases may be lower than the one-third observed in our cohort. In our study, we retrospectively identified sepsis onset up to three days before ICU admission, which may have led to an earlier and more sensitive detection of sepsis, thereby increasing the observed time interval to AKI onset. This methodological difference could explain the discrepancy in late SA-AKI prevalence.

Another retrospective cohort study conducted in Sweden including 21,668 ICU patients (of whom 1835 were classified as having sepsis) reported that SA-AKI by ADQI criteria using both SCr and urine output

occurred in 90% of sepsis patients, a higher proportion than the one observed in our cohort [13]. Furthermore, 97% of SA-AKI cases in this study were classified as early SA-AKI. This discrepancy is likely due to differences in sepsis definitions. In that study, organ dysfunction in sepsis was defined as norepinephrine administration and mechanical ventilation use, resulting in a cohort with a considerably high severity of illness. However, it is important to note that this study assumed ICU admission day as the onset of sepsis, which may have introduced misclassification. Additionally, a multicenter registry report from Korea, which used the same SA-AKI definition, but considered only SCr for AKI identification without incorporating urine output, reported that 89% of SA-AKI cases were identified on the first ICU day [14]. However, this study did not report the time difference between sepsis and AKI onset, and therefore the proportion of early vs. late SA-AKI remains unclear. Given these variations, further studies are needed to validate the early vs. late SA-AKI sub-phenotypes defined by ADQI, building upon our findings.

Our study has notable strengths as it leverages the largest cohort of SA-AKI patients using contemporary definitions and is the first to apply the new ADQI definition of SA-AKI to a large multicenter cohort in the United States [10]. By investigating a contemporary SA-AKI definition and its attributable harm—compared to sepsis or AKI alone—as well as examining SA-AKI phenotypes (early vs. late) and their associated outcomes (mortality, MAKE and increased resource use), this study offers important insights into these conditions in the ICU setting. These epidemiological data can support quality improvement initiatives in sepsis care, such as antibiotic stewardship to mitigate nephrotoxicity, risk-based monitoring strategies, and hospital resource allocation tailored to disease severity, all of which warrant further investigation to enhance their effectiveness. Our hypothesis is that early SA-AKI may be driven by microcirculatory vulnerability—such as diabetes, hypertension, and coronary artery disease—leading to rapid AKI progression, whereas late SA-AKI may reflect progressive kidney insult due to challenges in fluid management optimization after the resuscitation phase and/or nephrotoxin exposures. Factors such as CKD, liver cirrhosis, and cardiovascular disease, including heart failure, may contribute to this delayed injury [25–27]. While distinct clinical trajectories suggest that early and late SA-AKI may stem from distinct pathophysiological pathways, definitive causative mechanisms could not be fully elucidated in this study, warranting further investigation.

This study has also limitations, primarily related to its retrospective design, which relies on the accuracy and completeness of EHR data. For sepsis, the assumption of a baseline SOFA score of 0, consistent with the Sepsis-3 definition, may have led to the misclassification of patients with chronic organ dysfunction as having acute organ dysfunction. Additionally, it was not possible to determine from EHR data whether cultures were ordered specifically due to suspected sepsis or infection. For AKI, urine output data were intentionally marked as missing for patients without urinary catheters to prevent misclassification; however, this approach may have inadvertently led to under detection of AKI cases. Furthermore, differences in urinary catheter use and documentation practices across institutions may have introduced another potential source of misclassification. Additionally, baseline SCr was available as preadmission SCr in less than 30% of cases, meaning that for approximately 70% of patients, the lowest value during the index hospitalization was used. This may have contributed to AKI misclassification. The study included ICU admissions only, which limits the evaluation of ward patients with SA-AKI. The inclusion of patients transferred from outside hospitals is another limitation, as it may influence the timing and severity of SA-AKI diagnosis upon admission. Our study only considered a limited number of all potential nephrotoxins [28]. Missing data for some variables, such as BMI, were dealt with using imputation. While statistical techniques such as MICE were used, imputation may introduce bias or inaccuracies if the missing data were not missing at random. Finally, while we carefully considered confounders in our analysis, unmeasured confounding may still influence these results.

Conclusion

Using contemporary definitions of SA-AKI, this study provides an update on the epidemiology of SA-AKI in critically ill adult patients as well as demonstrated the significant morbidity and mortality of SA-AKI in comparison to sepsis and AKI in isolation. SA-AKI occurs in nearly half of sepsis patients and nearly 1 in 6 ICU admissions marking the importance to public health and healthcare systems. While early SA-AKI is more common, both early and late SA-AKI are associated with adverse outcomes. The presence of septic shock significantly worsens outcomes in SA-AKI. Updated epidemiology of a common condition, such as SA-AKI, is a critical first step towards identifying vulnerable populations, guiding quality assurance, and informing policy to promote health equity.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05351-5.

Additional file1 (PDF 1196 KB)

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Author contributions
T.T., A.H.F., and J.A.N. conceptualized the study. T.T. and L.J.L. acquired the data. T.T. conducted the data analysis. T.T. and A.H.F. drafted the original manuscript. L.J.L., A.C.O., K.F., J.C., S.C.H., A.J.T., and J.A.N. reviewed and edited the manuscript. J.A.N. supervised the study and provided resources. All authors read and approved the final manuscript.

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Availability of data and materials
Data will be shared upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Boards of both institutions, which granted a waiver of informed consent given its minimal risk and retrospective nature.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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