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Impact of Early Renal Recovery on 90-Day Outcomes in Critically ill Patients with Sepsis-Induced Acute Kidney Injury: A Retrospective Cohort Investigation

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HIGHLIGHTS

1. Early recovery improves survival.
2. Reduced dialysis dependency rates.
3. Enhanced kidney function preservation.
4. Fewer ICU-related complications observed.
5. Improved long-term patient outcomes

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ABSTRACT

Objective: This study aims to investigate the impact of early renal recovery on 90-day outcomes in critically ill patients with sepsis-associated acute kidney injury (SA-AKI). The primary objective is to assess whether early renal recovery within the first seven days after AKI diagnosis is associated with improved survival and reduced progression to chronic kidney disease (CKD). **Methods:** This retrospective cohort study was conducted at a tertiary care hospital between January 2015 and March 2017. Adult patients admitted to the intensive care unit (ICU) with sepsis and developing AKI within 48 hours of admission were included. AKI was diagnosed according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Patients were classified into three groups based on early recovery status: complete recovery, partial recovery, and unrecovered. **Results:** A total of 556 patients with SA-AKI were included in the study. Early renal recovery was observed in 47.7% of patients, partial recovery in 14.0%, and no recovery in 38.3%. The unrecovered group exhibited significantly higher 90-day mortality (65.7%) and need for chronic dialysis (68.1%) compared to the complete recovery (22.6%) and partial recovery (28.2%) groups. Multivariate logistic regression identified male sex, congestive heart failure, pneumonia, anemia, mechanical ventilation, and AKI Stage 3 as independent risk factors for unrecovered renal function. **Conclusion:** Early renal recovery within seven days of AKI diagnosis is associated with improved survival and reduced long-term renal dysfunction in patients with SA-AKI. The absence of early recovery significantly increases the risk of mortality and the need for chronic dialysis. Identifying patients at high risk for non-recovery could inform clinical strategies to improve outcomes in this population.

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INTRODUCTION

Sepsis-associated acute kidney injury (SA-AKI) is a prominent clinical condition affecting patients in intensive care units, representing one of the most severe complications of sepsis. SA-AKI accounts for approximately 60-70% of all AKI cases in critically ill patients (Poston & Koyner, 2019). Its occurrence significantly worsens patient prognosis, increasing the risk of mortality and progression to chronic kidney disease (Peerapornratana et al., 2019). The multifactorial nature of SA-AKI, involving inflammation, ischemia, and metabolic disturbances, makes it a challenging condition to manage in clinical settings. The underlying mechanisms of SA-AKI involve a combination of microvascular and macrovascular dysfunctions, resulting in inadequate renal blood flow and oxygenation. Recent studies have demonstrated that sepsis-induced changes in microcirculation, particularly endothelial dysfunction and altered perfusion, exacerbate renal damage (Uhel et al., 2020). This is further complicated by metabolic reprogramming, where renal cells shift from oxidative phosphorylation to glycolysis, a process that conserves energy but may hinder long-term recovery if prolonged (Waltz et al., 2020).

In recent years, there has been a growing emphasis on the identification of distinct SA-AKI phenotypes through the use of biomarkers and machine learning algorithms. These tools have facilitated the sub-phenotyping of SA-AKI patients, allowing clinicians to better predict outcomes and tailor treatments (Bhatraju et al., 2020). Biomarkers such as tissue inhibitors of metalloproteinases (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) have shown potential for early detection and risk stratification, enhancing clinicians' ability to intervene promptly (Zarbock et al., 2020).

Despite these advances in diagnostics, therapeutic options for SA-AKI remain limited. Current management strategies primarily focus on supportive measures, such as fluid resuscitation, vasopressors, and renal replacement therapy (RRT) (Peerapornratana et al., 2019). However, new research is exploring targeted interventions aimed at modulating immune responses and preventing kidney injury.

This study aims to investigate the early recovery status and long-term outcomes of patients with sepsis-associated acute kidney injury. The primary objective is to assess whether early renal recovery within the first seven days after AKI diagnosis is associated with improved survival and reduced progression to chronic kidney disease. Additionally, this study seeks to identify key risk factors for non-recovery of renal function, which could inform clinical decision-making and management strategies.

SUBJECTS AND METHODS:

Study design:

This retrospective cohort study was conducted at a tertiary care hospital from January 2023 to January 2024. Adult patients aged 18 years or older, who were admitted to the intensive care unit (ICU) with sepsis and developed acute kidney injury (AKI) within 48 hours of admission, were included in the study. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (Singer et al., 2016), which requires a change of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score secondary to an infection. AKI was diagnosed and staged based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Patients were excluded if they had pre-existing end-stage renal disease (ESRD), were missing serum creatinine (SCr) data following AKI diagnosis, or had a hospital stay of less than 48 hours.

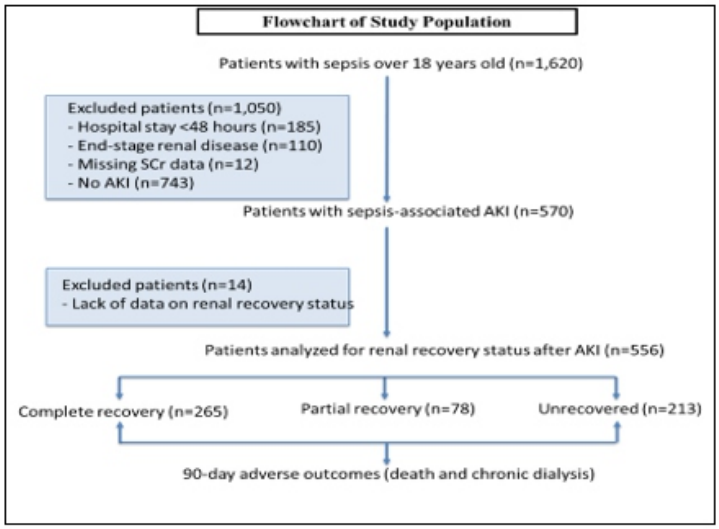

Figure 1: Flow Chart of Patient Selection

Study Variables and Definitions:

The key study variables included demographic data, comorbidities, clinical characteristics at ICU admission, and early recovery status of AKI. Early recovery status was assessed at Day 7 after AKI diagnosis, and patients were classified into three groups: (1) Complete recovery, defined as patients who no longer met AKI criteria; (2) Partial recovery, for those who showed an improvement in AKI stage but did not fully recover; and (3) Unrecovered, where patients showed no improvement or worsening of AKI.

Other variables included specific comorbid conditions such as hypertension, diabetes mellitus, chronic kidney disease (CKD), and congestive heart failure (Bellomo et al., 2012). Laboratory and clinical parameters like baseline creatinine, urine output, mechanical ventilation, vasopressor use, and renal replacement therapy (RRT) were also recorded. AKI staging was based on KDIGO 2012 guidelines, with: Stage 1: Increase in SCr by ≥0.3 mg/dL within 48 hours or 1.5–1.9 times baseline, or urine output <0.5 mL/kg/h for 6–12 hours. Stage 2: Increase in SCr by 2.0–2.9 times baseline or urine output <0.5 mL/kg/h for >12 hours. Stage 3: Increase in SCr by ≥3.0 times baseline, SCr ≥4.0 mg/dL, initiation of RRT, or urine output <0.3 mL/kg/h for ≥24 hours (Figure 1).

Study Outcomes:

The primary outcome of the study was a composite of 90-day mortality and the need for chronic dialysis (Hoste et al., 2015). Secondary outcomes included length of stay in both the ICU and hospital, and the presence of persistent renal dysfunction at hospital discharge or by Day 30, defined as SCr ≥2 times the baseline. Persistent renal dysfunction and progression to chronic kidney disease were assessed as potential long-term sequelae of AKI. In addition to clinical outcomes, risk factors for non-recovery of renal function were analyzed, including demographic factors (age, sex), baseline conditions (hypertension, diabetes, CKD), and clinical interventions (mechanical ventilation, vasopressor use, and RRT). Data were collected through the hospital's electronic medical records system, ensuring comprehensive capture of all relevant variables.

Statistical Analysis:

Statistical analysis was performed using SPSS version 24.0 (IBM, Armonk, NY). Continuous variables were presented as medians with interquartile ranges and compared using the Kruskal-Wallis test, while categorical variables were analyzed using chi-square tests. Kaplan-Meier survival curves were generated, and the log-rank test was used to compare survival between groups. Multivariate Cox regression was applied to assess the association between early recovery status and 90-day mortality, while multivariate logistic regression was used to evaluate the relationship between recovery status and the composite outcome, adjusting for potential confounders (Hosmer et al., 2013).

Sensitivity analyses were conducted by restricting the study population to subgroups, including patients who remained in the hospital on Day 7 after AKI diagnosis, patients without premorbid CKD, and those with AKI Stage 2 or 3, to assess the robustness of the results (Zhou et al., 2019). These sensitivity analyses helped ensure that the findings were consistent across different patient populations and clinical settings.

RESULTS

A total of 556 patients with sepsis-associated acute kidney injury (SA-AKI) were included in the study. Patients were stratified into three groups based on their early recovery status after AKI: the complete recovery group (n=265, 47.7%), the partial recovery group (n=78, 14.0%), and the unrecovered group (n=213, 38.3%) (Figure 1).

Baseline Characteristics:

Baseline characteristics of the patients are presented in Table 1. The median age across the groups was comparable (63-65 years, $P = 0.620$). A higher proportion of males was observed in the unrecovered group (70.4%) compared to the complete recovery (56.6%) and partial recovery (57.7%) groups, but the difference was not statistically significant ($P = 0.134$). The unrecovered group had significantly higher rates of congestive heart failure (18.8%, $P < 0.001$), premorbid chronic kidney disease (18.8%, $P = 0.011$), pneumonia (58.7%, $P = 0.051$), and anemia (55.4%, $P = 0.012$) compared to the other groups. The incidence of AKI Stage 3 was highest in the unrecovered group (62.4%, $P < 0.001$), while the complete recovery group had the largest proportion of patients with AKI Stage 1 (51.0%).

Table 1: Baseline Characteristics of Patients Stratified by Early Recovery Status After AKI.

Groups	Complete recovery (n=265)	Partial recovery (n=78)	Unrecovered (n=213)	P-value
Age (year)	63 (50–75)	64 (52–77)	65 (51–76)	0.620
Male sex (%)	150 (56.6%)	45 (57.7%)	150 (70.4%)	0.134
Comorbidities (No. and %)				
Hypertension (%)	100 (37.7%)	32 (41.0%)	110 (51.6%)	0.088
Diabetes mellitus (%)	60 (22.6%)	20 (25.6%)	70 (32.9%)	0.096
Congestive heart failure (%)	14 (5.3%)	9 (11.5%)	40 (18.8%)	<0.001
COPD (%)	30 (11.3%)	10 (12.8%)	35 (16.4%)	0.664
Premorbid CKD (%)	22 (8.3%)	13 (16.7%)	40 (18.8%)	0.011
Malignancy (%)	25 (9.4%)	6 (7.7%)	25 (11.7%)	0.470
Immunosuppression (%)	30 (11.3%)	5 (6.4%)	30 (14.1%)	0.115
Baseline creatinine (µmol/L)	85 (70–90)	86 (72–95)	88 (71–94)	0.348
Pneumonia (%)	115 (43.4%)	32 (41.0%)	125 (58.7%)	0.051
Temperature >38°C (%)	30 (11.3%)	10 (12.8%)	40 (18.8%)	0.094
Clinical data on admission/ [No. (%)]				
Pneumonia (%)	115 (43.4%)	32 (41.0%)	125 (58.7%)	0.051
Abdominal infection (%)	85 (32.1%)	22 (28.2%)	65 (30.5%)	0.278
Temperature >38 °C (%)	30 (11.3%)	12 (15.4%)	45 (21.1%)	0.094
Heart rate >90 beats per minute (%)	185 (69.8%)	52 (66.7%)	170 (79.8%)	0.026
Respiratory rate >20 beats per minute (%)	145 (54.7%)	43 (55.1%)	153 (71.8%)	<0.001
Hypotension (%)	150 (56.6%)	44 (56.4%)	135 (63.4%)	0.932
Modified SOFA score	7 (5–9)	8 (6–10)	9 (6–11)	<0.001
Modified APACHE II score	15 (12–19)	17 (14–21)	20 (15–24)	<0.001
AKI stage 1 (%)	135 (51.0%)	0 (0%)	40 (18.8%)	<0.001
AKI stage 2 (%)	70 (26.4%)	22 (28.2%)	40 (18.8%)	0.020
AKI stage 3 (%)	60 (22.6%)	56 (71.8%)	133 (62.4%)	<0.001

Laboratory Data on Admission/ [No. (%)]				
Leucocytes >12 ×10^9/L (%)	135 (50.9%)	40 (51.3%)	115 (54.0%)	0.949
Anemia (%)	110 (41.5%)	44 (56.4%)	118 (55.4%)	0.012
Thrombocytopenia (%)	100 (37.7%)	35 (44.9%)	90 (42.3%)	0.534
Overt DIC (%)	75 (28.3%)	20 (25.6%)	70 (32.9%)	0.451
Hypoalbuminemia (%)	180 (67.9%)	60 (76.9%)	155 (72.8%)	0.652
Hyperbilirubinemia (%)	45 (17.0%)	12 (15.4%)	55 (25.8%)	0.087
Lactic acidosis (%)	55 (20.8%)	10 (12.8%)	55 (25.8%)	0.035
Hypoxemia (%)	185 (69.8%)	55 (70.5%)	170 (79.8%)	0.102
Hyperkalemia (%)	15 (5.7%)	0 (0%)	20 (9.4%)	0.050
Mechanical ventilation (%)	160 (60.4%)	45 (57.7%)	155 (72.8%)	0.005
Vasopressors (%)	140 (52.8%)	45 (57.7%)	120 (56.3%)	0.749
Renal replacement therapy (%)	25 (9.4%)	15 (19.2%)	75 (35.2%)	<0.001

COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; DIC: Disseminated intravascular coagulation.Continuous variables are presented as median (interquartile range) and categorical variables are presented as [No.(%)]. *P<0.05 vs the complete recovery group; †P<0.05 vs the partial recovery group.

Table 2 summarizes the primary and secondary outcomes. The unrecovered group had significantly higher 90-day mortality (65.7%, P <0.001) and a higher composite outcome of death or chronic dialysis (68.1%, P < 0.001) compared to the complete recovery (22.6%) and partial recovery (28.2%) groups. The length of hospital stay was shorter in the unrecovered group (12 days, IQR 6–22) compared to the complete recovery (14 days, IQR 9–23) and partial recovery groups (16 days, IQR 10–24; P = 0.002). Persistent renal dysfunction was most prevalent in the unrecovered group (75.1%, P < 0.001).

Table 2: Outcomes of Patients Stratified by Early Recovery Status After AKI

Groups	Complete Recovery (N=265)	Partial Recovery (N=78)	Unrecovered (N=213)	P-value
ICU length of stay (days)	8 (4–12)	9 (5–15)	9 (5–17)	0.119
Hospital length of stay (days)	14 (9–23)	16 (10–24)	12 (6–22)	0.002
Persistent renal dysfunction (%)	7 (2.6%)	17 (21.8%)	160 (75.1%)	<0.001
90-day mortality (%)	60 (22.6%)	21 (26.9%)	140 (65.7%)	<0.001
Chronic dialysis (%)	0 (0%)	1 (1.3%)	3 (1.4%)	0.115
Composite outcome (%)	60 (22.6%)	22 (28.2%)	145 (68.1%)	<0.001

*P<0.05 vs the complete recovery group; †P<0.05 vs the partial recovery group.

Kaplan-Meier survival analysis demonstrated a significantly lower survival probability in the unrecovered group compared to the complete and

partial recovery groups (Figure 2). Cox regression analysis further confirmed that the unrecovered group had a hazard ratio (HR) of 3.60 (95% CI, 2.50–5.00; P < 0.001) for 90-day mortality, while the partial recovery group did not show a significant difference (HR = 1.20, 95% CI, 0.70–2.10; P = 0.45).

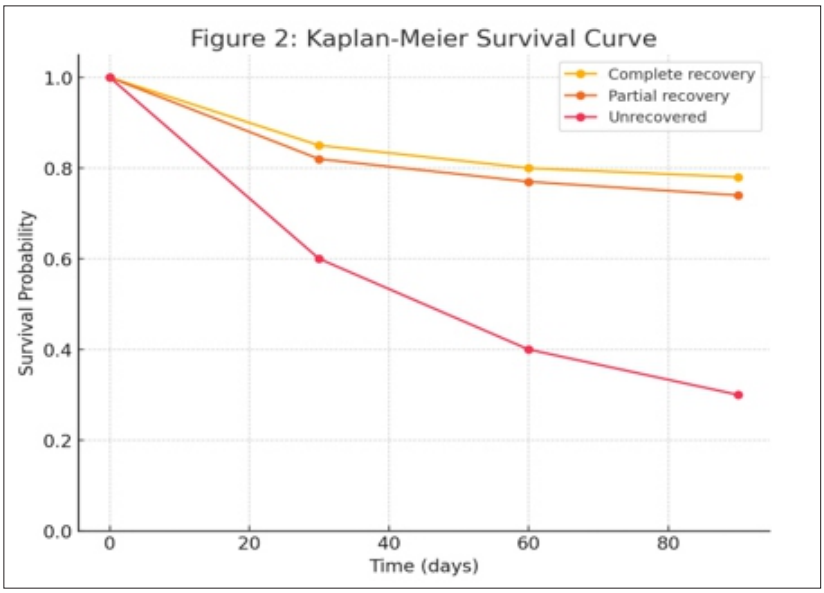

Figure 2: Kaplan-Meier Survival Curve of Patients Stratified by Early Recovery Status After AKI

Risk Factors for Unrecovered Renal Function

Multivariate logistic regression identified several independent risk factors for unrecovered renal function (Table 3). These included male sex (OR = 1.55, 95% CI, 1.05–2.30; P = 0.045), congestive heart failure (OR = 2.50, 95% CI, 1.30–4.90; P = 0.008), pneumonia (OR = 1.55, 95% CI, 1.05–2.35; P = 0.030), anemia (OR = 1.70, 95% CI, 1.10–2.50; P = 0.018), hyperbilirubinemia (OR = 2.00, 95% CI, 1.20–3.30; P = 0.005), mechanical ventilation (OR = 2.10, 95% CI, 1.35–3.20; P = 0.002), and AKI Stage 3 (OR = 6.60, 95% CI, 4.00–10.80; P < 0.001).

Table 3: Multivariate Logistic Regression Analysis for Risk Factors Associated with Unrecovered Renal Function After AKI

Factors	OR	95% CI	P-value
Age	1.01	0.99-1.03	0.620
Male Sex	1.55	1.05-2.30	0.045
Hypertension	1.28	0.85-1.92	0.210
Diabetes Mellitus	1.42	0.95-2.15	0.105
Congestive Heart Failure	2.50	1.30-4.90	0.008
Premorbid CKD	1.70	1.00-2.90	0.047
Pneumonia	1.55	1.05-2.35	0.030
Respiratory Rate >20 Beats Per Minute	1.82	1.20-2.75	0.010
Anemia	1.70	1.10-2.50	0.018
Hyperbilirubinemia	2.00	1.20-3.30	0.005
Mechanical ventilation	2.10	1.35-3.20	0.002
AKI Stage 1	1.16	0.81- 2.41	0.161
AKI Stage 2	1.55	0.90-2.80	0.110
AKI Stage 3	6.60	4.00-10.80	<0.001
Heart Rate >90 Beats Per Minute	1.50	0.95-2.35	0.090
Hypoxemia	1.55	1.05-2.30	0.030

CKD: Chronic kidney disease; AKI: Acute kidney injury.

Sensitivity analyses, conducted in subgroups of patients who remained in the hospital on Day 7, without premorbid CKD, and with AKI Stage 2 or 3, consistently showed that unrecovered renal function was an independent predictor for 90-day mortality and composite outcome (Figure 3).

Figure 3 (A): Multivariate Cox Regression of 90-day Mortality

Subgroup	HR (95% CI)	P-value
Overall - Partial Recovery	1.20 (0.70–2.10)	0.45
Overall - Unrecovered	3.60 (2.50–5.00)	<0.001
Staying in Hospital on Day 7 - Partial Recovery	1.50 (0.80–2.80)	0.25
Staying in Hospital on Day 7 - Unrecovered	3.80 (2.60–6.00)	<0.001
No Premorbid CKD - Partial Recovery	1.35 (0.75–2.40)	0.38
No Premorbid CKD - Unrecovered	4.20 (2.90–6.30)	<0.001
AKI Stage 2-3 - Partial Recovery	1.30 (0.75–2.40)	0.35
AKI Stage 2-3 - Unrecovered	4.10 (2.60–6.50)	<0.001

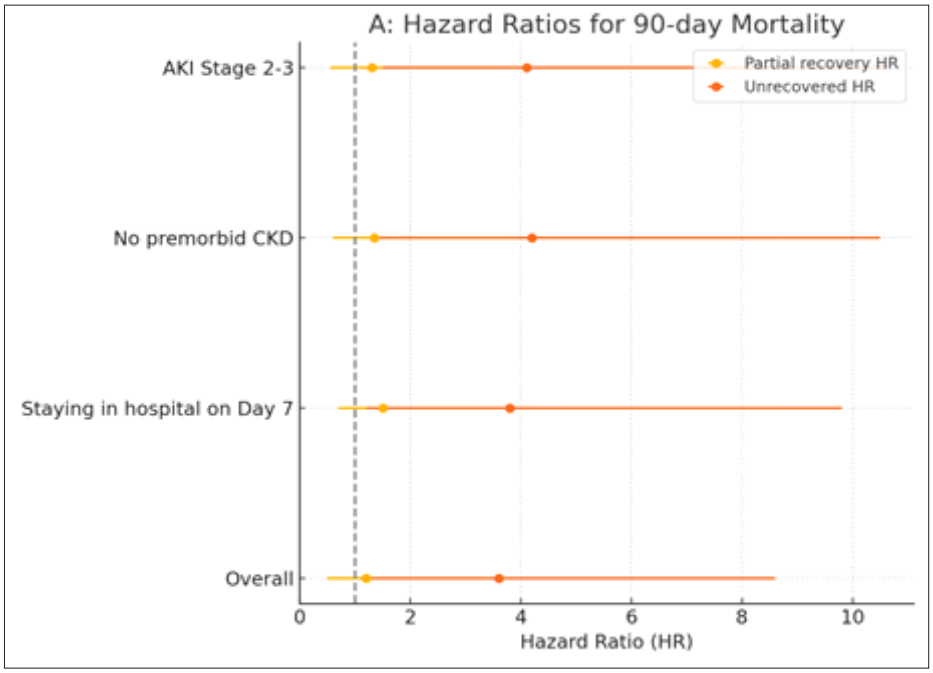

Figure 3 Association Between the Early Recovery Status After AKI and the Outcomes A:

Multivariate Cox regression of association between the early recovery status after AKI and the 90-day mortality in the overall cohort and by subgroups.

Figure 3 (B): Multivariate Logistic Regression of 90-day Composite Outcome

Subgroup	OR (95% CI)	P-value
Overall - Partial Recovery	1.25 (0.65–2.50)	0.58
Overall - Unrecovered	5.75 (3.50–9.00)	<0.001
Staying In Hospital on Day 7 - Partial Recovery	1.70 (0.80–3.70)	0.22
Staying In Hospital on Day 7 - Unrecovered	6.00 (3.30–11.00)	<0.001
No Premorbid CKD - Partial Recovery	1.30 (0.65–2.80)	0.48
No Premorbid CKD - Unrecovered	6.80 (4.00–11.30)	<0.001
AKI Stage 2-3 - Partial Recovery	1.40 (0.65–2.90)	0.40
Aki Stage 2-3 - Unrecovered	7.00 (4.00–12.50)	<0.001

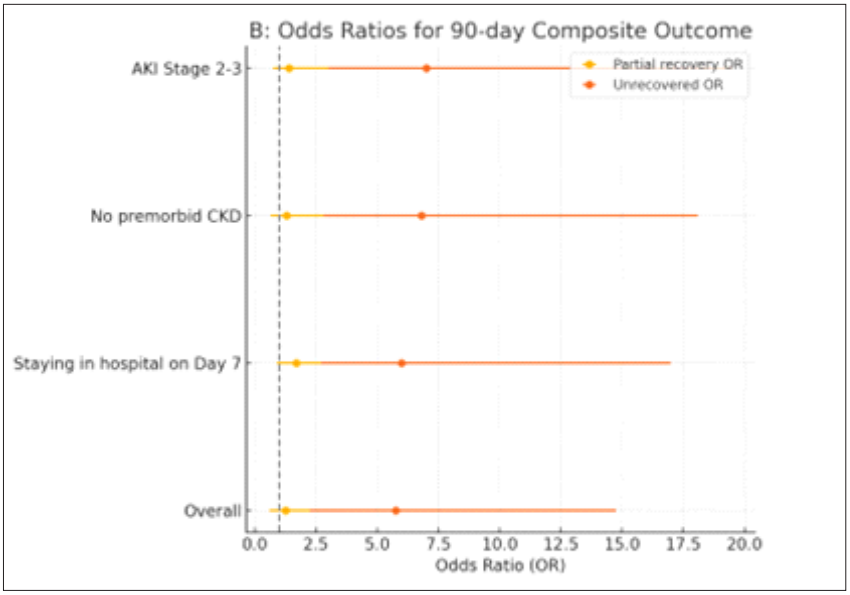

Figure 3: Association Between the Early Recovery Status After AKI and the Outcomes B:

Multivariate logistic regression of the association between the early recovery status after AKI and the 90-day composite outcome in the overall cohort and by subgroups.

DISCUSSION

In this study, we evaluated the effect of early renal recovery on 90-day outcomes in critically ill patients with sepsis-associated acute kidney injury (SA-AKI). The results indicate that patients who failed to recover renal function within the first seven days of AKI diagnosis faced significantly worse outcomes, including higher 90-day mortality and a greater likelihood of chronic dialysis, compared to those with complete or partial recovery. These findings corrob-orate previous studies that highlight the importance of early renal recovery in determining patient prognosis following SA-AKI (Monard et al., 2024; Peerapornratana et al., 2019; Poston & Koyner, 2019, Hoste et al., 2018). Specifically, the unrecovered group had a mortality rate of 65.7%, which was significantly higher than the 22.6% and 28.2% observed in the complete and partial recovery groups, respectively. This aligns with existing literature that suggests unrecovered renal function is an independent predictor of poor outcomes in septic AKI patients (Bouchard et al., 2015; Uhel et al., 2020; Kellum et al., 2017).

Renal recovery within the first week of AKI has

emerged as a critical factor in reducing mortality and preventing long-term complications, including chronic kidney disease (CKD) and end-stage renal disease (ESRD) (Pan et al., 2024; Bai et al., 2024). Our study supports this by demonstrating that patients who achieve full renal recovery within the first week not only have a lower risk of mortality but also show reduced rates of chronic dialysis and persistent renal dysfunction (Zarbock et al., 2020). In contrast, those with unrecovered renal function continue to experience ongoing renal impairment, which is associated with a higher incidence of poor clinical outcomes, such as progression to CKD or ESRD (Chertow et al., 2005; Bellomo et al., 2017).

The identification of independent risk factors for unrecovered renal function provides insight into the patient characteristics and clinical conditions that contribute to poorer renal recovery in the context of SA-AKI (Cho et al., 2024; Dochert et al., 2024). In our cohort, male sex, congestive heart failure, pneumonia, anemia, hyperbilirubinemia, mechanical ventilation, and AKI Stage 3 were independently associated with a lack of renal recovery. These findings are consistent with previous research that has identified severe illness, multiple organ dysfunction, and hemodynamic instability as key contributors to the persistence of AKI (Federspiel et al., 2018; Peters et al., 2018). The presence of congestive heart failure and pneumonia, in particular, suggests that comorbid conditions that impair cardiac function and pulmonary status may exacerbate the hemodynamic and inflammatory insults to the kidney during sepsis, reducing the likelihood of recovery (Uhel et al., 2020).

One notable aspect of our study is the finding that partial recovery, while associated with lower mortality than unrecovered renal function, did not confer the same level of survival benefit as complete recovery. This highlights the importance of full renal recovery as a target for therapeutic interventions in SA-AKI patients (Legrand et al., 2024; Zarbook et al., 2024). Partial recovery may indicate ongoing renal injury, which can predispose patients to further renal decline or other complications during their ICU stay (Ozrazgat-Baslanti et al., 2020). Therefore, it is critical for clinicians to aim for complete recovery where possible and to closely monitor patients with partial recovery to prevent the recurrence of renal injury (Peters et al., 2018).

In terms of interventions, early identification of patients at high risk for unrecovered renal function is essential. Biomarkers such as TIMP-2 and IGFBP7 have shown promise in predicting renal recovery in AKI patients, and their use in conjunction with clinic-al criteria could help guide therapeutic decisions (Kashani et al., 2013; Zarbock et al., 2020; Joannidis et al., 2017). For patients with severe AKI or those who require mechanical ventilation, early initiation of renal replacement therapy (RRT) and careful management of fluid balance may improve the likelihood of recovery (Kellum et al., 2017). Additionally, avoiding nephrotoxic agents and optimizing hemodynamic support can further promote renal recovery in this vulnerable patient population (Federspiel et al., 2018).

LIMITATIONS

There are several limitations to this study. First, it was a retrospective cohort study, which may introduce selection bias and limit the generalizability of the findings. Second, urine output was not included as a criterion for AKI diagnosis, which could have affected the classification of AKI stages and recovery status. Additionally, factors such as diuretic use and baseline kidney function were not fully accounted for, which may have influenced the outcomes of interest. Finally, the sample size was limited to a single institution, which may affect the external validity of the findings. Future multicenter prospective studies are needed to validate our findings and to explore interventions that can improve renal recovery in SA-AKI patients.

CONCLUSION

In conclusion, early renal recovery is a crucial determinant of survival and long-term outcomes in critically ill patients with sepsis-associated AKI. Unrecovered renal function within the first seven days is associated with a significantly increased risk of 90-day mortality and the need for chronic dialysis. Male sex, congestive heart failure, pneumonia, and mechanical ventilation are important predictors of poor renal recovery. These findings underscore the importance of early intervention and close monitoring of high-risk patients to improve renal outcomes and reduce mortality in SA-AKI. Future research should focus on developing and implementing strategies that promote complete renal recovery, ultimately improving the prognosis of patients with sepsis-induced AKI.

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