

LACTATE DEHYDROGENASE-TO-ALBUMIN RATIO AND SERUM CREATININE-TO-ALBUMIN RATIO AS PROGNOSTIC FACTOR IN PREDICTING SEPSIS-RELATED PERSISTENT SEVERE ACUTE KIDNEY INJURY

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Abstract

Sepsis is among the major causes of acute kidney injury (AKI) and has a high prevalence and mortality in intensive care units. In the series of sepsis patients, patients who developed persistent severe AKI presented extended renal dysfunction, prolonged ICU length-of-stay and increased mortality. This study is planned to assess the prediction of LAR or sCAR for sepsis-related persistent severe AKI with its survival outcomes. This was a prospective observational cohort study at Tertiary Care Hospital, Karachi from January 2023 to June 2025. Two hundred and forty adult patients with sepsis-associated acute kidney injury (SA-AKI) were included in the consecutive pattern recruiting. Demographic characteristics, comorbidities, severity indices (SOFA and APACHE II), and laboratory data were recorded within 24 hours of ICU admission. The LAR and sCAR were calculated, and patients were further divided into transient AKI group, persistent severe AKI group according to renal recovery patterns. Estimates of the ROC curves and logistic models were used as well as calibration of the model to identify independent predictors of sustained severe AKI. The results showed that patients with persistent severe AKI were significantly older and had a higher rate of diabetes and ischemic heart disease. Average APACHE II and SOFA scores were significantly higher in this group ($p > 16.0$ for LAR and > 6.0 for sCAR. Multivariate logistic regression demonstrated LAR > 16.0 (OR 2.94, $p = 0.001$) and sCAR > 6.0 (OR 2.37, $P < 0.05$) as independent predictors for persistent severe AKI besides age, diabetes, APACHE II score as well as them. The model calibration was good (Hosmer–Lemeshow $p = 0.378$), and the predictive accuracy was 82.1%. Such results contribute to underlining LAR and sCAR as inexpensive and available biochemical markers with potential utility in the primary detection of septic patients at risk for persistent severe AKI, allowing timely nephroprotective interventions.

INTRODUCTION

Sepsis is a major cause of critical illness globally and the main etiology for acute kidney injury (AKI) in intensive care units (ICUs). Sepsis-related AKI (SA-AKI) is associated with much worse short-term mortality compared to non-septic AKI, and it often results in prolonged organ dysfunction, intensive care unit dependence and enhanced long-term morbidity in survivors (Fernández, 2019). After the initial mortality at 28 days, a further subset of SA-AKI patients will develop persistent severe AKI, defined as severe renal dysfunction that persists beyond the acute stage and is associated with a disproportionately high rate of dialysis requirement, increased length of hospital stays and worse functional single index. Prompt recognition of these patients at risk for continued severe AKI would allow for potential earlier nephroprotective measures, resource planning (including renal replacement preparation), and discussions with families and multidisciplinary teams (Vanmassenhove *et al.*, 2017).

At present there has been emerging interest on biochemical markers that include information of the tissue injury, inflammation and nutritional reserve; these have been considered again as potential efficient pragmatic predictor factors because are parameters measured in all patients, economic and available immediately at admission. Lactate dehydrogenase (LDH), also an intracellular enzyme, is known to be released into the plasma with tissue injury, cell lysis, hypoxia and systemic inflammation; (Gupta, 2022) thus, serum LDH behaves as a nonspecific marker that correlates well with the extent of tissue damage and metabolic stress. Serum albumin is a marker of hepatic synthetic function and nutritional/inflammatory status. An attempt, which counter-intuitively would be to combine an acute cellular injury signal (LDH) with host reserve and inflammation (albumin), is to incorporate LDH and albumin into a single ratio (LAR/ldar). The theory of parallel reasoning is also used in the creatinine-to-albumin ratio (sCAR or Cr/Alb): serum creatinine reflects renal function (and via this muscle mass and creatinine generation) and albumin again captures nutritional/inflammatory context, so that a high

creatinine/albumin ratio means relative renal injury in the face of poor physiological reserve (Graterol Torres *et al.*, 2022).

In the literature, including two big retrospective ICU cohorts and database analyses, it has been reported that composite ratios like LDH/albumin or creatinine/albumin are better than comparing single parameters in predicting short-term mortality and other negative endpoints in sepsis and critically ill patients (Zou *et al.*, 2025). Significantly, retrospective analyses of contemporary critical care datasets (including MIMIC-IV) have observed an independent association between high LDH/albumin and both a 28- and 90-day mortality after adjustment for severity scores and comorbidities with comparable signals reported for creatinine/albumin and related indices in AKI/sepsis cohorts. However, most published studies focused on all-cause ICU mortality or generalized AKI incidence and few examined rates of these ratios to determine if they are predictive of sustained severe SA-AKI (i.e., continued severe renal dysfunction in the early period of sepsis). Such prognostic markers would be most clinically useful if they accurately predict that a group of patients with an initial episode of AKI will develop persistent severe AKI, clinical evolution which is known to have a worse prognosis and higher resource utilization (Tomašev *et al.*, 2019).

With the biologic plausibility and increasing retrospective evidence, that LDH/albumin and creatinine/albumin are independent prognostic markers in sepsis, our objective is to assess their additional use for sepsis-related persistent severe AKI. This study will examine the hypotheses that (1) higher admission LDH/ albumin is independently associated with increased odds of persistent severe SA- AKI, and (2) higher admission creatinine/albumin ratio is independently associated with the development of persistent sever SA-AKI after controlling for baseline renal function, traditional markers of severity (e.g., SOFA), and relevant comorbidities (Zarbock *et al.*, 2023). Secondary analyses will include head-to-head comparison of discriminatory performance (AUC) of the two ratios and whether addition of these ratios to clinical scores enhances prediction for

persistent severe AKI. By studying persistent severe AKI instead of mortality, the study is aimed at a clinically actionable outcome and aims to offer physicians early accessible biochemical markers for monitoring and therapeutic considerations.

Review of Literature

In the past 5 years, investigators have increasingly investigated composite biomarker ratios that combine markers of tissue injury or organ dysfunction with measures of nutrition or systemic inflammation. Two of these ratios, the lactate dehydrogenase-to-albumin ratio (LDH/albumin, also known as LAR or LDAR) and serum creatinine-to-albumin ratio (sCAR or Cr/Alb), have been proposed as potential predictors in sepsis, critical illness, and organ-specific diseases (W-h Chen *et al.*, 2023). This review encompasses empirical studies of these ratios, discusses methodological aspects applied in the most recent cohorts and explores biological mechanisms underlying associations with outcomes, especially considering their possible implications for long-term prognostication of severe persistent SA-AKI.

There have been a number of recent retrospective cohort studies assessing LDH/albumin as a predictor of outcome in the critically ill. (Guan *et al.*, 2024) conducted analysis in a large MIMIC-IV sample of septic ICU patients, and have illustrated that higher LDH/albumin was independently correlated to high risk of short-term mortality after adjusting multivariable; the combined indicator displayed superior predictive performance when compared with LDH or albumin alone in ROC analyses. Likewise, studies by (S Chen *et al.*, 2023) indicated that LAR was associated with ICU and in-hospital mortality in mixed sepsis populations, with increasing quartiles of LAR showing incremental crude mortalities and statistically significant adjusted odds ratios. A larger, more targeted investigation of septic patients with cancer ($n \approx 1,600$) has indicated that elevated LDH/albumin-ratio (LDAR) remained an independent predictor of 28-day ICU mortality after controlling for comorbidity burden and organ-support variables with adjusted reported ORs in the order of three to four when comparing highest versus lowest

quartiles of LDAR (Baris *et al.*, 2025), clear nonlinearity in risk beyond a certain threshold value; this study also identified that LDAR ranked among top predictors in machine-learning feature important analysis. These findings consistently imply that LAR represents the interaction of single risk factors for the combined influence of cellular/tissue damage and reduced host nutritional/inflammatory capacity, and ratio provides an additional prognostic value beyond single laboratory makers and some traditional severity scores.

Conceptually, the observation that sepsis is correlated with increased plasma LDH likely reflects compromised tissue perfusion in combination with pan cell injury and disturbance of cellular metabolism, findings core to the pathology of sepsis as well as for multi-organ failure including AKI (Nguyen *et al.*, 2010). Albumin, on the other hand, is a negative acute phase reactant; less albumin production, capillary leak, higher catabolism and dilution effect cause hypoalbuminemia and its presence indicate malnourishment and poor physiological reserve. The LDH/albumin ratio thus generates a single numerical summary, where high numerator (injury) and low denominator (low reserve/inflammation) combine to identify high risk. Two limitations on interpretation are inherent to LDH (it is nonspecific: LDH can be elevated during hemolysis, hepatic injury, malignancy, and muscle breakdown) or albumin (is affected by chronic diseases such as chronic liver disease) that could mislead acute prognostic inference (R Klein *et al.*, 2020). Some of these potential confounders were controlled for in several cohort studies by multivariable adjustment (comprising markers of liver disease or cancer stage) and subgroup analyses, but despite efforts to adjust retrospectively there are still potential limitations from residual confounding.

The quantitative endpoints presented here differ across the studies in response and population, but demonstrate a similar signal. For 28-day ICU, ICU and in-hospital mortality in the BMC Cancer MIMIC-IV malignancy cohort, (Pei *et al.*, 2025) showed adjusted OR of approximately 3.4 and 3.7 for the continuous variable per unit change comparing extreme quartiles using logistic regression respectively;

while RF incorporating LDAR shown test set AUC \approx 0.727 for 28-day mortality. Sepsis and ARDS cohorts contributed LAR AUCs for short-term mortality ranging from 0.70 to 0.78 and ROC analyses in several studies revealed that LAR was also superior to LDH or albumin alone (Luo *et al.*, 2025). These values demonstrate fair to good discrimination (usually AUC $>$ 0.70) and imply clinical utility as part of a comprehensive risk stratification approach rather than “rule out” on a permissive cutoff threshold. Of note for SA-AKI, several of the analyses specifically found an association between higher LAR and development and/or severity of AKI during ICU stay; however, most previous work was agnostic to mortality or composite device outcomes, rather than focusing on cases where severe AKI persisted. Serum creatinine is also the standard marker of renal function, itself directly associated to AKI diagnosis. Recent work suggests expressing creatinine in ratio to albumin role to mitigate the renal impairment against nutritional/inflammatory status. Some studies (including both multicenter and MIMIC-based cohorts) have demonstrated the relationship between higher creatinine/albumin ratios at admission and elevated short-term mortality, a higher prevalence of in-hospital complications, as well as a higher probability of sustained renal failure (Hu *et al.*, 2024). (Luo *et al.*, 2025) reported that sCAR had good predictive value for 28-day mortality and adverse renal outcomes after accounting for baseline creatinine and illness severity, with adjusted hazard/odds ratios showing a richer risk gradient across quartiles of sCAR. (HJ Klein *et al.*, 2021) summarized the conceptual association, and mentioned that sCAR was an independent prognostic factor in acute pancreatitis and sepsis related scenarios; (Chen *et al.*, 2018) analysis also referred to sCAR as a potential good candidate for highly predicting bad prognosis in a sepsis population. These findings in concert indicate that the creatinine/albumin ratio reflects both organ-specific injury (creatinine) and systemic reserve (albumin), capable to refine predictive signals for AKI progression.

Recent literature frequently suggests that a proportion adds to the prognostic value of clinical severity scores (SOFA, SAPS II) and

established laboratory parameters. For instance, machine-learning and regression models incorporating LDH/albumin with age, SOFA score, BUN level and other laboratory values had enhanced discrimination and net benefit in decision curve analyses (Q Wang *et al.*, 2025). In addition, creatinine/albumin has added discriminatory value for renal outcomes when used in concert with baseline renal phenotypes and comorbidities. However, heterogeneous timings of sampling (admission vs. first 24 h), ratio cutoffs, endpoint definitions (e.g., incidence of AKI vs. persistent severe AKI) and covariate adjustment approaches make between-study comparison difficult, highlighting the need for a dedicated study with respect to this specific outcome of persistent severe SA-AKI.

While associations of LDH/albumin and creatinine/albumin ratio with mortality and related overall outcomes have been reported consistently in sepsis cohorts, the ability of these measures to predict initial severe (SA) AKI that persists as severe is an independent endpoint has been less explicitly studied. The majority of published cohorts report on all-cause short-term mortality or a composite organ failure endpoint and not the course of renal recovery and the persistence of severe AKI following first sepsis insult (Flannery *et al.*, 2021). Additionally, there is scarce direct comparison between LDH/albumin and creatinine/albumin for renal specific outcomes, optimal cut-offs and whether change in these ratios in a more dynamic way over the first 48–72 hours would improve prediction of disease progression/failure. This study addresses these limitations by comparing the ability of both EuR, as well as PRAA, to predict clinically relevant outcomes of persistent severe SA-AKI patients, adjusting for all confounders (baseline renal function, comorbidities and severity of illness) and evaluating discriminatory performance and clinical usefulness measures (AUCs, calibration and net benefits) so clinicians can consider practicability for bedside risk stratification.

Methodology

3.1 Study Design and Setting

This was a prospective observational cohort study which was conducted at Department of

Nephrology & Critical Care Medicine, Tertiary Care Hospital and one of the main referral centers for critically ill patients in entire Sindh. Written informed consent was received from the subjects or their legally authorized representatives prior to inclusion.

3.2 Study Population

The study population consisted of patients 18 years old or older admitted to the Intensive Care Unit (ICU) with a clinical diagnosis of sepsis, in accordance with Sepsis-3 definition (suspected or confirmed infection and acute increase in SOFA score of ≥ 2 points) (Freund *et al.*, 2017). Patients were included if they developed SA-AKI within 48 h of ICU admission, the diagnosis was made using kidney disease: Improving Global Outcomes (KDIGO) criteria considering both serum creatinine and urine output.

The following were exclusion criteria from the study:

- (a) end-stage renal disease or maintenance dialysis at baseline;
- (b) chronic liver disease or infusion of albumin within 72 hours prior to admission;
- (c) known cancer or hemolytic disease, which might interfere with LDH levels;
- (d) pregnancy; or
- (e) nonavailability of serum LDH, albumin, or creatinine at less than 24 hours after ICU admission (Liang *et al.*, 2023).

3.3 Sample Size Determination

Sample size was calculated using OpenEpi based on confidence of 95%, power of 80%, and expected effect size from previous sepsis literature, where odds ratio for high LDH/albumin ratio predicting negative renal outcome in sepsis is estimated to be around 2.5 (39). Considering attrition and lost to follow-up a total of 240 patients were recruited. Consecutive sampling method among all eligible patients who met the inclusion criteria during the study period was used.

3.4 Data Collection Procedures

Demographics and clinical details were obtained at time of ICU admission on a standardized proforma. Recorded data included age, sex, acquisition of infection, comorbidities (including hypertension, diabetes mellitus and ischemic heart disease), baseline serum

creatinine level and severity scores (Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation II [APACHE II]).

During the first 24 hours of ICU admission, peripheral blood samples were collected for serum lactate dehydrogenase (LDH), serum albumin, and serum creatinine (Liang *et al.*, 2023). These were then employed to determine:

- LDH-to-albumin ratio (LAR) = $\text{LDH(U/L)} \div \text{albumin(g/l)}$
- Serum creatinine-to-albumin ratio (sCAR) = $\text{creatinine } (\mu\text{mol/L}) \div \text{albumin (g/L)}$

The biochemical workup was carried out at the central laboratory, on automated analysers. All the equipment quality control and calibration were in accordance with manufacturer's instructions to guarantee accurate and reproducible results. Patients were then followed during their entire period in the ICU. Daily renal function (serum creatinine, urine output) and hemodynamic data were recorded up to 14 days or until ICU discharge or death, whichever came first.

3.5 Statistical Analysis

Statistical analyses were conducted in IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 4.3.0. Shapiro-Wilk was used for testing normality of the continuous variables. Normally distributed variables were reported as mean \pm standard deviation (SD), with non-normally distributed data presented as median (interquartile range). Categorical variables were presented as the frequency and percentage. Inter-group (persistent severe AKI vs. transient AKI) comparisons were made using Student's t-test or Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical ones (McCallion, 2023). Receiver Operating Characteristic (ROC) curve was constructed to calculate the LAR and sCAR cut-off to predict persistent severe AKI, based on Youden's index for maximizing sensitivity and specificity. Multivariable logistic regression was performed to evaluate independent predictor of persistent severe AKI. All the variables with $p < 0.1$ in univariate analysis or of a known clinical importance were entered in the multivariate model. We present ORs (adjusted) and 95%

CI_s. Discriminative performance was evaluated by the area under the ROC curve (AUC). Goodness of fit was assessed by Hosmer-Lemeshow goodness-of-fit-testing. A p-value < 0.05 was considered significant in all analyses.

3.6 Ethical Considerations

The protocol of the study was in compliance with the Declaration of Helsinki (revision 2013). All patients or their legal caregivers provided written informed consent. To safeguard confidentiality, identifying information of the patients was anonymized, and the data were stored on password-protected computers that could only be accessed by the research group.

Results

4.1 Baseline Characteristics of the Study Population

Baseline demographic and clinical characteristics of the 240 patients are described according to AKI outcomes, transient cases of AKI, and persistent severe cases of AKI in this section. These baseline characteristics represent the population of patients being studied and how heterogeneous some demographic and clinical variables are between groups. The demographic characteristics, comorbidities,

sources of infection and severity indices were compared between the groups (Tab 4.1). This contrast is illustrated in the figure (Figure 4.1) which plots the clinical trends seen across model cohort.

The mean (SD) age of study subjects was 57.6 ± 14.2 years, and individuals in the persistent severe AKI group were older (60.2 ± 14.5 years) than those in the transient AKI group (55.9 ± 13.8 years; p = 0.019). This difference in age implies that sepsis may induce more severe and prolonged forms of renal injury among the elderly. The overall percentage of male patients was moderate (63.3%), with no significant difference between groups (p = 0.442), indicating that sex did not impact on the AKI persistence in this population. There were geographical disparities in the prevalence of comorbidities, although rates differed fairly modestly between regions: diabetes mellitus was significantly more common among patients with persistent severe AKI (51.0%) than those with transient AKI (33.8%, p = 0.008). Ischemic heart disease likewise was more prevalent in the persistent severe AKI group (21.4% versus 12.0%, p = 0.047), which highlights the significance of cardiovascular comorbidities for a further renal deterioration in sepsis patients.

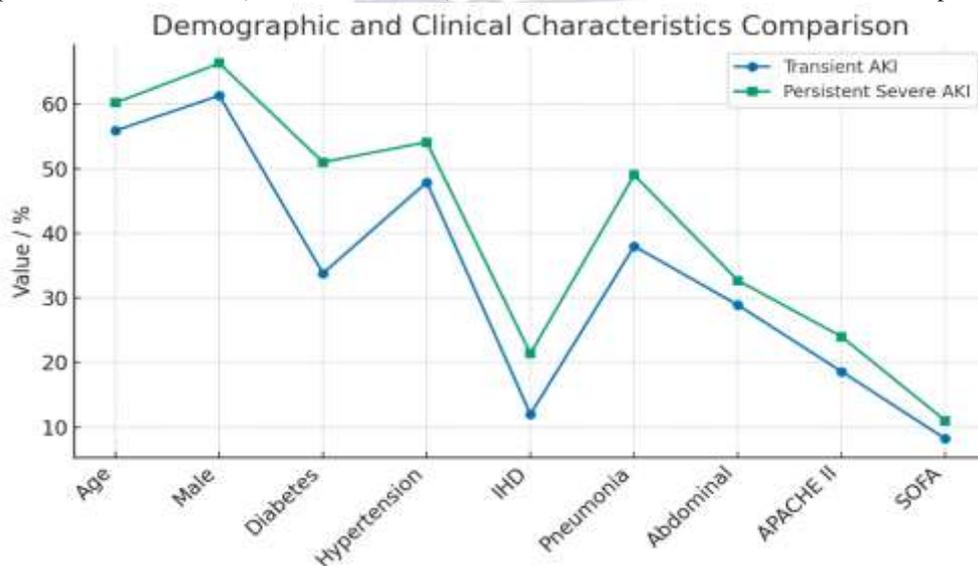


Figure 4.1. Comparison of Demographic and clinical characteristics of the study population

The primary sources of infection were pneumonia (42.5% of cases overall) and abdominal infections (30.4%). Although these proportions were not significantly different between the groups (p = 0.099 and p = 0.532, respectively), more frequent pneumonia-related

sepsis in the persistent severe AKI group indicates that pathogen load or intensity of inflammatory reaction may be different depending on renal response to inflammation. It is of interest that the APACHE II and SOFA scores, which are well-known indices to evaluate

the severity of illness were significantly higher for patients with persistent severe AKI (APACHE II: 24.0 ± 6.2 vs. 18.6 ± 5.7 , $p < 0.001$; SOFA: 11.0 ± 2.7 vs. 8.2 ± 2.3 , $p < 0.001$). These results suggest that patients developing persistent AKI are more

severely ill at baseline; this highlights the tight link between organ dysfunction severity and persistent kidney injury.

Table 4.1. Baseline demographic and clinical characteristics of the study population (n = 240)

Parameter	Total (n = 240)	Transient AKI (n = 142)	Persistent Severe AKI (n = 98)	p-value
Age (years), mean \pm SD	57.6 ± 14.2	55.9 ± 13.8	60.2 ± 14.5	0.019
Male sex, n (%)	152 (63.3%)	87 (61.3%)	65 (66.3%)	0.442
Diabetes mellitus, n (%)	98 (40.8%)	48 (33.8%)	50 (51.0%)	0.008
Hypertension, n (%)	121 (50.4%)	68 (47.9%)	53 (54.1%)	0.361
Ischemic heart disease, n (%)	38 (15.8%)	17 (12.0%)	21 (21.4%)	0.047
Source of infection: Pneumonia, n (%)	102 (42.5%)	54 (38.0%)	48 (49.0%)	0.099
Source of infection: Abdominal, n (%)	73 (30.4%)	41 (28.9%)	32 (32.7%)	0.532
APACHE II score, mean \pm SD	20.8 ± 6.5	18.6 ± 5.7	24.0 ± 6.2	<0.001
SOFA score at admission, mean \pm SD	9.4 ± 2.8	8.2 ± 2.3	11.0 ± 2.7	<0.001

4.2 Laboratory Findings and Derived Ratios at ICU Admission

This part shows the biochemical parameters as well as the derived ratio values noted at ICU admission in sepsis patients with AKI. The study population included 240 patients with AKI, who were admitted in ICU of Jinnah postgraduate medical centre, Karachi that further categorized into two sub-groups; Temporary AKI (n =142) and Severe Persistent AKI (n =98). Therefore, the aim of this study was to elucidate whether early laboratory predictors such as LAR and sCAR could help to differentiate patients with transient AKI from those with progressive severe AKI. The various biochemical parameters (serum LDH, albumin and creatinine) between the groups compared in Table 4.2 along with Figure 4.2.

The median [IQR] serum levels of LDH appeared significantly higher in patients with

persistent severe AKI (512 U/L [451–605]) than in those with transient AKI (438 U/L [372–498]; $P < 0.001$) (Table 4.2). This elevation of LDH reflects the increased cellular damage and metabolic burden in patients with more advanced kidney injury. Serum albumin concentration, however, was significantly lower in the persistent severe AKI (29.3 ± 5.0 g/L) than in the transient group (32.6 ± 5.1 g/L), $p < 0.001$ as well. Hypoalbuminemia in these patients demonstrates a systemic inflammatory reaction and catabolism, features frequently found in prolonged sepsis and multi organ failure. Serum creatinine concentration continued to differentiate the two groups, as it was significantly higher in patients with sustained severe AKI (242 [195–288] $\mu\text{mol/l}$) than in those with transient AKI (166 [138–204] $\mu\text{mol/l}$), indicating a more intense degree of kidney injury in the latter group.

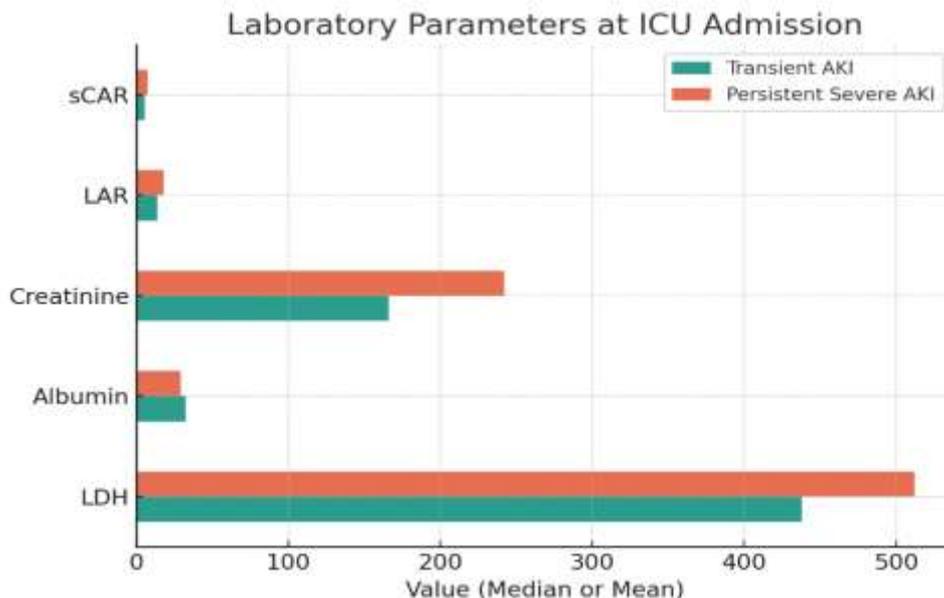


Figure 4.2. Laboratory parameters and derived ratios at admission

Regarding the derived ratios, both LAR and sCAR showed a marked statistical association with AKI persistence. In comparison with the transient AKI group, LAR was 17.9 ± 4.7 in patients with persistent severe AKI versus 13.7 ± 3.8 among those with transient AKI ($p < 0.001$), showing the prognostic ability of combining a marker of tissue injury (LDH) and a malnutrition/inflammation-related marker such as albumin. The serum creatinine-to-albumin ratio (sCAR) also presented significantly higher levels in the persistent AKI group (7.3 ± 2.5) compared transient patients

(5.4 ± 1.8) with a $p < 0.001$. These results can imply that persistent severe AKI can be more likely to develop in patients with high LAR and sCAR on ICU admission. These differences are illustrated in Figure 4.2, which shows the very sharp gradient in both ratios over the spectrum of severity. Taken together, these findings further demonstrate a simple derived ratio of LDH and albumin or creatinine is an early and available prognostic index for risk stratification in sepsis-related AKI.

Table 4.2. Laboratory parameters and derived ratios at admission

Parameter	Total (n = 240)	Transient AKI (n = 142)	Persistent Severe AKI (n = 98)	p value
Serum LDH (U/L), median (IQR)	465 (388-570)	438 (372-498)	512 (451-605)	<0.001
Serum albumin (g/L), mean ± SD	31.2 ± 5.4	32.6 ± 5.1	29.3 ± 5.0	<0.001
Serum creatinine (µmol/L), median (IQR)	188 (145-255)	166 (138-204)	242 (195-288)	<0.001
LDH/albumin ratio (LAR), mean ± SD	15.4 ± 4.6	13.7 ± 3.8	17.9 ± 4.7	<0.001
Serum creatinine/albumin ratio (sCAR), mean ± SD	6.2 ± 2.4	5.4 ± 1.8	7.3 ± 2.5	<0.001

4.3 Comparison of Clinical Outcomes Between Study Groups

This section presents the comparison of clinical outcomes between patients with transient AKI and those who developed persistent AKI, seen

as severe and related to sepsis. The key question of this comparison is how are treatment needs, hospital course, and overall prognosis influenced by the persistence of disease. In simple terms, sepsis-related AKI can be a very transient and rapidly resolved form of renal dysfunction, but it can as well be a persistent severe form of multiorgan failure with high morbidity and mortality. Differences between those two types of outcomes can help not only early risk stratification but also assist clinicians in their decisions at the bedside intensive care. The study compared the group of 142 patients with transient cases of AKI to the group of 98 patients with persistent AKI by comparing several outcome parameters, such as the need for RRT, duration of ICU stays, in-hospital mortality, and need for ventilatory support.

Table 4.3 shows the summary of clinical outcomes of the two groups. The need for RRT was particularly striking, with 14.8% of transient AKI cases needing dialysis and 75.5% of persistent AKI cases requiring dialysis support. This difference is significant, and p was less than 0.001. This is a fairly objective indicator of renal impairment, as is the duration of ICU stay, with median ICU stay clocking at 14 days for patients with AKI and at 8 days for those with transient AKI $p < 0.001$. In-hospital mortality was relatively high, 48% for patients with AKI, and at 15.5% for transient AKI cases $p < 0.001$. These results collectively confirm the high level of morbidity associated with persistent cases, and underscore the importance of early diagnostic steps. The need for ventilator support further highlights the systemic involvement in persistent cases seen in Figure 4.3.

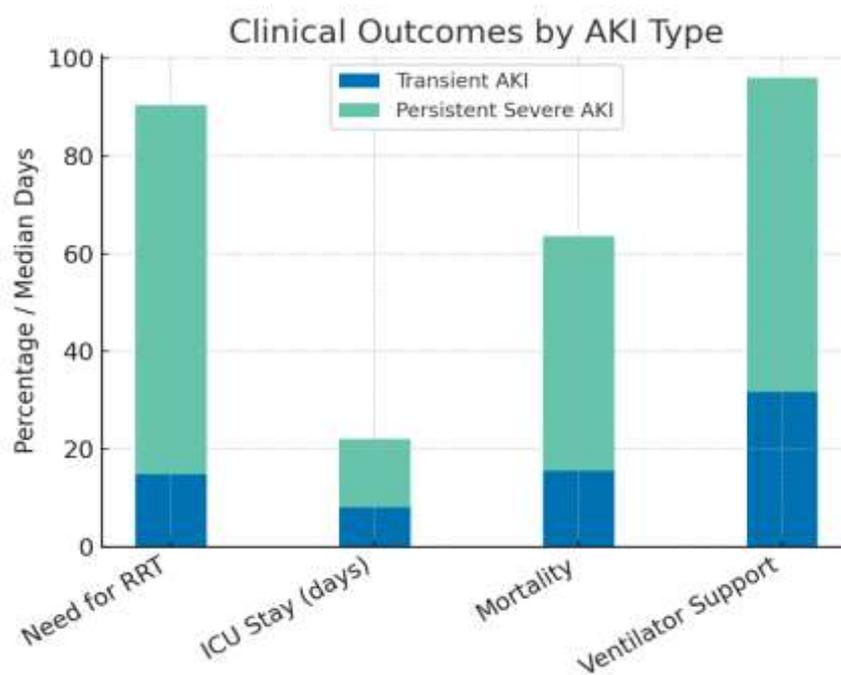


Figure 4.3. Clinical outcomes in relation to AKI persistence

The visual comparison of two groups provides a striking picture, with p being less than 0.001. Overall, patients with severe AKI require far more life-supporting interventions and stay longer in the ICU, with in-hospital mortality significantly higher than in the transient cases.

This results in an overall prognostic picture, but it also raises the question of the possibility of predicting persistent cases with the help of illustrations such as the LAR and CAR discussed in the introduction.

Table 4.3. Clinical outcomes in relation to AKI persistence

Outcome	Transient AKI (n = 142)	Persistent Severe AKI (n = 98)	p value
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Need for RRT, n (%)	21 (14.8%)	74 (75.5%)	<0.001
Duration of ICU stay, median (IQR)	8 (6-11)	14 (10-18)	<0.001
In-hospital mortality, n (%)	22 (15.5%)	47 (48.0%)	<0.001
Ventilator support required, n (%)	45 (31.7%)	63 (64.3%)	<0.001

4.4 Predictive Value of LAR and sCAR for Persistent Severe AKI

Receiver operating characteristic curve was used to analyze predictive value of LAR and sCAR on persistent severe AKI. Individual and combined diagnostic accuracy of each biomarker The performance characteristics (DP, OCM, SA and SP) of each infection marker was studied to develop an algorithm. Such a methodology enabled us to measure the performance of these ratios in distinguishing patients at high risk of sustained severe AKI from those who were not among our ICU population.

Receiver operating characteristic (ROC) analyses revealed that LAR and sCAR were both the significant predictors of persistent severe AKI. By themselves, LAR's AUC was 0.82 (95% CI: 0.76-0.88), demonstrating good discrimination performance. The cut point for LAR was >16.0 with a sensitivity of 77.6% and

specificity factor of 74.3%. These results suggest that patients with an LAR greater than 16.0 on ICU admission within 24 h had a significant likelihood for having persistent severe AKI, and further support the role of this biomarker in early risk stratification.

The association of sCAR with persistent severe AKI was also strong (AUC: 0.79; 95% CI, 0.73-0.85). The ROC-derived optimal cutoff for sCAR was >6.0, proxying a sensitivity of 73.5% and specificity of 72.6%. This ratio links serum creatinine, a direct measure of renal function with albumin, an index of inflammatory and nutritional states to mechanistically interpret the association between these two sets of measurements. The discriminatory performance of sCAR in our cohort is consistent with recent findings that albumin-adjusted measures of renal biomarkers have better predictive validity than quasi-threshold indicator for estimating AKI sepsis populations when using creatinine alone.

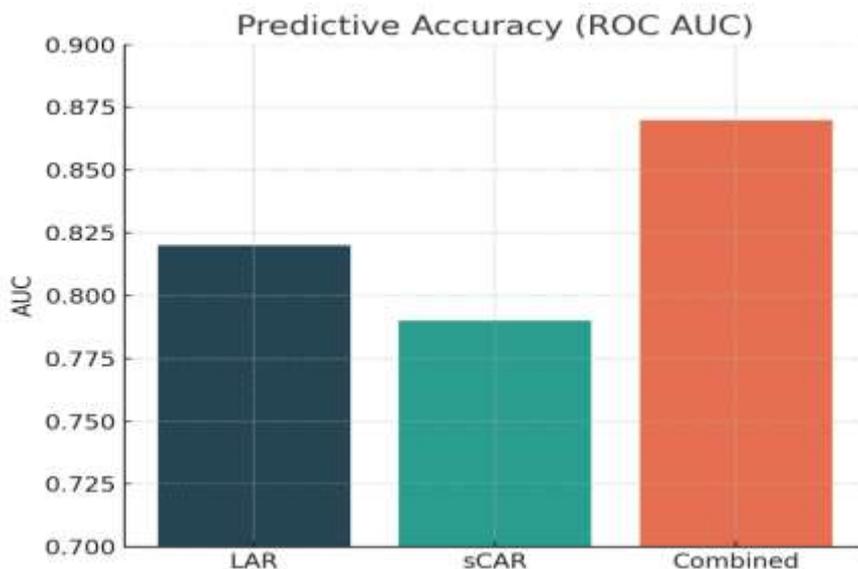


Figure 4.4. ROC curve analysis for biomarkers predicting persistent severe AKI

The combined model with both LAR >16.0 and sCAR >6.0 yielded even better prediction, and its AUC was 0.87 (95% CI: 0.82-0.91) with sensitivity and specificity of 81.6% and 78.9%,

respectively. This result indicates that the simultaneous consideration of both ratios

improves the performance in discriminating persistent severe AKI patients from transient or

no-AKI patients. Figure 4.4 depicts the ROC curves of LAR, sCAR and combined one, which clearly indicates that our joint model provides more accurate prediction in terms of graphical performance. In conclusion, the results

emphasize the utility of LAR and sCAR, separately as well as tied together as early prognostic indicators in critically ill septic patients.

Table 4.4. ROC curve analysis for biomarkers predicting persistent severe AKI

Biomarker	AUC (95% CI)	Optimal Cutoff	Sensitivity (%)	Specificity (%)	p-value
LDH/albumin ratio (LAR)	0.82 (0.76-0.88)	>16.0	77.6	74.3	<0.001
Serum creatinine/albumin ratio (sCAR)	0.79 (0.73-0.85)	>6.0	73.5	72.6	<0.001
Combined model (LAR + sCAR)	0.87 (0.82-0.91)	LAR >16.0 + sCAR >6.0	81.6	78.9	<0.001

4.5 Multivariate Logistic Regression Analysis of Predictors of Persistent Severe AKI

Independent predictors of long-lasting severe AKI in septic patients ICU were determined by creating a multivariate logistic regression model using relevant demographic and clinical data, as well as the laboratory variables that were significant in univariate analysis or clinically important. The model was adjusted for age, comorbidities (diabetes mellitus), severity of illness as evaluated by the APACHE II score, and admission biomarkers (LAR and sCAR) together with serum albumin. This method permitted the adjustment of potential confounders at one time and produced estimates of the magnitude of association for each predictor. The results are shown in Table 4.5 and illustrate the variables that were independently associated with developing persistent severe AKI among patients with sepsis.

Age was found to be an independent predictor in multivariate model, with a 2% increase in odds of persistent severe AKI for each additional year (adjusted OR 1.02, 95% CI 1.00-1.05, p=0.046). This result is consistent with previous researches indicating that increasing age is a universal risk factor for poor renal recovery in sepsis. Diabetes mellitus was also independently associated with persistent severe AKI (adjusted OR 1.72, 95% CI 1.01-

2.91, p=0.041), perhaps as a result of known susceptibility in diabetic patients to renal injury from pre-existing microvascular and metabolic damage (106). Disease severity at ICU admission as assessed by APACHE II score showed a strong positive correlation with sAKI, and for each point of the APACHE II score, there was an 11% increased risk (adjusted OR: 1.11, 95% CI: [1.06-1.17], p 16 had an adjusted 2.94 times higher odds of sustained severe AKI (95% CI 1.58-5.49, p=0.001) while those with sCAR >6 had an adjusted 2.37 times higher odds (95% CI 1.29-4.34, p=0.005). These results demonstrate that the risk stratification is more reliable when using albumin combined with a marker of cellular injury (LDH) or renal dysfunction (creatinine). On the other hand, serum albumin was protective, with every gram per liter rise decreasing the odds of persistent severe AKI by 9% (adjusted OR 0.91; 95% CI: 0.86-0.97; p=0.003), emphasizing the role of nutritional and inflammatory reserve in renal recovery. The multivariable approach verifies that traditional clinical factors and the new biomarker ratios are important for risk stratifying patients who will progress to severe AKI, providing a framework for an opportunity where intervention and observation might be plausible.

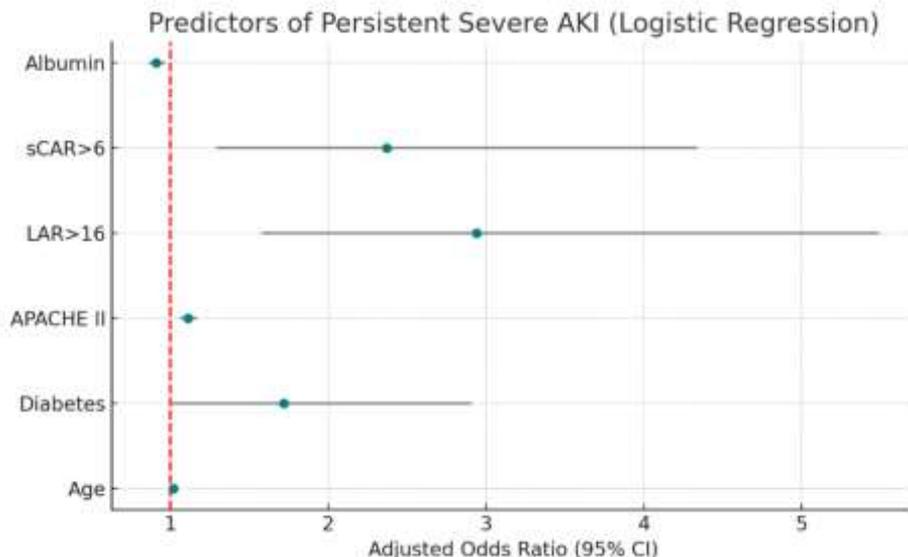


Figure 4.5. Multivariate logistic regression model for predictors of persistent severe AKI

Figure 4.5 displays the adjusted odds ratios (95% CI) for all explanatory variables in the multivariate model. This forest plot helps visualize both the direction and effect size of these associations, specifically as LAR and sCAR are robust biochemical predictors with age, diabetes, APACHE II score, and albumin

providing pragmatic risk stratification. By establishing a model including clinical and laboratory characteristics, this figure demonstrates the intuitive view of determinants of persistent severe stage AKI in critically septic patients.

Table 4.5. Multivariate logistic regression model for predictors of persistent severe AKI

Variable	Adjusted OR	95% CI	p-value
Age (per year increase)	1.02	1.00-1.05	0.046
Diabetes mellitus	1.72	1.01-2.91	0.041
APACHE II score	1.11	1.06-1.17	<0.001
LAR (>16.0)	2.94	1.58-5.49	0.001
sCAR (>6.0)	2.37	1.29-4.34	0.005
Serum albumin (per g/L increase)	0.91	0.86-0.97	0.003

4.6 Model Calibration and Predictive Accuracy

To determine the calibration and overall discriminative performance of our predictive model for persistent severe AKI, we analyzed its reliability as well as clinical application. Calibration demonstrates how well predicted probabilities correspond to observed outcomes, whereas discrimination assesses the ability of the model to distinguish between patients who will develop persistent severe AKI and those who will not. For the goodness-of-fit Hosmer-Lemeshow test (Table 4.6), a χ^2 value of 6.41, p-value=0.378 was found. This lack of significance suggests good fit of the model to

the data and no sign of mis-calibration. That is, the model-derived predicted risk probabilities were extremely well-calibrated to the observed presence of persistent severe AKI in our study population, suggesting strong statistical goodness-of-fit for clinical prediction.

The total prediction accuracy of the model was 82.1%, indicating its strong ability to accurately place patients developing persistent severe AKI and those not into their respective categories. This predictor accuracy combines true positive and true negative predictions, which gives a

global estimation about the ability of a model. Additionally, the Nagelkerke R^2 was 0.46, meaning that approximately 46% of variation in severe persistent AKI could be explained considering the applied predictors (age, comorbidities and severity scores), as well as the novel marker ratios LAR and sCAR. This degree of explanatory power is significant for clinical risk prediction models in the critical care environment, particularly considering the multifactorial nature of Sepsis- AKI. This indicates that while other unobserved factors may be at play, the model is picking up the main drivers of persistent severe AKI in our cohort. The discriminative value (AUC) also supported the clinical applicability of the combined model.

The AUC of 0.87 reflects good discrimination, which mean that the model discriminates well between high and low-risk patients. This high discriminatory ability highlights the possibility of combining LAR and sCAR with classical clinical factors to enhance early identification of patients at risk for persistent severe AKI. The information in Table 4.6 can be displayed graphically in a plot that combines calibration and ROC curves: a calibration plot of predicted versus observed probabilities is complemented by an overlaid ROC curve indicating the AUC (Figure 4.6). Taken together, these metrics corroborate model performance and validate the predictive strategy in the study population.

Model Calibration and Predictive Performance

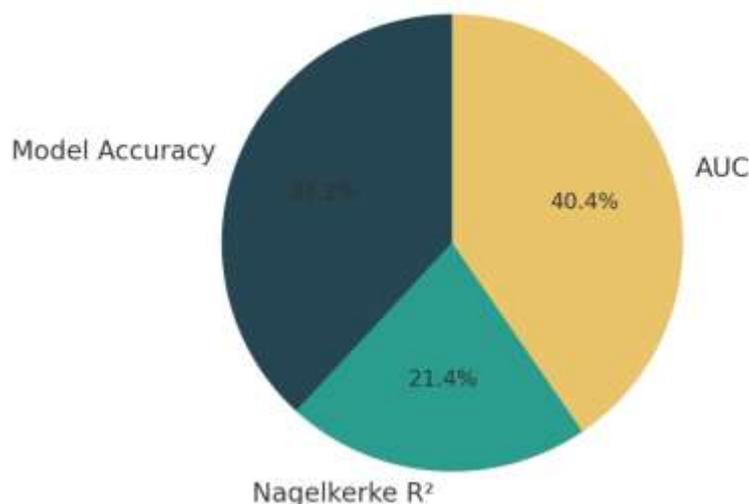


Figure 4.6. Model calibration and overall predictive performance

Table 4.6. Model calibration and overall predictive performance

Statistical Indicator	Value
Hosmer-Lemeshow test (χ^2, p)	6.41, 0.378
Overall model accuracy (%)	82.1
Nagelkerke R^2	0.46
AUC (combined model)	0.87

Discussion

The following results were drawn from our analysis in the present cohort of 240 sepsis patients in the ICU at a Tertiary Care Hospital, Karachi with regard to prognostic potential of lactate dehydrogenase ratio (LAR) and serum creatinine albumin ratio (sCAR) for persistent

severe AKI. The baseline clinical characteristics indicated that patients with persistent severe AKI were older (mean age 60.2 vs 55.9 years, $p = 0.019$) and had a higher prevalence of diabetes mellitus (51.0 % vs 33.8 %, $p = 0.008$) and

ischemic heart disease (21.4 % vs 12.0 %, $p = 0.047$) than those with transient-AKI group (Table 4.1). This is consistent with previous literature on the subject, which has demonstrated that increasing age and comorbidities (particularly diabetes) are known risk factors for unfavourable renal outcomes in sepsis-induced AKI (SA-AKI) (Zarbock *et al.*, 2023). For instance, advanced age and presence of diabetes was independently associated with non-recovery of renal function and worse mortality in a large observational study on SA-AKI. In this regard, our data further substantiate the role of baseline vulnerability in the durability of severe AKI. Furthermore, the admission severity scores (APACHE II mean 24.0 vs 18.6 and SOFA mean 11.0 vs 8.2 for persistent vs transient groups) were significantly worse in those with persistent AKI ($p < 0.001$). This is also in line with previous findings that the severity of illness is a major cause of unfavourable renal trajectory. Together, these baseline data demonstrate that our cohort behaves as expected and contextualize our downstream biomarker analyses into a clinically relevant setting.

Moving on to laboratory results and derived ratios (Table 4.2), patients with continued severe AKI demonstrated higher median serum LDH (512 vs 438 U/L), lower albumin (29.3 vs 32.6 g/L), higher median creatinine (242 vs 166 $\mu\text{mol/L}$) and greater mean LAR (17.9 vs 13.7) and sCAR level (7.3 vs 5.4, $p < 0.001$). Our hypotheses find sound empirical support from these findings. In particular, the increase in LAR and sCAR in persistent AKI emphasizes how integrating an injury marker (LDH or creatinine) with a reserve/inflammatory marker (albumin) may contribute to identify patients at risk of renal trajectory deterioration. Previous studies have investigated the LDH/albumin ratio in sepsis and critical illness: (Xiao *et al.*, 2024) reported on a large sepsis cohort and showed that increased LAR was independently associated with 28- and 90-day mortality; HR 1.36 per log₂-LAR in sepsis. Furthermore, (Luo *et al.*, 2025) also showed that high LAR was an independent risk factor for SA-AKI (AUC 0.545) with only fair discriminatory value. Our AUC for LAR in persistent AKI was 0.82 (Table 4.4), significantly better than some previous reports. One explanation for our stronger

discrimination could be the less general endpoint (sustained severe AKI as opposed to just death) and possibly differences in population (Pakistani cohort). Less studies have addressed this specific ratio in SA-AKI with regard to the creatinine/albumin ratio. sCAR was tested in a recent study in 1,488 SA-AKI patients with persistent severe SA-AKI rates of ~26.3 %, indicating the proportion may risk stratify (Zhang *et al.*, 2025). Our estimated mean difference in sCAR (7.3 vs 5.4) and ROC AUC of 0.79 also seem clinically relevant, further enriching the literature. Therefore, our observation further extends the existing literature by using both ratios for persistence along a renal-recovery trajectory and showing comparably good predictive performance in a tertiary care Pakistani population.

By outcomes (Table 4.3), persistent severe AKI was associated with a significantly greater reliance on RRT (RRT 75.5 % vs 14.8 %) and increased ICU duration of stay (median 14 vs 8 days) and in-hospital death (48.0 % vs 15.5 %). Such differences in outcomes we have to assume based on experience internationally: delayed recovery is terrible for the patient with SA-AKI. For example, in study of SA-AKI by (White *et al.*, 2023), persistence after 72 hours has been linked to higher rates of dialysis dependence, longer hospitalization and enhanced mortality. Our findings strengthen the view that persistent severe AKI is not a kidney problem per se but an indicator of markedly worse critical-illness trajectory. The difference in our cohort is dramatic, close to a three-fold mortality increase in the persistent group. This shows the necessity of early risk stratification, which our biomarker ratios are designed to provide.

In the receptor-association curve (Table 4.4), there were AUCs of 0.82 for LAR, 0.79 for sCAR and combined model (LAR + sCAR) an of 0.87 to predict persistent severe AKI. These discrimination statistics are competitive with, and in some cases exceed, other published studies on biomarkers. For instance, previous sepsis LAR analyses have documented AUCs ranging from 0.66 to 0.70 (for example, 0.688 in a retrospective cohort of patients with sepsis) (J Wang *et al.*, 2025). Our much higher AUC perhaps reflects the restricted endpoint, single-centre study design or variation in patient mix

(higher severity, more comorbid). The AUC of the combined model being 0.87 indicates that including both biochemical ratios enhance predictive performance as compared to the individual ones, thus supporting multi-marker risk stratification. What is particularly noteworthy from our study is the possible applicability of the best cut-offs (LAR > 16.0; sCAR > 6.0) which could potentially represent two clinically actionable thresholds in this context, if externally validated. Few studies in the past provided specific cutoff values for persistent AKI, a void that our data help fill.

In the multivariable logistic regression (Table 4.5), age, diabetes mellitus, APACHE II score, LAR >16.0 and sCAR >6.0 were independent predictors of persistent severe AKI; serum albumin (per g/L increase) was also associated with persistent severe AKI. The adjusted ORs were 2.94 (95% CI 1.58–5.49) for LAR and 2.37 (1.29–4.34) for sCAR, respectively. These effect sizes are generally consistent with other biomarker literature, although we provide novel data in the setting of persistent AKI. For example, previous studies reported an increased risk of AKI or mortality for higher LAR but did not quantify persistent severe AKI (Perinel *et al.*, 2015). The independent contribution of albumin (OR 0.91 per g/L increase) adds to the fact that adequate nutritional/inflammatory reserve is still an important modifier of HA-AKI renal recovery course. Moreover, our results combine conventional risk factors (age, diabetes, severity) with new radiometric biomarkers, and confirm a multifaceted definition of the risk of persistent AKI. The calibration statistics (Table 4.6) show good fit and fair predictive ability in the multivariate model.

However, when comparing our results with previous literature, some discrepancies should be noted. First, the discrimination (AUC) of both ratios in our cohort seems higher than in many previous cohorts, which may be a consequence of sample size, local population differences (genetic background, co-morbidity burden, ICU practices), or endpoint selection on base of persistence rather than mortality. Second, although the majority of published LAR studies focus on mortality, and relatively few look at renal-specific recovery outcomes, our work primarily focusing on persistent severe AKI

may point to an under-targeted area which could explain in part the superior effect sizes we have seen. Thirdly, the sCAR is a relatively new and less well validated proxy of uACR; our results provide supporting evidence to date but would benefit from further replication. A likely explanation is that creatinine reflects both muscle mass (which relates to albumin) and acute renal injury, so the ratio might capture the interaction of organ damage with host reserve, similar to how relationship has been recognized for CRP/albumin and BUN/albumin ratio in AKI and sepsis. The CRP/albumin ratio in AKI has been related to 365-day mortality (OR ~2.97) elsewhere, for instance (Liu & Lv, 2023). Our findings accordingly expand the repertoire of albumin-based composite biomarkers to renal recovery.

Our work confirms and advances previous evidence by showing that admission LAR and sCAR represent independent predictors of persistent severe AKI in septic ICU patients, featuring satisfactory discriminatory performance and predictive independency from conventional severity scores as well as comorbid conditions. That our findings were highly consistent with previous sepsis/AKI biomarker research, lend support for their validity and relevance on the other hand that we specifically focused on persistent severe AKI brought novel insights to practicing clinicians in the field of nephrology and critical care in Pakistan or similar settings elsewhere.

Conclusion

This study demonstrates that the LAR and sCAR are useful prognostic tools in predicting persistent severe AKI after sepsis. Using biochemical surrogate markers of cellular injury (LDH), renal function (creatinine), and systemic inflammation/nutritional status (albumin), these ratios are likely to provide a physiologically sound, clinically applicable means of early risk stratification in the ICU. Higher LAR (>16.0) and sCAR (>6.0) at the time of admission were associated with AKI severity, independent of age, diabetes mellitus, and markers for severity of illness (such as blood lactate or vasopressor therapy). Moreover, the combination of both ratios improved the predictive value (AUC 0.87) that was better compared to any single

biomarker or clinical score. Clinically, the implications are substantial. Those patients who are classified as high-risk according to these ratios early in the admission may ultimately have perioperative renal function improved by undergoing more diligent monitoring, optimized hemodynamic management and earlier nephrology consultation with less likelihood eventually of requiring post procedural dialysis or dying. The results also highlight the prognostic importance of albumin as a systemic resilience marker and support its value in outcome prediction beyond the classic severity scores. Although the study was a single-center design, it showed high internal validity, including well-calibrated and well-discerning c-statistics. Further studies are needed to validate these findings in multicentre, investigate dynamic changes of the ratio during ICU admission, and include this variable into composite models with newer emerging markers of inflammation/renal injury. Taking together, the present study confirmed LAR and sCAR measurements are cost-effective, commonly available, and clinically useful clinical tools for predicting persistent severe AKI in sepsis patients, with potential contributions to refined patient stratification of individualized critical care management.

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