

Clinical Outcomes of Early- versus Late-Onset Sepsis-Associated Acute Kidney Injury in Patients with Septic Shock: A Retrospective Cohort Study

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Abstract

Background

Sepsis-associated acute kidney injury (SA-AKI) is one of the most common forms of organ failure in patients with septic shock and has a substantial impact on mortality and renal outcomes. This study aimed to compare the clinical characteristics and outcomes of early- and late-onset SA-AKI in patients with septic shock.

Methods

This retrospective cohort study included 203 adult patients with septic shock who developed SA-AKI in a level 3 intensive care unit (ICU). Patients were classified as early-onset SA-AKI (within 48 hours; $n = 174$) or late-onset SA-AKI (48 hours–7 days; $n = 29$). Primary outcomes were the requirement for continuous renal replacement therapy (CRRT) and 28-day mortality; secondary outcomes were ICU length of stay and major adverse kidney events (MAKE) at 28 and 365 days.

Results

SA-AKI developed within the first 48 hours of septic shock in 85.7% of patients. Baseline characteristics, APACHE II and SOFA scores, vasopressor requirements, and mechanical ventilation parameters were comparable between groups (all $p > 0.05$). No significant differences were observed in ICU length of stay, AKI at ICU discharge, 28-day mortality (46.0% vs. 48.3%), 28-day MAKE (78.7% vs. 79.3%), or 365-day MAKE (80.5% vs. 86.2%) (all $p > 0.05$). However, CRRT requirement was significantly higher in the early-onset SA-AKI group (56.9% vs. 34.5%; $p < 0.05$).

Conclusion

SA-AKI predominantly develops early in patients with septic shock. Although the timing of AKI was not associated with mortality or MAKE, early-onset SA-AKI was associated with a greater need for CRRT. SA-AKI timing may indicate kidney support needs rather than prognosis.

INTRODUCTION

Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection. Septic shock represents a clinical subset of sepsis associated with profound circulatory, cellular, and metabolic abnormalities and a substantially increased risk of mortality [1]. Despite significant advances in diagnostic and therapeutic approaches and the availability of current international guidelines, septic shock remains one of the leading causes of death in intensive care units [2]. The development of multiple organ dysfunction is a major determinant of mortality in patients with

septic shock [1,2]. Among the organ failures that develop in these patients, acute kidney injury (AKI) is one of the most common complications and has a particularly strong impact on prognosis.

Sepsis-associated acute kidney injury (SA-AKI) is the most common cause of AKI in intensive care units and has a substantial impact on both short-term mortality and long-term renal outcomes [3,4]. Recent studies have demonstrated that SA-AKI is not merely a transient impairment of kidney function but rather a complex process involving mechanisms beyond the classical ischemia–necrosis model including systemic inflammation, microcirculatory and endothelial injury and mitochondrial energy dysfunction [3–5]. Accordingly, SA-AKI is now considered not as a single clinical entity but as a heterogeneous syndrome comprising distinct subphenotypes that vary according to the timing, severity, and clinical course of AKI. Increasing evidence suggests that early- and late-onset AKI phenotypes may be associated with distinct clinical characteristics and outcomes [6]. The clinical significance of distinguishing early- and late-onset SA-AKI may extend beyond the timing of onset alone. This distinction may also provide insights into the predominant pathophysiological mechanisms and the dynamics of subsequent second hits. Early-onset SA-AKI may be more closely associated with factors that predominate during the initial hours of septic shock, including hemodynamic instability, systemic vasodilation, intravascular volume depletion, renal venous congestion and fluid overload, and vasopressor requirements; thus, it may represent a phenotype that develops concurrently with acute circulatory dysfunction [1,2,6]. In contrast, late-onset SA-AKI may reflect a clinical phenotype associated with secondary hits, including persistent inflammation despite initial resuscitation, ongoing microcirculatory dysfunction, endotheliopathy, nosocomial infections or episodes of secondary sepsis, exposure to nephrotoxins, the hemodynamic effects of mechanical ventilation and positive pressure, cumulative fluid overload, and worsening multiple organ dysfunction [6,7]. The literature has reported conflicting findings regarding the prognostic significance of early- and late-onset SA-AKI [5,8–11]. While some observational studies have found no significant difference in short-term mortality between early- and late-onset SA-AKI, others have reported that late-onset SA-AKI may be associated with poorer renal recovery, longer intensive care unit stays, and a greater need for organ support. A substantial proportion of existing studies have included heterogeneous sepsis populations rather than focusing exclusively on patients with septic shock. Therefore, evaluating the impact of early versus late AKI onset on mortality, organ support requirements, and the intensive care course in a homogeneous cohort consisting solely of patients with septic shock is of clinical importance. Accordingly, this study aimed to compare the clinical characteristics and outcomes of SA-AKI according to the timing of AKI onset (early vs. late) in patients with septic shock.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study was conducted between January 2023 and January 2026 in a level 3 adult intensive care unit (ICU) of a university hospital in Istanbul, Türkiye. The hospital has a total bed capacity of 1,200 and provides healthcare services across more than 40 medical specialties. Its four

ICUs have a combined capacity of 59 beds and admit approximately 1,900 medical, surgical, and trauma patients annually. The ICU operates under a closed-unit model, with extracorporeal therapies including extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT), hemoperfusion/hemoabsorption, and plasma exchange, available 24 hours a day, 7 days a week and performed by intensivists and ICU residents.

Study Population

All patients admitted to the ICUs during the study period were screened ($n = 4,220$). Among patients diagnosed with sepsis, adult patients who developed septic shock according to the Sepsis-3 criteria and subsequently developed sepsis-associated acute kidney injury (SA-AKI) were assessed for eligibility (1). Patients without sepsis ($n = 2,476$), those with missing data ($n = 392$), patients with advanced-stage malignancy ($n = 341$), pregnant or breastfeeding patients ($n = 74$), and patients younger than 18 years ($n = 46$) were excluded. Among the remaining patients with sepsis, those without septic shock ($n = 465$) and those with septic shock who did not develop AKI ($n = 223$) were excluded from the analysis (Fig. 1).

Ultimately, 203 patients with septic shock and SA-AKI were included in the study. Patients were divided into two groups according to the timing of AKI onset: the early-onset SA-AKI group, consisting of patients who developed AKI within the first 48 hours after the onset of septic shock ($n = 174$, 85.7%), and the late-onset SA-AKI group, consisting of patients who developed AKI between 48 hours and 7 days after the onset of septic shock ($n = 29$, 14.3%).

Standard Treatment

Septic shock management in our ICU was conducted in accordance with the 2021 Surviving Sepsis Campaign (SSC) guidelines. The management protocol included early recognition, source control, obtaining microbiological cultures, initiation of broad-spectrum antibiotics, crystalloid fluid resuscitation (30 mL/kg) and vasopressor therapy when the mean arterial pressure (MAP) fell below 65 mmHg (2). Norepinephrine was used as the first-line vasopressor, with dose titration to achieve a target MAP of ≥ 65 mmHg. Hydrocortisone (200 mg/day) was added when the norepinephrine dose exceeded 0.25 $\mu\text{g/kg/min}$ or when hemodynamic instability persisted despite increasing vasopressor requirements, and a second vasopressor agent was initiated when clinically indicated. Overall, the management of all patients was guided by the principles of early recognition, prompt treatment, and organ support strategies recommended by the SSC guidelines.

Data Collection

After eligible patients were identified, data were retrospectively obtained from the hospital electronic medical records and daily ICU monitoring forms. Patient age, sex, Charlson Comorbidity Index, and clinical and laboratory parameters obtained at ICU admission were recorded. APACHE II and Glasgow

Coma Scale scores were calculated at ICU admission. At the time of septic shock diagnosis, the presence and stage of AKI, SOFA score, and Vasoactive-Inotropic Score (VIS) were assessed. These parameters were subsequently reassessed daily during the first 5 days of ICU stay. The presence and stage of AKI were determined according to the AKI criteria established by Kidney Disease: Improving Global Outcomes (KDIGO) in 2012 [12].

Patients were classified into early- and late-onset SA-AKI groups according to the timing of SA-AKI onset. Vital signs, laboratory data, mechanical ventilation parameters, and disease severity scores were recorded daily for 5 consecutive days. Treatments, including vasoactive medications and antibiotics; interventions, including mechanical ventilation and renal replacement therapy; and complications were also recorded. ICU length of stay and 28-day mortality were recorded for all patients.

Major adverse kidney events (MAKE), a composite outcome measure encompassing major adverse kidney outcomes, were also assessed at days 28 and 365 after ICU admission. MAKE was defined as the occurrence of any of the following: death, the need for renal replacement therapy, or persistent kidney dysfunction, defined as a serum creatinine level that failed to return to baseline and remained at least twice the baseline value.

Study Outcomes

The primary outcomes were the rate of CRRT use and 28-day mortality. Secondary outcomes included the proportion of patients with AKI at ICU discharge, 28-day and 365-day MAKE rates, intensive care unit length of stay (LOS), duration of mechanical ventilation, changes in SOFA and VIS scores, and trends in hemodynamic and laboratory parameters over time.

Sample Size

In a previous study conducted among patients with sepsis followed in the intensive care unit, the rate of CRRT use was 23% among patients who developed early-onset SA-AKI and 4% among those who developed late-onset SA-AKI [8]. Based on a 95% confidence level, 80% power and a 1:6 allocation ratio planned to match the structure of our data, the required sample size was calculated as a minimum of 146 patients for the early SA-AKI group and 24 patients for the late SA-AKI group.

Ethical Considerations

Before the study commenced, institutional permission and ethical approval were obtained from the Marmara University Clinical Research Ethics Committee (Approval No: 09.2026.26.0537). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Given the retrospective study design and the use of anonymized data obtained during routine clinical care, the requirement for informed consent was waived in accordance with institutional regulations and applicable ethical guidelines.

Statistical Analysis

Data collected in the study were analyzed using IBM SPSS Statistics version 22.0. The normality of distribution for numerical variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Categorical variables were expressed as frequencies and percentages. Normally distributed numerical variables were presented as mean $\pm$ standard deviation, whereas non-normally distributed variables were presented as median and interquartile range (IQR). Between-group comparisons of numerical variables were performed using the independent samples t-test, or the Mann–Whitney U test when the assumptions of the t-test were not met. Categorical variables were compared using the chi-square test, or Fisher's exact test when the assumptions of the chi-square test were not met. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 174 patients (85.7%) with early-onset SA-AKI and 29 patients (14.3%) with late-onset SA-AKI were included in the study. Demographic characteristics were comparable between the two groups (Table 1). No significant differences were observed between the groups in terms of age, sex, or Charlson Comorbidity Index. There were also no significant differences in APACHE II scores (early-onset SA-AKI: 21 [18–26] vs. late-onset SA-AKI: 20 [18–25]) or baseline SOFA scores (early-onset SA-AKI: 10 [9–13] vs. late-onset SA-AKI: 9 [8–11]). During the 5-day follow-up, GCS scores were comparable between the groups except on day 4, when the GCS score was higher in the early-onset SA-AKI group (10 [5–15] vs. 9 [3–10]). SOFA and VIS scores remained comparable between the groups throughout the 5-day follow-up period (Fig. 2). All patients in both groups received norepinephrine infusion. The proportions of patients receiving epinephrine, vasopressin, terlipressin, methylene blue, and corticosteroids were similar between the groups (Table 1).

Table 1
Demographic characteristics, VIS and disease severity scores

Parameters	Early SA-AKI group (174; 85.7%) Median (IQR)	Late SA-AKI group (29; 14.3%) Median (IQR)	P value
Age, mean $\pm$ SD	64.67 $\pm$ 18.02	57.76 $\pm$ 22.63	0.127
Gender, n (%)			0.325
Male	77 (44.3)	10 (34.5)	
Female	97 (55.7)	19 (65.5)	
Charlson comorbidity index	5 (3–7)	5 (1–7)	0.341
ICU Severity Scores			
APACHE II	21 (18–26)	20 (18–25)	0.890
GCS, day 1	8 (3–14)	8 (4–11)	0.551
SOFA, day 1	10 (9–13)	9 (8–11)	0.055
VIS, day 1	18.0 (8.0–36.5)	15.0 (8.5–47.0)	0.790
Adrenaline, n (%)	70 (40.2)	11 (37.9)	0.815
Vasopressin, n (%)	37 (21.3)	7 (24.1)	0.728
Terlipressin, n (%)	20 (11.5)	4 (13.8)	0.459
Methylene blue, n (%)	14 (8.0)	1 (3.4)	0.336
Steroid, n (%)	115 (66.1)	19 (65.5)	0.952
ICU: Intensive care unit; SA-AKI: Sepsis-associated acute kidney injury; APACHE: Acute physiology and chronic health evaluation; GCS: Glasgow coma scale; SOFA: Sequential organ failure assessment; VIS: Vasoactive-inotropic score; SD: Standard deviation; IQR: Interquartile range.			

The need for mechanical ventilation was 92.0% in the early-onset SA-AKI group and 96.6% in the late-onset SA-AKI group, with no significant difference between the groups. Throughout the 5-day follow-up period, FiO_2 , $\text{PaO}_2/\text{FiO}_2$, PEEP, and pressure support (PS) values were comparable between the groups. On blood gas analysis, pH was lower in the early-onset SA-AKI group on day 1 (7.39 [7.32–7.45] vs. 7.45 [7.40–7.48]). pH values were comparable between the groups on subsequent days ($p > 0.05$). Base excess was lower in the early-onset SA-AKI group on days 1 and 2; however, no significant between-group differences were observed on the following days (day 1: -2.0 [-7.4 – 2.7] vs. 2.3 [0.9 – 3.6]; day 2: -0.9 [-5.5 – 3.4] vs. 1.1 [-0.1 – 5.6]; $p < 0.05$). Lactate levels were comparable between the groups throughout the 5-day follow-up period (Table 2).

Table 2
Mechanical ventilation and blood gas parameters

Parameters	Early SA-AKI group (174; 85.7%) Median (IQR)	Late SA-AKI group (29; 14.3%) Median (IQR)	P value
Mechanical ventilation and blood gas parameters			
Mechanical ventilation, n (%)	160 (92.0)	28 (96.6)	0.701*
Mechanical ventilation duration (days)	8.0 (5.0-18.75)	10.5 (6.0-13.75)	0.526
FiO ₂ (%)			
Day 1	40 (30–50)	40 (30–50)	0.847
Day 2	40 (30–50)	40 (35–60)	0.288
Day 3	40 (30–50)	42,5 (32,5–60)	0.100
Day 4	35 (30–50)	40 (30–55)	0.216
Day 5	35 (30–45)	35 (30-42.5)	0.959
PEEP			
Day 1	7 (5–8)	6 (5–8)	0.138
Day 2	7 (6–8)	7 (5–8)	0.435
Day 3	7 (6–8)	6 (5–7)	0.277
Day 4	6 (5–8)	6 (5–9)	0.843
Day 5	6 (5–8)	6 (5–9)	0.618
Pressure support			
Day 1	16 (12–18)	14 (11–17)	0.048
Day 2	16 (12–20)	15 (12–18)	0.332
Day 3	16 (12–19)	15 (12–18)	0.691
Day 4	15 (12–18)	14 (12–18)	0.542
Day 5	16 (13–18)	14 (12–19)	0.340
PaO ₂ /FiO ₂ ratio			
FiO ₂ : Fraction of inspired oxygen; PEEP: Positive end-expiratory pressure; PaO ₂ /FiO ₂ : Partial pressure of oxygen/ fraction of inspired oxygen; IQR: Interquartile range. *=Fisher's exact test			

Parameters	Early SA-AKI group (174; 85.7%) Median (IQR)	Late SA-AKI group (29; 14.3%) Median (IQR)	P value
Mechanical ventilation and blood gas parameters			
Day 1	281 (172–368)	253 (204–311)	0.592
Day 2	305 (218–406)	289 (163–396)	0.469
Day 3	300 (204–389)	260 (141–332)	0.081
Day 4	285 (204–372)	256 (176–391)	0.790
Day 5	285 (205–402)	295 (202–398)	0.874
pH			
Day 1	7.39 (7.32–7.45)	7.45 (7.40–7.48)	< 0.001
Day 2	7.41 (7.36–7.46)	7.46 (7.38–7.49)	0.091
Day 3	7.41 (7.36–7.46)	7.42 (7.37–7.49)	0.513
Day 4	7.43 (7.37–7.48)	7.44 (7.36–7.49)	0.906
Day 5	7.44 (7.38–7.48)	7.46 (7.37–7.51)	0.297
Base excess			
Day 1	-2.0 (-7.4-2.7)	2.3 (0.9–3.6)	0.002
Day 2	-0.9 (-5.5-3.4)	1.1 (-0.1-5.6)	0.010
Day 3	-0.7 (-3.3-4.4)	1.5 (-2.1-3.9)	0.661
Day 4	2.0 (-2.7-5.0)	1.5 (0.2–6.1)	0.356
Day 5	2.7 (-1.2-6.5)	0.8 (-1.9-7.1)	0.160
Lactate			
Day 1	2.8 (2.2–3.8)	2.3 (2.1–3.7)	0.160
Day 2	2.3 (1.6–3.7)	1.8 (1.5–3.2)	0.162
Day 3	1.8 (1.3–2.6)	1.7 (1.4-3.0)	0.849
Day 4	1.8 (1.4–2.6)	1.8 (1.3–2.3)	0.547
FiO ₂ : Fraction of inspired oxygen; PEEP: Positive end-expiratory pressure; PaO ₂ /FiO ₂ : Partial pressure of oxygen/ fraction of inspired oxygen; IQR: Interquartile range. *=Fisher's exact test			

Parameters	Early SA-AKI group (174; 85.7%) Median (IQR)	Late SA-AKI group (29; 14.3%) Median (IQR)	P value
Mechanical ventilation and blood gas parameters			
Day 5	1.6 (1.3–2.4)	1.8 (1.4–2.1)	0.859
FiO ₂ : Fraction of inspired oxygen; PEEP: Positive end-expiratory pressure; PaO ₂ /FiO ₂ : Partial pressure of oxygen/ fraction of inspired oxygen; IQR: Interquartile range. *=Fisher's exact test			

Regarding hemodynamic monitoring parameters, MAP values did not differ significantly between the groups ($p > 0.05$). Heart rate was comparable throughout the follow-up period, except on day 2, when the minimum heart rate was higher in the early-onset SA-AKI group. Regarding laboratory parameters, hemoglobin levels and platelet counts were similar between the groups. Leukocyte counts were higher in the early-onset SA-AKI group on days 1 and 2; however, no significant between-group differences were observed on the subsequent days (day 1: 12.6 [8.7–18.5] vs. 10.7 [8.4–13.0]; day 2: 13.3 [9.0–19.3] vs. 11.5 [6.9–14.4]; $p < 0.05$). Lymphocyte and neutrophil counts were comparable between the groups throughout the 5-day follow-up period (Table 3).

Table 3
Hemodynamic monitoring and laboratory parameters

Parameters	Early SA-AKI group (174; 85.7%) Median (IQR)	Late SA-AKI group (29; 14.3%) Median (IQR)	P value
Minimum MAP	64 ± 9	66 ± 10	0.217
Maximum MAP	92 ± 14	96 ± 15	0.179
Minimum heart rate, mean ± SD	81 ± 17	77 ± 15	0.263
Maximum heart rate, mean ± SD	117 ± 19	111 ± 18	0.103
Hemoglobin	9.7 (8.4–11.2)	9.5 (8.2–10.2)	0.115
Platelet	182 (108–298)	188 (93–230)	0.341
Lymphocyte	1.0 (0.6–1.7)	1.0 (0.5–1.6)	0.940
Neutrophil	10.0 (6.6–15.4)	8.3 (5.6–12.3)	0.127
Bilirubin	1.1 (0.7–1.8)	1.0 (0.7–1.9)	0.793
Creatinine			
Day 1	1.80 (1.14–2.78)	0.81 (0.60–1.06)	< 0.001
Day 2	1.84 (1.20–2.55)	0.87 (0.69–1.05)	< 0.001
Day 3	1.60 (1.12–2.22)	0.95 (0.71–1.17)	< 0.001
Day 4	1.38 (0.93–2.11)	0.99 (0.76–1.29)	0.004
Day 5	1.26 (0.88–1.96)	1.11 (0.96–1.58)	0.251
MAP: Mean arterial pressure; SD: Standard deviation; IQR: Interquartile range.			

Procalcitonin levels, among the evaluated infection biomarkers, were higher in the early-onset SA-AKI group during the first 3 days ($p < 0.05$). No significant between-group difference in procalcitonin levels was observed on days 4 and 5. No significant difference in CRP levels was observed between the groups throughout the 5-day follow-up period (Fig. 2). The most common source of infection in both groups was the lungs. No significant difference was observed between the groups in terms of the source of infection, and the proportions of pulmonary, bloodstream, and urinary tract infections, as well as culture-negative infections, were comparable between the groups (Table 4). Gram-negative pathogens were more frequently isolated in both groups. Among Gram-negative pathogens, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were more frequent in the late-onset SA-AKI group than in the early-onset SA-AKI group (31.0% vs. 14.4% and 31.0% vs. 10.3%, respectively; $p < 0.05$). The frequencies of *Acinetobacter baumannii* and other Gram-negative pathogens were similar between the groups. The

proportions of Gram-positive pathogens and fungal infections did not differ significantly between the groups (Table 4).

Table 4
Infection-related parameters

Parameters	Early SA-AKI group (174; 85,7%) Median (IQR)	Late SA-AKI group (29; 14,3%) Median (IQR)	P value
Procalcitonin			
Day 1	4.20 (0.76–27.09)	1.54 (0.22–15.31)	0.025
Day 2	5.92 (1.47-44.00)	1.29 (0.23–11.50)	0.003
Day 3	7.03 (1.62–50.05)	3.80 (0.53-13.0)	0.046
Day 4	5.89 (1.11–29.25)	2.49 (0.31-14.0)	0.090
Day 5	4.30 (0.97-18.0)	2.06 (0.33–6.97)	0.132
CRP			
Day 1	158 (60–242)	135 (52–186)	0.307
Day 2	164 (78–257)	139 (86–206)	0.335
Day 3	152 (84–227)	134 (69–185)	0.215
Day 4	122 (64–202)	114 (61–185)	0.464
Day 5	109 (59–182)	113 (64–182)	0.947
Infection sources			
Lung	74 (42.5)	15 (51.7)	0.356
Bloodstream	26 (14.9)	4 (13.8)	0.567*
Urinary tract	8 (4.6)	1 (3.4)	0.623*
Central venous catheter	6 (3.4)	0 (0)	0.392*
Intra-abdominal	15 (8.6)	2 (6.9)	0.550*
Surgical site	2 (1.1)	2 (6.9)	0.099*
Soft tissue	2 (1.1)	1 (3.4)	0.372*
Culture-negative	41 (23.6)	4 (8.9)	0.177
Positive culture			
Gram-negative			
Acinetobacter baumannii	33 (19.0)	5 (17.2)	0.826
CRP: C-reactive protein, IQR: Interquartile range. *=Fisher's exact test			

Parameters	Early SA-AKI group (174; 85,7%) Median (IQR)	Late SA-AKI group (29; 14,3%) Median (IQR)	P value
Klebsiella pneumoniae	23 (13.2)	8 (27.6)	0.046
Pseudomonas aeruginosa	17 (9.8)	8 (27.6)	0.007
Escherichia coli	7 (4.0)	2 (6.9)	0.377*
Other Gram negative	8 (4.6)	3 (10.3)	1.000*
Gram-positive			
Staphylococcus aureus	12 (6.9)	3 (10.3)	0.364*
Streptococcus pneumoniae	4 (2.3)	0 (0)	0.537*
Other Gram-positive	8 (4.6)	2 (6.9)	0.432*
Fungal			
Candida albicans	5 (2.9)	0 (0)	0.459*
Candida auris	1 (0.6)	1 (3.4)	0.266*
Other fungal	2 (1.1)	0 (0)	0.734*
CRP: C-reactive protein, IQR: Interquartile range. *=Fisher's exact test			

The proportions of patients with AKI at ICU discharge were similar between the two groups (55.7% vs. 55.2%, $p > 0.05$). Among patients with AKI at discharge, the AKI stage did not differ significantly between the groups (Table 5). During the ICU stay, the need for CRRT was significantly higher in the early-onset SA-AKI group than in the late-onset SA-AKI group (56.9% vs. 34.5%, $p < 0.05$). However, the total duration of CRRT was similar between the groups.

Table 5
Acute kidney injury, CRRT, length of stay, and 28-day mortality

Parameters	Early SA-AKI group (174; 85,7%) n (%)	Late SA-AKI group (29; 14,3%) n (%)	P value
AKI at discharge			0.954
Yes	97 (55.7)	16 (55.2)	
No	77 (44.3)	13 (44.8)	
AKI stage			0.904
Non-AKI	77 (44.3)	13 (44.8)	
AKI, stage 1	33 (19.0)	4 (13.8)	
AKI, stage 2	9 (5.2)	2 (6.9)	
AKI, stage 3	55 (31.6)	10 (34.5)	
CRRT	99 (56.9)	10 (34.5)	0.021
Total CRRT duration, days, median (IQR)	6 (3–13)	5.5 (3.5–6.5)	0.610
Major Adverse Kidney Events			
MAKE at 28 days	137 (78.7)	23 (79.3)	0.944
MAKE at 365 days	140 (80.5)	25 (86.2)	0.610*
Length of stay			
ICU LOS, days, median (IQR)	12.5 (7.0-24.5)	13.0 (7.5–23.5)	0.685
Mortality			
28-day mortality	80 (46.0)	14 (48.3)	0.818
AKI: acute kidney injury; MAKE: major adverse kidney events; LOS: length of stay, CRRT: Continuous renal replacement therapy, IQR: Interquartile range.			

Regarding clinical outcomes, ICU length of stay was similar between the groups (12.5 [7–24.5] vs. 13.0 [7.5–23.5] days). No significant between-group differences were observed in the rates of MAKE at 28 days (78.7% vs. 79.3%) or 365 days (80.5% vs. 86.2%) ($p > 0.05$). 28-day mortality rates were also similar between the groups ($p > 0.05$), with mortality rates of 46.0% in patients with early-onset SA-AKI and 48.3% in those with late-onset SA-AKI (Table 5).

DISCUSSION

In this retrospective cohort study, we investigated the association between the timing of AKI onset and clinical outcomes in a homogeneous ICU cohort consisting exclusively of patients with septic shock who developed sepsis-associated acute kidney injury (SA-AKI). Our findings demonstrated that SA-AKI predominantly developed during the early phase of septic shock, with no significant differences in short-term mortality or MAKE between early- and late-onset SA-AKI. However, the need for renal replacement therapy was significantly higher in the early-onset SA-AKI phenotype. These findings suggest that the timing of SA-AKI onset may not be an independent determinant of prognosis but may serve as a distinguishing phenotypic marker with greater relevance to renal replacement therapy requirements and resource planning than to mortality.

In the current literature, SA-AKI is recognized as a complex syndrome that extends beyond the classical model of “renal hypoperfusion and tubular necrosis” and involves systemic inflammation, endothelial barrier dysfunction, impaired microcirculatory flow, and cellular metabolic adaptive responses [4–7,13]. This pathobiological heterogeneity is consistent with the diverse clinical trajectories and outcome profiles observed in patients with SA-AKI. Accordingly, a phenotyping approach to AKI, and particularly to SA-AKI, has gained increasing attention in recent years, with the classification of subgroups according to the timing, severity, persistence, and patterns of recovery of AKI being proposed [6,8–11]. In this context, the distinction between early- and late-onset SA-AKI may represent not only a chronological classification but also one that reflects differences in predominant underlying mechanisms [6,8,10,11]. In our cohort, the predominance of SA-AKI occurring within the first 48 hours supports the notion that the early-onset phenotype is more frequently encountered in clinical practice. This finding is consistent with the distribution reported in multicenter ICU studies [8,11]. During the early phase of septic shock, pronounced vasodilation, relative hypovolemia, capillary leak, and vasopressor requirements may impair renal perfusion pressure and microcirculatory flow, thereby contributing to early loss of kidney function [4,6,14]. Experimental and imaging-based studies have demonstrated that severe microcirculatory heterogeneity may develop in sepsis even when global renal blood flow appears to be preserved [4,10,14]. These observations support the possibility that early-onset SA-AKI represents a phenotype closely associated with hemodynamic and microcirculatory stress.

The higher need for CRRT observed in the early-onset SA-AKI group in our study is clinically relevant. This finding is consistent with the observations of Monard et al., who reported a more frequent need for renal replacement therapy in the early-onset SA-AKI phenotype [8]. This finding may indicate that early-onset SA-AKI represents a subgroup characterized by more pronounced metabolic and hemodynamic disturbances. Large randomized trials investigating the timing of AKI and renal replacement therapy in septic shock have demonstrated that the need for kidney support is closely associated with disease severity, hemodynamic instability, and metabolic burden. These studies have emphasized that decisions regarding renal replacement therapy should be based not solely on biochemical thresholds but also on the clinical context and patient phenotype [15–17]. High-impact trials such as IDEAL-ICU and STARTR-AKI have demonstrated that an early initiation strategy does not confer a mortality benefit across all patient populations, although kidney support may be unavoidable in certain subgroups [15,16]. Our

findings support the possibility that the early-onset SA-AKI phenotype may represent a subgroup that more frequently requires CRRT in clinical practice.

No significant difference in 28-day mortality was observed between the early- and late-onset SA-AKI groups in our study. This finding is consistent with a substantial proportion of recent cohort studies investigating the distinction between early- and late-onset SA-AKI. Similarly, previous studies have reported no significant difference in short-term mortality between early- and late-onset SA-AKI groups [8,9]. Large-scale epidemiological studies of AKI have also demonstrated that mortality is more strongly associated with the overall burden of organ failure, comorbidity profile, and disease severity [3,10,13,18]. Within this framework, the timing of AKI onset may be better considered a component of the underlying disease phenotype rather than an independent determinant of mortality.

It is also noteworthy that MAKE, a robust composite outcome incorporating mortality, the need for renal replacement therapy, and persistent kidney dysfunction, did not differ between the groups. In a MIMIC-IV analysis by Shi et al., the absence of a difference in MAKE-30 between early- and late-onset SA-AKI was consistent with our findings for MAKE at both 28 and 365 days [9]. This similarity suggests that although the timing of SA-AKI may influence short-term kidney deterioration and the need for organ support, its impact on longer-term composite renal outcomes may be limited. However, particularly in sepsis studies characterized by high mortality rates, differences between individual MAKE components may be masked by the high mortality burden. Alternatively, the smaller sample size of the late-onset SA-AKI group may have limited the ability to detect true between-group differences.

The higher procalcitonin and leukocyte levels observed during the first few days in the early-onset SA-AKI group may indicate a more pronounced initial inflammatory burden in this group. Current pathophysiological models emphasize the important roles of inflammatory intensity and endothelial activation in the development of SA-AKI [4,6,7,13,19]. The predominance of Gram-negative pathogens in the distribution of infectious etiologies is consistent with the existing literature [20]. Gram-negative pathogens are known to enhance the lipopolysaccharide-mediated inflammatory response and contribute to the pathogenesis of SA-AKI [4,6,7].

However, direct clinical evidence evaluating the independent role of pathogen class in the development of early- or late-onset SA-AKI remains limited. In our cohort, the higher frequency of certain Gram-negative pathogens in the late-onset SA-AKI group may suggest that the late-onset phenotype differs in terms of infection dynamics. In particular, the higher prevalence of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in the late-onset group may indicate an association with prolonged ICU stay, secondary infections, or treatment-resistant infectious processes. Nevertheless, current consensus statements and reviews emphasize that pathogen class is not an independent determinant of early-versus late-onset SA-AKI; rather, host response, hemodynamic disturbances, and treatment-related exposures appear to be the principal determinants. Therefore, our microbiological findings should be interpreted as supportive clinical characteristics of the phenotype rather than explanatory factors.

Although our study has several strengths, including the comparison of early- and late-onset AKI phenotypes in a homogeneous cohort consisting exclusively of patients with septic shock who developed SA-AKI and the evaluation of both short- and long-term renal outcomes, several limitations should be acknowledged. First, the retrospective, single-center design limits the ability to establish causal relationships and does not completely eliminate the potential for selection bias. The single-center setting may also limit the generalizability of our findings because patient characteristics and clinical management protocols may reflect local practices. Second, the sample sizes of the early- and late-onset SA-AKI groups were imbalanced, particularly because the late-onset group was relatively small, which may have limited the statistical power to detect clinically meaningful differences between the groups. Third, although the onset of septic shock was used as the reference point for determining AKI timing, the exact onset of sepsis may be difficult to determine in routine clinical practice. This may have resulted in misclassification of patients into the early- and late-onset groups. Although the need for CRRT was one of the important findings of the study, the initiation of CRRT may have been based on clinical judgment rather than standardized protocol-based criteria, potentially introducing inter-clinician variability and practice-related bias. In addition, despite the similar duration of CRRT between the groups, detailed technical parameters, including ultrafiltration strategies, CRRT dose, blood and effluent flow rates, and hemodynamic tolerance, were not analyzed. Finally, several potentially important variables that may influence the development and clinical course of SA-AKI, including fluid balance,

CONCLUSION

This study provides a comprehensive analysis of the impact of the timing of SA-AKI onset on clinical outcomes in patients with septic shock admitted to the ICU. Our findings demonstrate that SA-AKI predominantly develops during the early phase of septic shock and that there are no significant differences between early- and late-onset SA-AKI in terms of 28-day mortality, ICU length of stay, or short- and long-term MAKE outcomes. Although hemodynamic parameters, organ function measures, and laboratory findings were largely comparable between the groups during the 5-day follow-up period, the substantially higher need for CRRT in the early-onset SA-AKI group suggests that this phenotype may be associated with a greater acute hemodynamic and metabolic burden. The similar rates and stages of AKI at ICU discharge suggest that renal outcomes may converge over time between patients who require more intensive renal support early in the course and those with late-onset SA-AKI.

These findings indicate that the timing of SA-AKI onset may be better regarded as a clinical phenotypic marker of the need for acute kidney support rather than a primary determinant of mortality. Therefore, in patients with septic shock, early-onset SA-AKI should prompt close monitoring for the need for CRRT; however, AKI timing alone should not be considered sufficient for prognostic assessment and should instead be interpreted in conjunction with disease severity and the overall burden of organ dysfunction.

Declarations

Ethics approval and consent to participate

The study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Approval No: 09.2026.26.0537). The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study and the use of anonymized patient data. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Clinical trial number

Not applicable.

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Author Contribution

MSS: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. ET: Investigation, Data curation, Writing – review & editing. BDOA: Investigation, Data curation, Writing – review & editing. ÖFŞ: Investigation, Data curation, Writing – review & editing. DK: Investigation, Data curation, Writing – review & editing. SA: Investigation, Data curation, Writing – review & editing. FG: Conceptualization, Methodology, Supervision, Writing – review & editing. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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None.

Data Availability

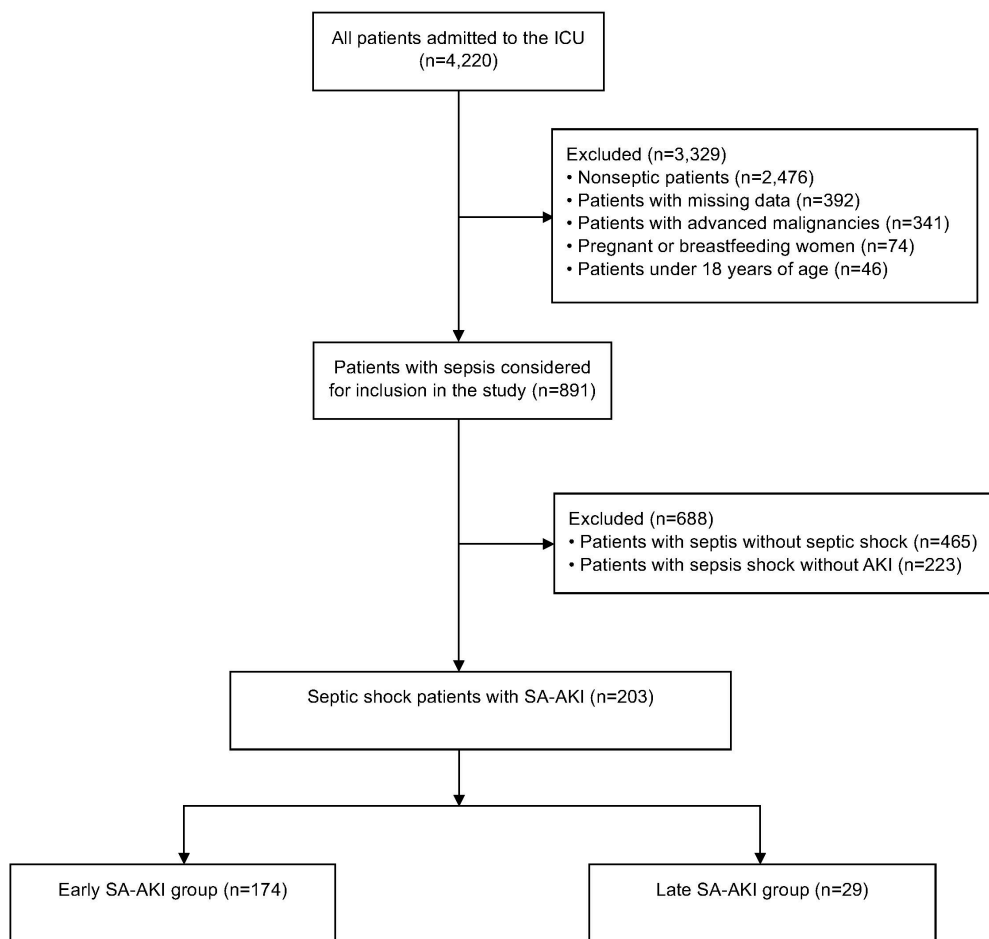
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:801–10. doi:10.1001/jama.2016.0287.
2. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Intensive Care Med*. 2021;47:1181–247. doi:10.1007/s00134-021-06506-y.
3. Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015;41:1411–23. doi:10.1007/s00134-015-3934-7.
4. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int*. 2019;96:1083–99. doi: 10.1016/j.kint.2019.05.026.
5. Gómez H, Kellum JA. Sepsis-induced acute kidney injury. *Curr Opin Crit Care*. 2016;22:546–53. doi: 10.1097/MCC.0000000000000356.
6. Zarbock A, Nadim MK, Pickkers P, Gomez H, Bell S, Joannidis M, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. *Nat Rev Nephrol*. 2023;19:401–17. doi:10.1038/s41581-023-00683-3.
7. Kuwabara S, Goggins E, Okusa MD. The pathophysiology of sepsis-associated AKI. *Clin J Am Soc Nephrol*. 2022;17:1050–69. doi: 10.2215/CJN.00850122.
8. Monard C, Bianchi N, Kelevina T, Altarelli M, Schneider A. 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;43:101332. doi: 10.1016/j.accpm.2023.101332.
9. Shi B, Ye J, Chen W, Liao B, Gu W, Yin H, et al. Prognosis of critically ill patients with early and late sepsis-associated acute kidney injury: an observational study based on the MIMIC-IV. *Ren Fail*. 2025;47:2441393. doi: 10.1080/0886022X.2024.2441393.
10. Takeuchi T, Flannery AH, Liu LJ, Ghazi L, Cama-Olivares A, Fushimi K, et al. Epidemiology of sepsis-associated acute kidney injury in the ICU with contemporary consensus definitions. *Crit Care*. 2025;29:128. doi: 10.1186/s13054-025-05351-5.

11. White KC, Serpa-Neto A, Hurford R, Clement P, Laupland KB, See E, 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;49:1079–89. doi:10.1007/s00134-023-07138-0.
12. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2:1–138.
13. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet.* 2012;380:756–66. doi: 10.1016/S0140-6736(11)61454-2.
14. Prowle JR, Molan MP, Hornsey E, Bellomo R. Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: a pilot investigation. *Crit Care Med.* 2012;40:1768–76. doi: 10.1097/CCM.0b013e318246bd85.
15. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med.* 2018;379:1431–42. doi:10.1056/NEJMoa1803213.
16. STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group. Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med.* 2020;383:240–51. doi:10.1056/NEJMoa2000741.
17. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med.* 2016;375:122–33. doi: 10.1056/NEJMoa1603017.
18. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol.* 2018;14:607–25. doi:10.1038/s41581-018-0052-0.
19. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. *Nat Rev Dis Primers.* 2021;7:52. doi:10.1038/s41572-021-00284-z.
20. Vincent JL, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA.* 2020;323:1478–87. doi:10.1001/jama.2020.2717.

Figures



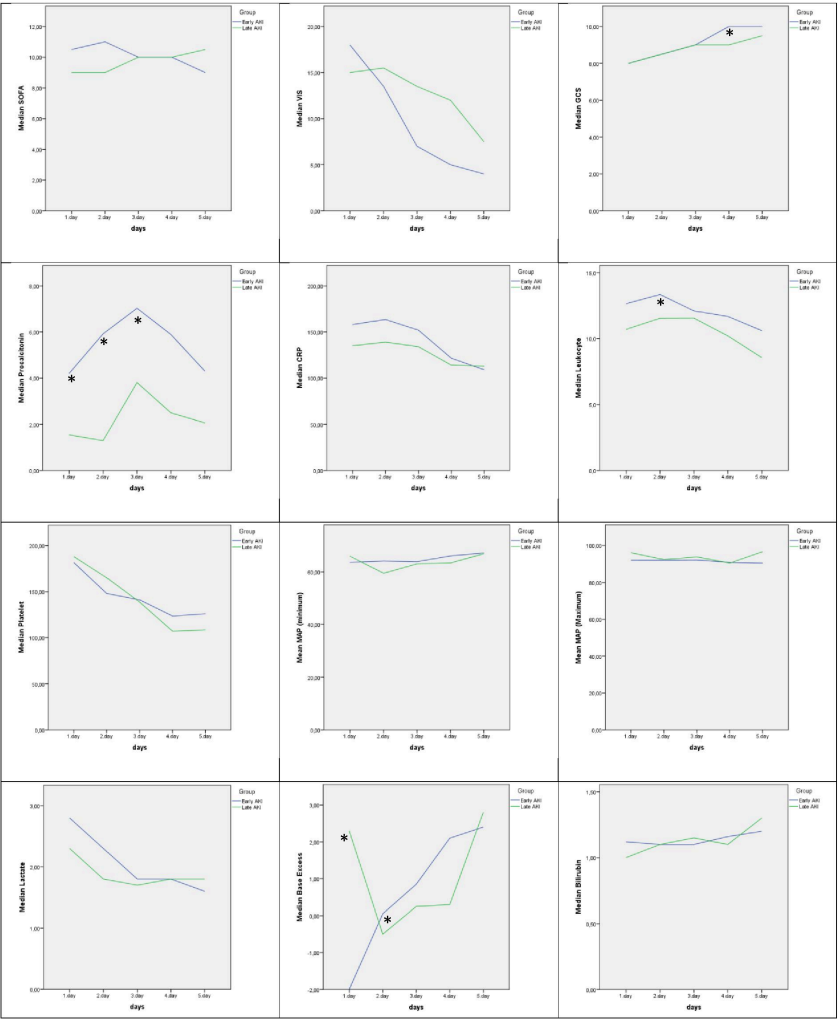
ICU: Intensive care unit; AKI: Acute kidney injury, SA-AKI: Sepsis-associated acute kidney injury

Figure 1. Flow diagram of patient selection

Figure 1

See image above for figure legend.

Figure 2. SOFA, VIS, GCS, laboratory parameters and MAP trend graphics.



SOFA: Sequential organ failure assessment; VIS: Vasoactive-inotropic score; GCS: Glasgow coma scale; CRP: C-reactive protein; MAP: Mean arterial pressure. *: p<0.05

Figure 2

See image above for figure legend.

Supplementary Files

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