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Factors and outcomes related to new-onset acute kidney injury in septic medical intensive care unit patients

Kamil Inci,[1] Gulbin Aygencel,[1] Nazlihan Boyaci Dundar,[1] Ozant Helvaci,[2] Melda Turkoglu[1]

[1]Division of Critical Care, Department of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Turkiye
[2]Division of Nephrology, Department of Internal Medicine, Gazi University Faculty of Medicine, Ankara, Turkiye

ABSTRACT

OBJECTIVE: Sepsis-induced acute kidney injury (AKI) is a significant threat, contributing to worse outcomes in intensive care unit (ICU) patients. Thus, understanding the complex relationship between sepsis and renal dysfunction in ICU patients is crucial. We aimed to investigate the factors that may predispose to the development and the clinical consequences of new-onset AKI in septic medical ICU patients in this study.

METHODS: This retrospective cohort was conducted between December 2019 and April 2023 in the tertiary medical ICU of Gazi University Hospital, Ankara, Turkiye. Participants included septic medical ICU patients aged ≥18 without AKI on ICU admission. Data included demographics, comorbidities, disease severity and prognostic scoring, ICU admission, and ICU follow-up data. Statistical analyses, including logistic regression, were performed to identify independent risk factors for new-onset AKI development and ICU mortality.

RESULTS: Patients with new-onset AKI (36% incidence) had higher APACHE-II (21 [16–27] vs. 16 [12–18]) and SOFA (6 [3–9] vs. 3 [2–5]) scores and lower GCS (10 [6–15] vs. 14 [10–15]) on ICU admission ($p<0.01$ for all results). Independent risk factors for both new AKI development and ICU mortality included invasive mechanical ventilation (IMV) (OR (95% CI): 5.02 [1.59–15] for AKI and OR (95% CI): 13.2 [3–58.8] for ICU mortality, $p<0.01$), new-onset shock (OR (95% CI): 3.98 [1.42–11.1] for AKI, OR (95% CI): 14.5 [4.4–43.5] for mortality, $p<0.01$), and higher APACHE-II score (OR (95% CI): 1.08 [1.01–1.16]), for AKI, $p=0.05$ and (OR (95% CI): 1.04 [1.01–1.08], for mortality, $p=0.01$). AKI was more frequent in patients whose source of infection was the respiratory system (45% vs. 29%, $p=0.01$) and catheter-related bloodstream infection (CRBSI) (17% vs. 8%, $p=0.03$) than those who did not. New AKI development was associated with longer ICU stay (9 [5–18] vs. 5 [3–10] days, $p<0.01$) and was independently associated with ICU mortality (OR (95% CI): 28.6 [6.6–125], $p<0.01$).

CONCLUSION: This study reveals new-onset AKI incidence of 36% in septic medical ICU patients. Additionally, it underlines the potential impact of infection sources on new AKI development. New-onset shock, IMV, and disease severity were independently associated with both new-onset AKI and ICU mortality in this population.

Keywords: Acute kidney injury; intensive care unit; sepsis.

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Sepsis is a severe condition characterized by a dysregulated host response to infection [1]. The importance of this syndrome often results in the admission of patients to an intensive care unit (ICU) for immediate and comprehensive management [2]. Among the various complications that are associated with sepsis, the development of acute kidney injury (AKI) is identified as a critical concern, resulting in higher morbidity and mortality [3].

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Correspondence: Kamil INCI, MD. Gazi Universitesi Tip Fakultesi, Ic Hastaliklari Anabilim Dali, Yogun Bakim Klinigi, Ankara, Turkiye.
Tel: +90 312 202 44 44 e-mail: kamilinci@gmail.com

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Several studies highlight the significant impact of sepsis on organ systems, especially the kidneys, which are susceptible to the cascading effects of the systemic inflammatory response [4]. Sepsis-associated AKI (SA-AKI) not only amplifies the severity of illness but also significantly contributes to the overall morbidity and mortality associated with sepsis-associated conditions [5]. Critical care research focuses on the complex relationship between sepsis and renal dysfunction, as understanding the predisposing factors and underlying mechanisms is essential for guiding interventions to improve patient outcomes [6].

Development of AKI adds a new complex layer to septic ICU patients already experiencing many challenges [7]. The ICU setting itself introduces unique factors such as invasive procedures, hemodynamic instability, nosocomial infections, and exposure to nephrotoxic agents, which may further contribute to the development of AKI in septic patients [8]. Additionally, research on the connection between sepsis, AKI, and ICU treatment reveals the complexities of this trio [9]. Despite valuable insights from previous data, patients with AKI on ICU admission are also included in data analysis in a significant portion of these studies [3, 5]. Excluding these patients may be crucial for a more meaningful exploration of specific factors influencing new-onset AKI. Thus, the results of this study may help explore the specific factors influencing new-onset AKI in septic medical ICU patients in a more goal-directed way.

In this study, we aim to bridge existing knowledge gaps by investigating the clinical, demographic, and ICU-related factors that may predispose to the development of AKI in a specific subgroup, septic medical ICU patients. Additionally, we will examine the outcomes associated with new-onset AKI in this population, providing valuable insights for refining therapeutic strategies and enhancing prognostic accuracy in the critical care setting.

Highlight key points

- A 36% incidence of new-onset acute kidney injury in septic medical ICU patients was revealed.
- New-onset shock, invasive mechanical ventilation, and disease severity independently correlate with both acute kidney injury occurrence and ICU mortality.
- Early recognition and intervention can improve outcomes for septic ICU patients with new-onset acute kidney injury.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort was conducted in the tertiary, nine-bed medical ICU of Gazi University Hospital from December 2019 to April 2023. The research protocol complied with the Declaration of Helsinki and was approved by the Gazi University Ethics Committee (date: 19.12.2023, number: 2023-1524).

Participants

Septic patients were included if they were ≥18 years old and without AKI on ICU admission according to RIFLE criteria [10], Table 1. Sepsis was defined by the Sepsis-3 criteria [11]. Patients were excluded if they stayed less than 48 hours in the ICU, if they were transferred from other ICUs or hospitals within more than 24 hours since the diagnosis of sepsis. Postoperative patients, patients with hematological malignancies, and terminally ill patients were also excluded.

Data Collection

Demographic and laboratory data were collected from medical archives and electronic hospital records. Patients' age, gender, data regarding hospitalization before ICU admission, Glasgow Coma Scale (GCS), Acute Physiol-

Table 1. Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification

Class	Glomerular filtration rate criteria	Urine output criteria
Risk	Serum creatinine × 1.5	<0.5 ml/kg/hour × 6 hours
Injury	Serum creatinine × 2	<0.5 ml/kg/hour × 12 hours
Failure	Serum creatinine × 3, or serum creatinine ≥4 mg/dl with an acute rise >0.5 mg/dl	<0.3 ml/kg/hour × 24 hours, or anuria × 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks	
End-stage kidney disease	End-stage kidney disease >3 months	

ogy and Chronic Health Evaluation II (APACHE- II) score, Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) category, Sequential Organ Failure Assessment (SOFA) score, ICU admission diagnosis, comorbidities, need for hemodialysis, the primary site of infection, and ICU mortality rates were recorded. APACHE-II and SOFA scores and RIFLE category were determined within 24 hours of ICU admission. The highest RIFLE category during the ICU stay was recorded, and the patients who developed AKI according to RIFLE criteria during ICU stay were accepted as ones with new-onset AKI.

Statistical Analysis

Continuous variables were expressed as median with [interquartile range] or mean±standard deviation based on their distribution. Categorical variables were presented as frequencies and percentages. Patients were divided into two groups according to the development of AKI in the ICU (new-onset AKI+ and new-onset AKI- groups), and data were compared between the two groups. Then, the patients were divided and compared according to their ICU mortality as survivors and non-survivors. The Chi-squared test was used to compare categorical variables and the Mann-Whitney U test was used to compare the medians of continuous variables. Logistic regression analysis was used to determine independent risk factors for the new AKI development and ICU mortality. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS v. 22.0 (IBM Corp., New York, USA).

RESULTS

Comparison of baseline characteristics and ICU follow-up data according to the development of new-onset AKI and mortality are given in Table 2 and Table 3. Patients with new-onset AKI had higher APACHE-II (21 [16–27] vs. 16 [12–18]) and SOFA (6 [3–9] vs. 3 [2–5]) scores and lower GCS (10 [6–15] vs. 14 [10–15]) on ICU admission (p<0.01 for all results), Table 2. Patients admitted to the ICU from hospital wards had higher rates of new-onset AKI than the patients admitted from the emergency room (53% vs. 46%, respectively, p=0.03) Table 2. New-onset AKI was more frequent in patients who presented with shock on ICU admission than those who did not (60% vs. 29%, respectively, p<0.01) as an expected result of renal ischemia, Table 2. New-onset AKI was more frequent in patients whose source of infection was the respiratory system (45% vs. 29%, p=0.01) and catheter-related bloodstream infection (CRBSI) (17% vs. 8%, p=0.03) than those who did not, Table 2. Patients with new-onset AKI had longer ICU length of stay (10 [5–19] vs. 5 [3–10] days), higher rates of shock (79% vs. 19%) and higher rates of acute respiratory distress syndrome (ARDS) (40% vs. 11%) during the ICU stay, Table 2. They also had higher rates of invasive mechanical ventilation (IMV) requirement (88% vs. 31%), p<0.0.1 for all results), Table 2. Ten percent (24) of the patients needed at least one episode of hemodialysis. Independent risk factors for new-onset AKI were IMV (OR (95% CI): 5.02 [1.59–15], p<0.01), new-onset shock during the ICU stay (OR (95% CI): 3.98 [1.42–11.1], p<0.01) and APACHE-II score (OR (95% CI): 1.08 [1.01–1.16], p<0.01), Table 4. Independent risk factors for ICU mortality were new-onset AKI (OR (95% CI): 28.6 [6.6–125], p<0.01), new-onset shock during the ICU stay (OR (95% CI): 14.5 [4.4–43.5], p<0.01), IMV (OR (95% CI): 13.2 [3–58.8], p<0.01) length of ICU stay (OR (95% CI): 1.13 [1.025–1.25], p<0.01) and APACHE-II score (OR (95% CI): 1.04 [1.01–1.08], p=0.01), Table 5.

DISCUSSION

Our research offers significant findings into the factors and outcomes related to the development of new-onset AKI in septic medical ICU patients. We found the incidence of new-onset AKI to be 36% in this patient population. Patients with new-onset AKI had higher APACHE-II and SOFA scores and lower GCS on ICU admission. Independent risk factors for new-onset AKI were the IMV requirement, new-onset shock, and APACHE-II score. Independent risk factors for ICU mortality were new-onset AKI, new-onset shock during the ICU stay, IMV requirement, length of ICU stay, and APACHE-II score. The association between the severity of illness on ICU admission and the development of new-onset AKI is compatible with existing literature data [12]. Our patients with new-onset AKI demonstrated higher APACHE-II and SOFA scores, along with lower GCS scores. These results emphasize the importance of early recognition and monitoring of these patients for the development of AKI, as higher severity of illness appears to correlate with the risk of new-onset AKI.

In an extensive literature review and meta-analysis by Liu et al. [13], 42 observational studies and 55911 patients were analyzed, and prevalence of AKI in patients

Table 2. Comparison of baseline characteristics, ICU admission and follow-up data according to development of new-onset AKI in septic medical ICU patients

	All patients (n=241)	New-onset AKI (+) (n=86)	New-onset AKI (-) (n=155)	p
Baseline characteristics and ICU admission data				
Age*	69 (58–78)	70 (61–76)	68 (56–78)	0.55
Female (%)	48	42	51	0.94
APACHE-II score*	17 (13–22)	21 (16–27)	16 (12–18)	<**0.01**
SOFA score*	4 (2–6)	6 (3–9)	3 (2–5)	<**0.01**
Glaskow Coma Scale*	9 (13–15)	10 (6–15)	14 (10–15)	<**0.01**
Creatinine (mg/dl)*	0.7 (0.4–0.9)	0.7 (0.4–0.8)	0.7 (0.4–0.9)	0.86
Admission from (%)				
Emergency room	55	46	59	**0.03**
Hospital wards	45	53	41	**0.03**
Comorbidities (%)				
Hypertension	51	50	52	0.42
COPD, asthma	40	42	39	0.44
Diabetes mellitus	28	21	32	0.05
Cerebrovascular disease	24	22	26	0.32
Solid organ malignancy	19	22	17	0.21
Coronary artery disease	15	13	16	0.31
Source of infection (%)				
Respiratory system	35	45	29	**0.01**
Urinary tract	20	17	21	0.29
CRBSI	12	17	8	**0.03**
Abdominal	6	7	5	0.47
Shock on ICU admission (%)	29	60	12	<**0.01**
ICU follow-up				
Mortality (%)	37	87	9	<**0.01**
Length of ICU stay (days)*	6 (3–11)	10 (5–19)	5 (3–10)	<**0.01**
New-onset shock (%)	41	79	19	<**0.01**
ARDS (%)	21	40	11	<**0.01**
Noninvasive ventilation (%)	22	21	23	0.49
Invasive ventilation (%)	51	88	31	<**0.01**
Parenteral nutrition (%)	10	13	8	0.17
Nosocomial infection (%)	42	67	28	<**0.01**
Blood product replacement (%)	38	64	24	<**0.01**

*: Median (25^{th}–75^{th} percentile); ICU: Intensive care unit; AKI: Acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; COPD: Chronic obstructive pulmonary disease; CRBSI: Catheter-related bloodstream infection; ARDS: Acute respiratory distress syndrome; n: Number.

diagnosed with sepsis was found 36–64%. Our study discriminates itself from previous literature through its targeted focus on a specific cohort. Unlike prior investigations that involved a heterogeneous population comprising coronary, cardiothoracic, neurologic, neurosurgical, obstetric, and trauma patients, as well as those from various types of hospitals [13, 14], our study exclusively included patients from the tertiary university medical ICU and provided a more specific and in-depth analysis fitted to this subgroup. In our study, 36% of the patients who were admitted to ICU with sepsis developed AKI during their ICU stay. Our lower AKI incidence may be related to the characteristics of our patient group, which only included patients who had sepsis on ICU admission.

Table 3. Comparison of baseline characteristics, ICU admission and follow-up data according to ICU mortality in septic medical ICU patients

	All patients (n=241)	Non-survivors (n=89)	Survivors (n=152)	p
Baseline characteristics and ICU admission data				
Age*	69 (58–78)	68 (61–77)	70 (57–78)	0.82
Female, n (%)	116 (48)	38 (43)	78 (51)	0.12
APACHE-II score*	17 (13–22)	22 (16–27)	15 (12–18)	<**0.01**
SOFA score*	4 (2–6)	6 (4–9)	3 (1–5)	<**0.01**
Glasgow Coma Scale*	9 (13–15)	10 (6–15)	14 (10–15)	<**0.01**
Admission from n (%)				
Emergency room	132 (55)	39 (44)	93 (61)	<0.01
Hospital wards	109 (45)	50 (56)	59 (39)	<0.01
Comorbidities, n (%)				
Hypertension	124 (51)	42 (47)	82 (54)	0.20
COPD, asthma	97 (40)	40 (45)	57 (38)	0.16
Diabetes mellitus	68 (28)	18 (20)	50 (33)	**0.03**
Cerebrovascular disease	59 (24)	18 (20)	41 (27)	0.15
Solid organ malignancy	45 (19)	21 (24)	24 (16)	0.09
Coronary artery disease	36 (15)	13 (15)	23 (15)	0.54
Source of infection, n (%)				
Respiratory system	84 (35)	38 (43)	46 (30)	**0.04**
Urinary tract	48 (20)	16 (18)	32 (21)	0.35
CRBSI	28 (12)	16 (18)	12 (8)	**0.02**
Abdominal	14 (6)	2 (2)	12 (8)	0.06
Shock on ICU admission, n (%)	71 (29)	48 (54)	23 (15)	<**0.01**
ICU follow-up				
New-onset AKI, n (%)	86 (36)	62 (70)	24 (16)	<**0.01**
Length of ICU stay, days*	6 (3–11)	9 (5–18)	5 (3–10)	<**0.01**
Shock, n (%)	98 (41)	76 (85)	22 (14)	<**0.01**
ARDS, n (%)	51 (21)	38 (43)	13 (9)	<**0.01**
Noninvasive ventilation, n (%)	53 (22)	17 (19)	36 (24)	0.29
Invasive ventilation, n (%)	124 (51)	82 (92)	42 (28)	<**0.01**
CVC placement, n (%)	113 (47)	67 (75)	46 (30)	<**0.01**
Requirement of hemodialysis				
Intermittent, n (%)	15 (6)	10 (11)	5 (3)	**0.02**
CRRT, n (%)	18 (7)	15 (17)	3 (2)	<**0.01**
Parenteral nutrition, n (%)	24 (10)	10 (11)	14 (9)	0.36
Nosocomial infection, n (%)	101 (42)	58 (65)	43 (28)	<**0.01**
Blood product replacement, n (%)	92 (38)	54 (61)	38 (25)	<**0.01**

*: Median (25^{th}–75^{th} percentile); ICU: Intensive care unit; AKI: Acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; COPD: Chronic obstructive pulmonary disease; CRBSI: Catheter-related bloodstream infection; ARDS: Acute respiratory distress syndrome; CVC: Central venous catheter; CRRT: Continuous renal replacement therapy; n: Number.

In the meta-analysis by Liu et al. [13], abdominal infections as the source of sepsis were found as a significant predictor of AKI. According to previous data, risk factors and outcomes of AKI have been widely described in critically ill patients [14–16]. On the other hand, previous research does not sufficiently define the data regarding the relation between the development of AKI and specific infectious sources. Interestingly, our study

Table 4. Multivariate analysis, Independent risk factors for new-onset AKI

	Wald score	OR (95% CI)	p
Invasive mechanical ventilation	7.5	5.02 (1.59–15)	**<0.01**
New-onset shock	6.9	3.98 (1.42–11.1)	**<0.01**
APACHE-II score	3.7	1.08 (1.01–1.16)	**0.05**

AKI: Acute kidney injury; OR: Odd ratios; CI: Confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation.

Table 5. Multivariate analysis, independent risk factors for ICU mortality

	Wald score	OR (95% CI)	p
New-onset AKI	22.9	28.6 (6.6–125)	**<0.01**
New-onset shock	13.2	14.5 (4.4–43.5)	**<0.01**
Invasive mechanical ventilation	11.7	13.2 (3.0–58.8)	**<0.01**
APACHE-II score	7.5	1.13 (1.025–1.25)	**<0.01**
Length of ICU stay	5.9	1.04 (1.01–1.08)	**0.01**

ICU: Intensive care unit; OR: Odd ratios; CI: Confidence interval; AKI: Acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation.

highlights the impact of the source of infection on the development of new-onset AKI. Specifically, patients with respiratory system infections and CRBSIs showed higher rates of new-onset AKI in our cohort. Although this study found that CRBSIs and respiratory tract infections had an impact on the development of acute renal failure, these results should be interpreted cautiously, depending on the lack of data regarding infectious agents, antimicrobial resistance patterns, and drug regimens used during the ICU stay in the study population.

Consistent with existing data, our study highlights the association between hemodynamic instability and new-onset AKI [17, 18]. Patients presenting with shock on ICU admission and the ones with new-onset shock during the ICU stay were more likely to develop new-onset AKI, reflecting the expected result of renal ischemia in the context of compromised hemodynamics.

Multivariate analysis of our data identified key independent risk factors for new-onset AKI and ICU mortality. The requirement of IMV, new-onset shock during the ICU stay, and the APACHE-II score emerged as consistent predictors for both new-onset AKI and ICU mortality. These findings emphasize the prognostic significance of these parameters and their role in risk stratification for patients with sepsis in the ICU. On the other hand, these results should also be interpreted carefully. Determining whether these factors emerge secondarily to AKI development or contribute to the initiation of AKI is challenging. This complexity makes it difficult to decide on the cause-and-effect relationship among these factors.

Our finding of a lower new-onset AKI incidence in diabetic patients compared to non-diabetic ones was a surprising result that is contradictory to previous data, even though the difference was not statistically significant [19]. However, it is crucial to interpret this finding cautiously. Our study lacks detailed information on previous diabetes regulation of these patients, and excluding patients with AKI may be biased towards early-stage disease without end-organ involvement of diabetes.

The association between new-onset AKI and other adverse clinical outcomes is also notable in our study. Patients with new-onset AKI had a higher length of ICU stay, higher rates of new-onset shock and ARDS, and higher rates of IMV requirement during the ICU stay. Again, it was tough to determine whether these results were the cause or the effect in the study population and to underline the critical impact of renal complications on overall patient outcomes.

Our study has several limitations. It is a retrospective, single-center study. The diagnosis of AKI was made based solely on creatinine and urine output, and no other specific biomarkers were used. Although the definition of sepsis-associated acute kidney injury was recently established by the Acute Disease Quality Initiative (ADQI) Working Group (which defines the AKI diagnosis as kidney damage that occurs within seven days of sepsis diagnosis) using the Kidney Disease Improving Global Outcomes (KDIGO) criteria [20], we used RIFLE criteria to define AKI in our cohort and not to set a day limit for AKI diagnosis after sepsis. Since we aimed to find new AKI development and related factors in patients admitted to medical ICU with sepsis, we used the term "new-onset AKI" instead of "sepsis-associated AKI" in our study. Even though KDIGO criteria is the most frequently used tool to diagnose AKI in the ICU, previous data have shown that the RIFLE criteria is also a good tool for predicting AKI and mortality in ICU patients with no significant difference from KDIGO [21]. Therefore, the results of our study hold validity to contribute to the literature.

Conclusion

Our study, focusing on new-onset AKI in septic medical ICU patients, reveals an incidence of 36% and draws attention to the potential impact of infection sources. New-onset shock, IMV, and disease severity were independently associated with both new-onset AKI and ICU mortality. Studies employing more standardized AKI definitions and utilizing biochemical markers during the diagnostic phase may better explain the cause-and-effect relationship between new-onset AKI and sepsis in medical ICU patients.

Ethics Committee Approval: The Gazi University Clinical Research Ethics Committee granted approval for this study (date: 19.12.2023, number: 2023-1524).

Authorship Contributions: Concept – KI, OH; Design – KI, NBD; Supervision – KI; Data collection and/or processing – KI, NBD; Analysis and/or interpretation – KI, GA, MT; Literature review – NBD, KI; Writing – KI, GA; Critical review – KI, NBD, GA, MT.

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