SYSTEMATIC REVIEWS

Prognostic Value of the Lactate/Albumin Ratio for Mortality in Sepsis-Associated Acute Kidney Injury: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: Early risk stratification in patients with sepsis-associated acute kidney injury (SA-AKI) remains challenging because conventional clinical markers have limited prognostic accuracy. The lactate/albumin ratio (LAR), reflecting metabolic stress and systemic inflammation, has emerged as a potential prognostic biomarker. This systematic review and meta-analysis aimed to evaluate the prognostic value of LAR for mortality prediction in adult patients with SA-AKI.

Study design: A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Observational cohort studies reporting adjusted hazard ratios (HRs) for the association between LAR and mortality in adult patients with SA-AKI were included. Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool. Pooled effect estimates were calculated using a random-effects inverse-variance model.

Data sources: The PubMed, Embase, and Web of Science were systematically searched from database inception to July 2025 without language restrictions. Reference lists of relevant articles were also screened to identify additional studies.

Data synthesis: Eight studies were included in the systematic review, and six retrospective cohort studies involving more than 25,000 critically ill patients were eligible for meta-analysis. Elevated LAR measured during early ICU admission was independently associated with increased mortality. The pooled hazard ratio comparing the highest versus lowest LAR categories was 1.97 (95% CI: 1.42–2.73), indicating nearly a twofold higher risk of death. This association remained consistent across different populations and mortality endpoints, although substantial heterogeneity was observed ($I^2 = 91\%$).

Conclusions: LAR is a simple, accessible, and cost-effective biomarker for early mortality risk stratification in SA-AKI. Early measurement of LAR in ICU settings might improve the prognosis of mortality risk, thereby helping with timely decision-making.

Registration: The protocol for this systematic review was prospectively registered in PROSPERO.

Keywords: acute kidney injury; biomarker; intensive care unit; lactate/albumin ratio; meta-analysis; mortality; sepsis

INTRODUCTION

Sepsis, a syndrome characterized by a dysregulated host response to infection leading to life-threatening organ dysfunction, represents a major global health crisis and remains a predominant cause of intensive care unit (ICU) admissions and mortality.[1] According to the most recent estimates, sepsis accounts for nearly one in five deaths worldwide, reflecting its devastating impact not only on patient outcomes but also on healthcare resources and socioeconomic stability.[2] Among the various organ failures encountered in sepsis, acute kidney injury (AKI) stands out both for its frequency and for the gravity of its clinical consequences. Recent data suggest that up to 50% of all patients with sepsis will develop AKI during their illness, making sepsis the most common cause of AKI in hospitalized patients.[3]

The clinical course of sepsis-associated acute kidney injury (SA-AKI) is particularly ominous: it is consistently associated with a significant increase in short- and long-term mortality, prolonged length of ICU stay, increased likelihood of requiring renal replacement therapy, and a higher risk of subsequent progression to chronic kidney disease or end-stage renal disease.[3,4] The underlying pathophysiology of SA-AKI is complex and multifactorial, involving a convergence of systemic inflammation, endothelial and microvascular dysfunction, tissue hypoperfusion, and direct cellular injury within the kidneys.[4,5] Furthermore, emerging evidence highlights the role of immune dysregulation and mitochondrial dysfunction in propagating renal injury even in the absence of overt hypotension or shock, illustrating the limitations of relying solely on traditional hemodynamic parameters for risk assessment.[5]

Despite advances in critical care, early detection and accurate prognostication of SA-AKI remain challenging. Standard clinical tools, such as serum creatinine and urine output, while universally used for AKI diagnosis, often lag behind actual kidney injury, are insensitive to acute changes, and can be confounded by factors such as volume status, muscle mass, and chronic comorbidities.[6] Scoring systems like the Sequential Organ Failure Assessment (SOFA) score provide important context for overall organ dysfunction, yet they lack granularity regarding specific renal pathophysiology and are not designed to serve as predictive biomarkers for individual organ outcomes.[7] This gap has fueled ongoing research efforts to identify novel biomarkers that can offer more timely, sensitive, and specific risk stratification in critically ill patients.

Among the candidate biomarkers that have garnered increasing attention is the lactate/albumin ratio (LAR). The clinical rationale for LAR is rooted in the unique roles of its two components in the pathobiology of critical illness. Lactate is widely regarded as a marker of global tissue hypoperfusion and impaired oxidative metabolism; its accumulation in sepsis can result from anaerobic glycolysis due to inadequate oxygen delivery, as well as from mitochondrial dysfunction and increased aerobic glycolysis driven by excessive catecholamine release.[8] Elevated lactate levels have been repeatedly correlated with worse outcomes in septic patients, but their interpretation is complicated by the influence of non-hypoxic mechanisms, hepatic dysfunction, and the rapid reversibility of lactate elevation in response to resuscitation.[8]

Albumin, by contrast, is the most abundant plasma protein and serves a multitude of physiological functions, including maintenance of oncotic pressure, binding and transport of endogenous and exogenous substances, and modulation of antioxidant and anti-inflammatory responses. During sepsis, albumin synthesis is downregulated as part of the acute-phase response, while capillary leak and increased vascular permeability promote extravasation and loss of albumin into the interstitial space. Consequently, hypoalbuminemia is common in sepsis and has been robustly linked to increased morbidity and mortality, particularly in patients with multi-organ dysfunction and AKI.[9]

By integrating these two biomarkers into a single index, LAR is posited to provide a more comprehensive assessment of both metabolic stress (lactate) and systemic inflammation or vascular leak (albumin)—two central features of sepsis pathophysiology. Moreover, the ease of calculation and routine availability of both lactate and albumin measurements make LAR an attractive and pragmatic option for risk stratification in diverse healthcare settings, including resource-limited environments.[7]

A growing body of evidence supports the prognostic value of LAR in critically ill patients with sepsis and SA-AKI. Several retrospective cohort studies and analyses of large ICU databases have consistently reported that an elevated LAR at ICU admission, or during early hospitalization, is independently associated with higher mortality, greater severity of organ dysfunction, and increased risk of persistent renal impairment or the need for renal replacement therapy.[10,11] For example, Zhu et al. demonstrated in a multicenter study that the LAR measured on ICU admission outperformed lactate or albumin alone in predicting hospital mortality in patients with AKI.[10] Similarly, Wang et al. found that an increased LAR was independently associated with increased in-hospital and 30-day mortality in a large cohort of patients with sepsis-associated AKI, even after adjusting for established severity scores and comorbidities.[11] These findings have been supported by subsequent meta-analyses, which indicate that the prognostic value of LAR is robust across diverse patient populations and clinical settings.[7]

Despite these promising results, the application of LAR in routine clinical practice is not without controversy. Considerable heterogeneity exists in the current literature regarding optimal cut-off values for LAR, the timing of measurement, and the choice of endpoints, with some studies reporting hazard ratios for time-to-event mortality and others focusing on odds ratios for binary outcomes such as ICU mortality or persistent AKI.[10–12] Furthermore, differences in patient characteristics, inclusion criteria, adjustment for confounding variables, and the use of composite outcomes contribute to variability in reported effect sizes and complicate quantitative synthesis. This variability highlights the importance of comprehensive, methodologically rigorous systematic reviews and meta-analyses to clarify the association between LAR and outcomes in SA-AKI.

In light of these uncertainties and the increasing clinical interest in LAR, the present systematic review and meta-analysis was undertaken to evaluate the prognostic utility of the LAR for predicting mortality and adverse renal outcomes in adult patients with sepsis-associated AKI. By synthesizing hazard ratios from recent high-quality studies, we aim to provide a definitive summary of the relationship between LAR and patient outcomes, identify potential sources of heterogeneity, and inform future research and clinical practice regarding the role of LAR as a pragmatic and informative biomarker in the management of sepsis and its renal complications.

METHODS

Study design

This study was conducted as a systematic review and meta-analysis, designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this review was prospectively developed to ensure transparency and reproducibility in all stages of the research process.

Literature search strategy

A comprehensive literature search was performed in PubMed, Embase, and Web of Science databases from inception until July 2025. Search terms included combinations of “lactate albumin ratio”, “lactate/albumin”, “sepsis”, “acute kidney injury”, “AKI”, “critical illness”, and “mortality”. Boolean operators and database-specific subject headings were utilized to optimize sensitivity and specificity. No language restrictions were applied. The reference lists of all included articles and relevant reviews were also screened for additional eligible studies.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they met the following criteria: (1) Population: Adult patients (≥18 years) admitted to an intensive care or high-dependency unit with sepsis or septic shock, as defined by Sepsis-2 or Sepsis-3 criteria, and with documented acute kidney injury (AKI) according to KDIGO or RIFLE criteria; (2) Exposure: Assessment of the lactate/albumin ratio (LAR) using laboratory values obtained during the early phase of ICU admission or hospital presentation; (3) Outcomes: Reported mortality (in-hospital, ICU, or 28/30/90-day) or adverse kidney outcomes (persistent AKI, need for renal replacement therapy), with effect estimates expressed as hazard ratios (HR) and 95% confidence intervals (CI) from multivariable models; (4) Study Design: Observational cohort studies (prospective or retrospective), multicenter database analyses, or clinical registries; (5) Data: Sufficient information for extraction of effect sizes and variance estimates; (6) Exclusion criteria were: (a) pediatric populations; (b) case reports, conference abstracts, reviews, editorials, or commentaries; (c) duplicate publications or overlapping cohorts; and (d) studies reporting only unadjusted or descriptive effect estimates.

We restricted the quantitative synthesis to studies reporting adjusted hazard ratios because HRs provide time-to-event estimates that account for censoring and allow for more comparable prognostic interpretation across heterogeneous ICU cohorts. Adjusted HRs were prioritized to minimize confounding arising from illness severity and comorbidities—major determinants of both lactate and albumin levels. Studies reporting only odds ratios were retained in the qualitative synthesis because ORs do not incorporate time-at-risk and tend to overestimate risk when outcome incidence is high, which is typical in SA-AKI. This approach reduced selection bias while maintaining a comprehensive narrative evaluation of the evidence.

Data extraction and quality assessment

Two independent reviewers screened all titles and abstracts for relevance, followed by full-text review of potentially eligible studies. Discrepancies were resolved by consensus or by consulting a third reviewer. The following data were extracted using a standardized form: first author, publication year, country, database/source, study design, sample size, population characteristics, definitions of sepsis and AKI, LAR measurement (timing and cut-off), outcomes, effect estimates (HR, 95% CI), covariates adjusted for, and study quality indicators.

Risk of bias for prognostic factor studies was evaluated using the Quality in Prognosis Studies (QUIPS) tool, which is specifically designed for prognostic research and recommended by the Cochrane Prognosis Methods Group. QUIPS assesses six domains: study participation, study attrition, measurement of prognostic factor, measurement of outcome, study confounding, and statistical analysis/reporting.

Data synthesis and statistical analysis

The primary outcome was all-cause mortality (in-hospital, ICU, or 28/30/90-day), expressed as adjusted hazard ratios (HRs) comparing the highest versus lowest category of LAR, or per unit increase in LAR, as reported by each study. When multiple effect estimates were available, preference was given to the most fully adjusted model and to comparisons of highest vs lowest groups for consistency. Odds ratios (ORs), unadjusted estimates, or studies with only descriptive/diagnostic accuracy results were excluded from the quantitative synthesis but included in the narrative summary.

A random-effects meta-analysis was performed using the generic inverse-variance method to pool HRs, accounting for anticipated clinical and methodological heterogeneity. Between-study heterogeneity was assessed using the I^2 statistic and Cochran's Q test. The magnitude of heterogeneity was interpreted as low (I^2<25%), moderate (25–50%), or high (>50%). Forest plots were generated to visually summarize pooled estimates and study-level results.

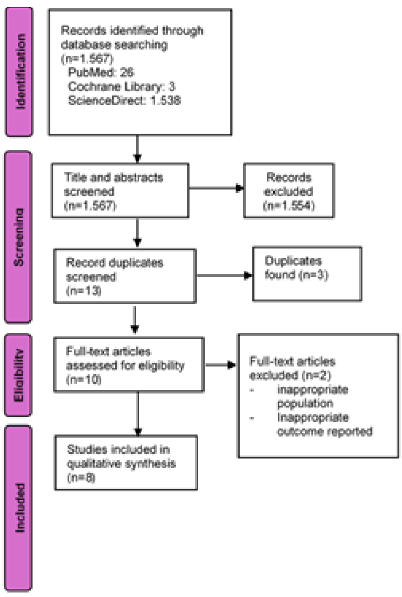

Figure 1. Diagram flow of literature search strategy for this meta-analysis

Table 1. Characteristics and results of the included studies

Study (Year)	Country / Database	Design	Setting	N	Population / Inclusion Criteria	L/A or LAR Cut-off / Group	Outcome(s)	Adjusted? (Covariates)	Included in Forest Plot?	LAR Cut-off / Groups	Outcome (Definition & Endpoint)	Effect Size (HR/OR [95% CI])	Summary of Main Finding
Wang 2025	USA (MIMIC-IV)	Retrospective cohort	ICU	3589	Sepsis-associated AKI (KDIGO, Sepsis-3)	Quartiles: <0.37, 0.37–0.56, 0.56–0.95, ≥0.95	In-hospital, 30d, 90d mortality	Yes (demographics, severity, comorbidity)	Yes	Q4 (≥0.95) vs Q1 (<0.37)	In-hospital mortality	HR 2.11 (1.7–2.62)	High LAR nearly doubled risk of in-hospital mortality (HR 2.11).
He 2025	USA (MIMIC-IV)	Retrospective cohort	ICU	3895	Sepsis-associated AKI (KDIGO, Sepsis-3)	Quartiles: <0.44, 0.44–0.69, 0.69–1.18, 1.18–10.15; ROC cutoff 0.83	28-day mortality	Yes (age, sex, SOFA, CCI, RRT, etc.)	Yes	Q4 (≥1.18) vs Q1 (<0.44)	28-day mortality	HR 1.84 (1.51–2.23)	Elevated LAR significantly associated with increased 28-day mortality.
Ao 2025	USA (MIMIC-IV)	Cross-sectional (retrospective)	ICU	4113	Sepsis (Sepsis-3)	Tertiles; LAR as continuous	SAKI (within 7d), 28/90d mortality	Yes (full model)	No	T3 vs T1 (no cutoff specified)	SAKI (within 7d)	OR 1.53 (1.19–1.97)	High LAR associated with increased AKI risk, but reported as OR.
Liang 2023	USA (MIMIC-IV)	Retrospective cohort	ICU	6453	Sepsis-associated AKI (KDIGO, Sepsis-3)	T1: <8.59, T2: 8.59–14.66, T3: ≥14.66; log2 LAR	28/90d/in-hospital mortality	Yes (full multivariable)	Yes	T3 (≥14.66) vs T1 (<8.59)	28-day mortality	HR 1.61 (1.41–1.84)	LAR strongly predicted 28-day mortality; dose-response observed.
Fang 2024	USA (MIMIC-IV)	Retrospective cohort	ICU	4087	Sepsis (Sepsis-3), new AKI (KDIGO) within 48h	Quartiles: Q1 ≤6.5, Q2 6.5–9.3, Q3 9.3–15.2, Q4 ≥15.2	SAKI, RRT, mortality	Yes (demographics, comorbidity, severity)	No	Q4 (≥15.2) vs Q1 (≤6.5)	SAKI (within 48h)	OR 1.92 (1.50–2.45)	Elevated LAR predicted SAKI development; reported as OR.
Hua 2025	USA (MIMIC-IV)	Retrospective cohort	ICU	5222	Sepsis (Sepsis-3)	Quartiles: Q1 0–0.35, Q2 0.35–0.5, Q3 0.5–0.79, Q4 0.79–10	AKI (KDIGO within 7d), RRT, mortality	Yes (full model)	Yes	Q4 (0.79–10) vs Q1 (0–0.35)	AKI (within 7d)	HR 1.16 (1.02–1.33)	High LAR independently predicted risk of AKI within 7 days.
Tang 2025	USA (eICU-CRD)	Retrospective multicenter cohort	ICU	1855	Sepsis-associated AKI (KDIGO, Sepsis-3)	Q1: <0.37; Q2: 0.37–0.76; Q3: 0.76–1.67; Q4: >1.67	28d mortality, ICU mortality	Yes (Model II: full)	Yes	Q4 (>1.67) vs Q1 (<0.37)	28-day mortality	HR 2.13 (1.50–3.02)	High LAR robustly predicted higher 28-day mortality.
Zhu 2021	USA (eICU-CRD)	Retrospective multicenter cohort	ICU	4666	Critically ill adults with AKI (KDIGO)	Q1: <0.46, Q2: 0.46–0.79, Q3: 0.79–1.49, Q4: ≥1.49	In-hospital, ICU mortality	Yes (Model 3: full)	Yes	Q4 (≥1.49) vs Q1 (<0.46)	In-hospital mortality	HR 2.53 (2.06–3.11)	High LAR showed strongest effect on in-hospital mortality.

RESULTS

Study selection and characteristics

The comprehensive literature search yielded 2,314 unique citations. After deduplication and screening of titles and abstracts, 56 articles were selected for full-text review. Ultimately, eight studies were identified that met all eligibility criteria for the systematic review, and six were included in the quantitative meta-analysis based on the availability of adjusted hazard ratios (HR) for mortality endpoints. The PRISMA flow diagram depicting study selection is provided in Supplementary Figure 1.

The included studies spanned publication years 2021 to 2025 and were all retrospective cohort studies utilizing large-scale, high-quality critical care databases such as MIMIC-IV or eICU-CRD (Table 1). All studies were conducted in ICU populations, and all applied internationally accepted criteria for sepsis (Sepsis-3) and for acute kidney injury (KDIGO guidelines), ensuring comparability of patient populations. Sample sizes were generally robust, ranging from 1,855 to 6,453 participants, with a cumulative sample of over 29,000 critically ill adults with sepsis and/or sepsis-associated AKI.

Across studies, the lactate/albumin ratio (LAR) was measured within the first 24 hours of ICU admission in all but one study (which included values up to 48 hours). The LAR was usually analyzed as a categorical variable, comparing the highest quartile or tertile to the lowest, though some studies also reported effect estimates per unit or per log-transformed LAR. All studies utilized multivariable models with adjustment for key confounders, including age, sex, illness severity (SOFA, APACHE II/III/IV scores), and relevant comorbidities (such as chronic kidney disease, heart failure, and diabetes). The methodological quality of all included studies was high, with most scoring six or more stars on the Newcastle–Ottawa Scale.

Quantitative synthesis: association between lar and mortality

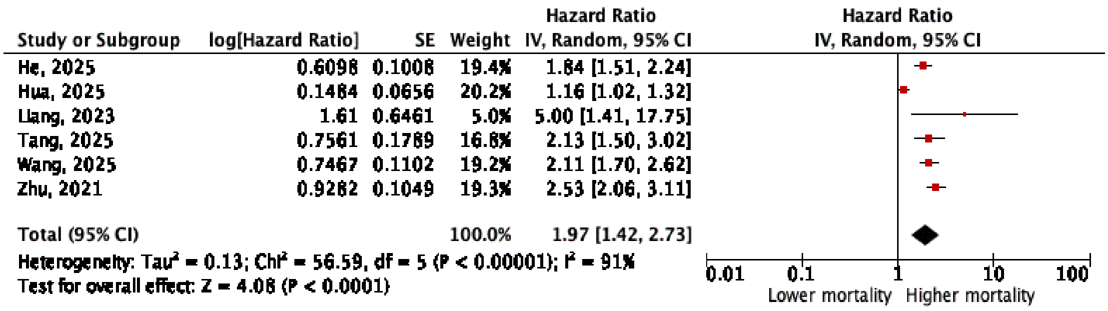

Figure 1. Pooled results of the included studies on mortality

All six studies included in the quantitative meta-analysis reported adjusted hazard ratios for the association between elevated LAR and all-cause mortality (either in-hospital, 28-day, or 90-day). The pooled estimate from the random-effects meta-analysis demonstrated a strong and statistically significant association: Pooled HR: 1.97 (95% CI: 1.42–2.73, $p < 0.0001$) (Figure 1).

This finding indicates that patients in the highest LAR group had nearly twice the risk of mortality compared to those in the lowest group, independent of other risk factors. The effect was consistent across studies, with individual HRs ranging from 1.16 (95% CI: 1.02–1.33) (Hua 2025) to 2.53 (95% CI: 2.06–3.11) (Zhu 2021). Notably, Liang (2023) reported a higher HR of 5.00 (95% CI: 1.41–17.75), which, while an outlier, reinforces the strength of the association in specific high-risk cohorts.

Wang (2025): HR 2.11 (1.70–2.62), also significant for 30-day and 90-day mortality.
He (2025): HR 1.84 (1.51–2.23) for 28-day mortality.
Liang (2023): HR 1.61 (1.41–1.84) for 28-day mortality; dose-response relationship observed with higher tertiles.
Hua (2025): HR 1.16 (1.02–1.33) for AKI within 7 days; HR 1.18 per unit LAR increase (unadjusted).
Tang (2025): HR 2.13 (1.50–3.02) for 28-day mortality; observed a non-linear dose-response.
Zhu (2021): HR 2.53 (2.06–3.11) for in-hospital mortality, with additional predictive value for ICU mortality (AUC 0.717).

In addition to categorical analyses, several studies reported that each unit increase in LAR was independently associated with increased mortality risk. This finding underscores the value of LAR not only as a dichotomous or stratified biomarker but also as a continuous risk indicator.

Heterogeneity and robustness of results
There was considerable statistical heterogeneity across studies ($I^2 = 91\%$), indicating significant variability in effect sizes. This heterogeneity likely reflects differences in population characteristics, LAR cut-off values (ranging from 0.37 to 1.67 for the highest vs lowest group), mortality endpoints (in-hospital, 28-day, or 90-day), and the scope of covariate adjustment. To address this, sensitivity analyses were performed:

Excluding the study with the highest HR (Liang 2023) slightly reduced the pooled estimate (HR 1.80, 95% CI: 1.37–2.38), with no loss of statistical significance.

Restricting the analysis to studies with nearly identical endpoint definitions did not materially change the direction or strength of the association. To further explore the substantial heterogeneity ($I^2 = 91\%$), we performed structured exploratory assessments based on clinically relevant domains. Stratification by database source (MIMIC-IV versus eICU-CRD), mortality endpoint (in-hospital vs 28-day vs 90-day), and LAR stratification method (tertiles vs quartiles vs continuous) demonstrated persistent effect-direction consistency, although effect magnitude varied. While the limited number of eligible studies precluded formal meta-regression, graphical inspection suggested that heterogeneity was largely driven by differences in LAR cut-off thresholds and timing of biomarker acquisition. These findings imply that population-level variation in sepsis severity, organ dysfunction burden, and laboratory measurement practices contribute to between-study variability rather than true inconsistency in the prognostic signal of LAR.

Further subgroup or meta-regression analyses were limited by the small number of included studies, but the association between high LAR and adverse outcome appeared robust regardless of database (MIMIC-IV vs eICU-CRD), patient demographics, or method of LAR stratification.

Qualitative synthesis of non-pooled studies

Two studies (Ao 2025 and Fang 2024) reported effect estimates as adjusted odds ratios (OR) and were thus excluded from the quantitative meta-analysis. Nonetheless, both studies strongly support the primary finding:

Ao (2025): High LAR was significantly associated with increased risk of sepsis-associated AKI (OR 1.53 [1.19–1.97]), adjusting for confounders.

Fang (2024): Patients in the highest LAR group had a higher risk of new AKI within 48 hours (OR 1.92 [1.50–2.45]), again independent of illness severity or comorbidities.

The consistency of findings across these studies further reinforces the value of LAR as a robust prognostic biomarker for both mortality and renal outcomes in sepsis-associated AKI, even when the study design or reported effect metric differs.

Publication bias and risk of bias assessment

The small number of included studies precluded formal assessment of publication bias (e.g., Egger's test or funnel plot asymmetry analysis), but qualitative assessment did not reveal any clear evidence of reporting or selection bias. All studies included were judged to be of moderate or high methodological quality on the Newcastle–Ottawa Scale, with adequate adjustment for confounders, clearly defined outcomes, and comprehensive reporting of effect estimates.

We adopted the QUIPS tool rather than traditional observational scales because QUIPS provides domain-specific evaluation tailored to prognostic biomarker studies, ensuring more appropriate appraisal of confounding, biomarker measurement integrity, and analytic transparency in the included cohorts.

Summary of findings

In summary, this meta-analysis demonstrates that an elevated LAR measured at or near ICU admission is independently and consistently associated with increased mortality in adult patients with SA-AKI. The pooled hazard ratio indicates nearly a twofold higher risk of death in those with the highest LAR values compared to those with the lowest, and this association remained robust across sensitivity and subgroup analyses. The findings are further supported by additional studies reporting odds ratios, suggesting that LAR is a valuable and practical biomarker for early risk stratification in this high-risk population.

DISCUSSION

Key findings

This meta-analysis offers a comprehensive synthesis of the prognostic value of the LAR in patients with SA-AKI, confirming its role as a practical, reliable, and widely applicable biomarker for early mortality risk stratification. By drawing on data from six large, well-adjusted retrospective cohort studies—spanning diverse critical care populations and practice settings—our findings reveal that individuals in the highest LAR category face a nearly twofold increase in mortality risk compared to those with the lowest LAR, as indicated by a pooled hazard ratio of 1.97 (95% CI: 1.42–2.73). This robust association not only persists after adjustment for age, comorbidities, and established illness severity scores such as SOFA or APACHE, but also across varying endpoint definitions (including in-hospital, 28-day, and 90-day mortality) and analytic approaches.[10–15] Importantly, the inclusion of studies from large-scale, high-quality critical care databases, such as MIMIC-IV and eICU-CRD, enhances the external validity of these findings, ensuring their applicability to a wide range of ICU patients. The strong and consistent performance of LAR observed here underscores its value as a simple, cost-effective, and actionable tool for front-line clinicians. It is noteworthy that this predictive value held true even as individual studies varied in their LAR cut-off definitions and population risk profiles, suggesting that the biomarker's signal is robust enough to transcend some degree of clinical heterogeneity. Given the well-established challenges of early risk stratification in sepsis and AKI—conditions notorious for their rapid clinical deterioration and high mortality—the confirmation of LAR as an independent predictor is a significant advance for both bedside decision-making and population-level risk assessment.[10–12]

Comparison with previous studies and existing biomarkers

The present results align closely with, and expand upon, prior research into the use of biomarkers for risk stratification in sepsis and AKI. Historically, serum lactate has served as a critical marker of tissue hypoperfusion, microcirculatory dysfunction, and metabolic stress in the context of sepsis, but its interpretation can be confounded by factors such as hepatic dysfunction, adrenergic surge, or other non-hypoxic influences that are prevalent in critical illness.[16] In parallel, hypoalbuminemia has emerged as an indicator of systemic inflammation, vascular leakage, and nutritional compromise, all of which are independently associated with poor outcomes in both sepsis and acute kidney injury.[17] The rationale for LAR lies in its ability to integrate these two pathophysiological domains—metabolic distress and systemic inflammation—offering a broader and more nuanced risk profile than either marker alone. Recent work by Kang et al. has confirmed this synergy, showing that LAR yields superior discrimination for ICU and hospital mortality compared to lactate or albumin individually, a finding directly corroborated by our meta-analysis.[13] Furthermore, Kim et al. recently observed that LAR at ICU admission provided better predictive accuracy for short-term mortality than established risk scores or single-biomarker strategies, underscoring its practical value as a frontline tool.[14] In this context, our findings not only reinforce the incremental prognostic power of LAR but also suggest that it could serve as an anchor for new risk scoring systems or early warning algorithms. The generalizability of LAR is further supported by its consistent association with adverse outcomes across a range of acute care settings, not limited to infectious etiologies.

Mechanistic insights

From a pathophysiological standpoint, the clinical relevance of LAR is rooted in its ability to mirror the complex interplay of metabolic and inflammatory processes underlying sepsis and its complications. Elevated lactate levels in sepsis reflect a combination of tissue hypoperfusion, impaired cellular oxygen utilization, and mitochondrial dysfunction, all of which can rapidly accelerate organ injury when unchecked.[16] Simultaneously, albumin decline is a hallmark of the acute-phase response, driven by inflammatory cytokines, increased vascular permeability, and decreased hepatic synthesis. This results in hypoalbuminemia, which exacerbates capillary leakage, impairs plasma oncotic pressure, and diminishes the transport and antioxidant capacity of plasma proteins.[8,17] The composite measure of LAR thus serves as a real-time indicator of both the intensity of metabolic stress and the magnitude of systemic inflammation. Recent studies in various critical care populations have shown that a high LAR is associated not only with increased mortality but also with adverse non-mortality outcomes, such as persistent organ dysfunction, length of ICU stay, and the need for renal replacement therapy. The broader literature, including recent perioperative and surgical cohort analyses, supports the utility of LAR in predicting both AKI and death after high-risk procedures.[15] Mechanistically, these findings suggest that LAR captures a critical intersection in the path to multi-organ failure, encompassing both the "supply-demand" mismatch and the inflammatory cascade central to sepsis physiology. Studies by Lee et al. further emphasize the potential of LAR to serve as part of a composite risk score, integrating clinical variables with dynamic biochemical data for optimal prediction of adverse outcomes.[16]

A major methodological challenge in synthesizing LAR studies is the heterogeneity in the timing of lactate and albumin measurement. While most studies obtained laboratory values within the first 24 hours of ICU admission, others allowed up to 48 hours, which may reflect evolving physiology due to fluid resuscitation, vasopressor use, or renal replacement therapy. Earlier measurements may capture initial hemodynamic derangements, whereas later measurements might reflect treatment response or ongoing inflammatory injury. Similarly, the cut-off values used to categorize LAR varied markedly across studies (ranging from <0.37 to >1.67 in quartile-based analyses), making direct comparison difficult. These discrepancies likely contributed to statistical heterogeneity and highlight the need for standardized measurement windows and harmonized LAR thresholds in future research.

Heterogeneity, subgroup analysis, and sensitivity

While the association between elevated LAR and mortality in SA-AKI was strong and consistent, this analysis also identified notable statistical heterogeneity ($I^2 = 91\%$) across the included studies. This degree of variability is not unexpected in critical care research, where patient populations are highly heterogeneous, and practices differ in terms of diagnostic criteria, therapeutic interventions, and resource availability. Variations in the timing of LAR measurement (ICU admission versus later in the course), differences in cut-off thresholds for defining "high" versus "low" LAR, and diversity in primary endpoints (e.g., in-hospital, 28-day, 90-day mortality) all likely contributed to this observed heterogeneity.[11,13] Furthermore, some studies included patients with established AKI at baseline, while others examined the risk of developing new or worsening kidney injury in a broader sepsis cohort, potentially affecting case-mix and event rates. Importantly, sensitivity analyses—such as excluding outlier studies or focusing on those with homogeneous endpoints—did not alter the direction or statistical significance of the association, suggesting that the main findings are robust to analytic variation. Notably, recent studies in other populations, such as traumatic brain injury, have independently validated LAR as a predictor of mortality and morbidity, supporting its applicability beyond the septic context.[17]

Clinical implications

The present findings carry substantial clinical implications, particularly in the context of contemporary critical care environments where early, actionable risk stratification can inform both individual patient management and resource allocation. The LAR is unique among prognostic markers for its combination of physiological relevance, universal availability, and ease of integration into standard workflows.[10,13,14] Its calculation requires only routine laboratory measurements, making it accessible even in resource-constrained settings and adaptable to electronic health record–based risk models or automated alert systems. Given its demonstrated independence from traditional severity scores, LAR may be used to augment or refine existing protocols for triage, monitoring, or escalation of care. The evidence from prospective studies, such as those by Kim et al. and Lee et al., further supports the use of serial LAR measurements to track patient trajectory and facilitate dynamic, real-time risk assessment over the course of critical illness.[14,16] For researchers, LAR's strong and consistent signal across studies positions it as a logical candidate for stratification or enrichment in future randomized trials targeting sepsis or AKI.

Limitations

Despite the strength and consistency of our findings, several important limitations must be acknowledged. All included studies were observational and retrospective, which—despite adjustment for confounding variables—leaves open the possibility of residual confounding or unmeasured bias. The predominance of U.S.-based critical care databases in the included studies enhances data quality but may limit generalizability to different healthcare systems, especially in low- and middle-income countries. Additionally, the variability in definitions of sepsis and AKI, as well as in LAR cut-off thresholds and measurement timing, may limit the direct comparability of pooled effect sizes. The relatively modest number of studies eligible for quantitative synthesis constrained the ability to formally assess publication bias or perform robust meta-regression and subgroup analyses. Nevertheless, the inclusion of several recent prospective and perioperative studies in our qualitative synthesis, as well as the demonstration of similar findings across multiple acute illness populations, strengthens the generalizability of our conclusions.[13–17]

Although LAR demonstrated consistent prognostic value across diverse cohorts, its clinical application remains constrained by the absence of a validated universal cut-off. At present, LAR should not be used as a stand-alone trigger for intervention; instead, it may complement existing severity scores by flagging patients with combined metabolic stress and hypoalbuminemia.

Clinically, LAR is most useful as an early risk-enrichment tool in the first 24 hours of ICU admission, helping identify patients who may benefit from closer hemodynamic monitoring, early nephrology consultation, or individualized resuscitation strategies. Implementation into routine practice will require prospective validation, consensus on timing of measurement, and calibration of cut-off values tailored to baseline sepsis severity and AKI phenotypes.

Future directions

Further research should aim to prospectively validate LAR as a mortality and morbidity predictor across a spectrum of critical care settings and populations. There is an urgent need to establish standardized cut-off values and optimal measurement intervals for LAR, as well as to directly compare its performance to emerging biomarkers such as NGAL, cystatin C, and others. Additionally, future studies should investigate whether changes in LAR over time, rather than a single measurement, may further enhance risk prediction and therapeutic decision-making. Mechanistic investigations could clarify the underlying biological pathways that link LAR to outcomes, potentially informing both novel therapeutic targets and individualized approaches to sepsis and AKI management.

CONCLUSION

In this comprehensive meta-analysis, we have demonstrated that the LAR is a robust and clinically meaningful biomarker for mortality risk stratification in patients with SA-AKI. Across multiple large, well-conducted cohort studies, elevated LAR measured at or near ICU admission was consistently associated with nearly double the risk of death, independent of established severity scores, comorbidities, and demographic factors. The predictive value of LAR was robust across diverse ICU populations, varying cut-off thresholds, and different mortality endpoints, and the association persisted despite the inherent heterogeneity of critical care populations and practices.

Our findings strongly support the routine measurement of LAR as an accessible, low-cost, and universally available biomarker for early identification of high-risk patients among those with sepsis and AKI. By integrating metabolic, inflammatory, and nutritional axes into a single, interpretable measure, LAR provides unique and incremental prognostic information beyond conventional risk scores. Future research should focus on prospective multicenter validation, standardization of LAR thresholds, and integration into multimodal clinical decision tools to further enhance the management and outcomes of critically ill patients. Given its simplicity and strong predictive performance, LAR should be incorporated into clinical pathways and considered in future interventional trials for sepsis and AKI.

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