

## Lactate-to-Albumin Ratio as a Prognostic Biomarker in Sepsis: Current Evidence and Future Direction

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### ABSTRACT

**Background:** Sepsis remains a leading cause of morbidity and mortality in critically ill patients, despite advances in antimicrobial therapy, supportive care, and early recognition protocols. Traditional biomarkers such as lactate have been central to risk stratification, but their specificity and predictive power remain limited. Elevated lactate levels are often linked to tissue hypoperfusion and anaerobic metabolism, yet hyperlactatemia may also occur in non-hypoxic states, making lactate an imperfect prognostic tool. Similarly, serum albumin has been recognized as a marker of systemic inflammation and nutritional status, with hypoalbuminemia strongly associated with poor outcomes in sepsis. The lactate-to-albumin ratio (LAR) has emerged as a promising composite biomarker that integrates both metabolic stress and systemic inflammatory response, potentially offering superior predictive accuracy compared to lactate or albumin alone. Several studies across intensive care settings have demonstrated that LAR is independently associated with increased short- and long-term mortality in septic patients. LAR not only correlates with severity indices such as SOFA and APACHE II scores but also provides incremental prognostic information beyond conventional biomarkers. Importantly, LAR may be less influenced by confounding conditions that alter lactate or albumin individually, thereby improving its clinical applicability. Its utility has been explored in diverse patient populations, including those with septic shock, community-acquired infections, and post-surgical sepsis. However, despite encouraging evidence, key questions remain unanswered. Optimal cut-off values for LAR differ between studies, influenced by patient demographics, comorbidities, and healthcare settings. Moreover, the biological mechanisms linking albumin depletion and lactate elevation remain incompletely understood, raising questions about causality versus association. Future research must focus on validating standardized thresholds, integrating LAR into existing sepsis bundles, and exploring its potential as a guide for therapeutic interventions, such as resuscitation and albumin supplementation strategies. In conclusion, LAR represents a simple, cost-effective, and widely available biomarker with significant potential to refine prognostication in sepsis. As critical care shifts toward precision medicine, incorporating composite indices like LAR into sepsis management protocols may enhance risk stratification, improve decision-making, and ultimately contribute to better patient outcomes.

**Keywords:** *Lactate-to-Albumin Ratio, Prognostic Biomarker, Sepsis*

## INTRODUCTION

Sepsis is defined as a dysregulated host response to infection leading to life-threatening organ dysfunction, and it continues to be one of the most challenging conditions encountered in critical care medicine. Despite advances in antimicrobial therapy, hemodynamic support, and early recognition strategies, sepsis remains associated with high morbidity and mortality worldwide, with estimates suggesting over 48.9 million cases and 11 million deaths annually [1]. Prognostication in sepsis is critical, as early risk stratification allows clinicians to identify high-risk patients, tailor interventions, and allocate intensive care resources more effectively. Current severity scoring systems such as Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) provide prognostic information but are often complex, time-consuming, and not readily available in emergency settings [2]. This has spurred interest in simple, reliable, and accessible biomarkers that could improve prognostication.

Among widely studied biomarkers, lactate has been regarded as a cornerstone in sepsis evaluation. Elevated lactate levels reflect tissue hypoperfusion and impaired oxygen utilization, and persistently high lactate is strongly associated with mortality [3]. Nevertheless, lactate is not a perfect biomarker: it may be elevated in non-hypoxic states, such as hepatic dysfunction,  $\beta$ -adrenergic stimulation, or mitochondrial impairment [4]. Similarly, serum albumin is a negative acute-phase reactant that declines during systemic inflammation, and hypoalbuminemia has been linked to poor prognosis in sepsis through mechanisms including impaired oncotic pressure, reduced antioxidant capacity, and dysregulated microcirculation [5]. While each biomarker individually provides valuable prognostic information, their limitations have led to the exploration of composite indices.

The lactate-to-albumin ratio (LAR) has emerged as a promising integrative marker combining two biologically and clinically relevant parameters. By simultaneously reflecting metabolic derangement and systemic inflammatory response, LAR may provide a more comprehensive representation of disease severity than either lactate or albumin alone. Several studies have reported that elevated LAR values are independently associated with increased short- and long-term mortality in sepsis and septic shock patients [6,7]. Importantly, LAR appears to correlate well with established severity scores, suggesting that it could complement or even partially substitute them in certain clinical settings.

Despite these encouraging findings, gaps remain in our understanding of LAR as a prognostic biomarker. The lack of consensus on optimal cut-off values, variability across populations, and limited exploration of its role in guiding therapy highlight the need for further investigation. Moreover, mechanistic insights into how albumin depletion modulates lactate dynamics in sepsis remain incomplete, warranting translational research. Therefore, this review aims to provide a comprehensive synthesis of current evidence regarding the role of LAR in sepsis prognostication, highlight its potential clinical applications, and discuss future research directions.

### Lactate metabolism in sepsis

Lactate is a byproduct of anaerobic glycolysis, but its elevation in sepsis reflects more than just tissue hypoxia. During sepsis, impaired oxygen delivery due to hypoperfusion, microcirculatory dysfunction, and mitochondrial impairment all contribute to increased lactate production [8]. Moreover, accelerated

glycolysis triggered by  $\beta$ -adrenergic stimulation also results in lactate accumulation, even in the presence of adequate oxygenation [9]. This “stress hyperlactatemia” complicates the interpretation of lactate as a biomarker, since elevated values may not exclusively signify tissue hypoxia. Importantly, the persistence of hyperlactatemia rather than a single elevated value is more closely linked to poor prognosis, as it indicates ongoing metabolic imbalance and insufficient resuscitation [10].

### **Albumin alterations in systemic inflammation**

Albumin, the most abundant plasma protein, plays key roles in maintaining colloid osmotic pressure, binding endogenous and exogenous compounds, and exerting antioxidant effects [11]. In sepsis, albumin levels decline due to multiple mechanisms: reduced hepatic synthesis, increased vascular permeability, and heightened catabolism [12]. Hypoalbuminemia contributes to worsened outcomes by promoting edema, impairing drug binding, and reducing microcirculatory stability [13]. Moreover, albumin depletion reduces antioxidant defenses, thereby amplifying oxidative stress and inflammation. As a result, hypoalbuminemia is consistently associated with increased morbidity and mortality in septic patients, independent of nutritional status [14].

### **Integrative role of lactate and albumin in sepsis prognosis**

While lactate reflects metabolic stress and tissue oxygen imbalance, albumin represents systemic inflammation and nutritional reserve. The integration of these two biomarkers into the lactate-to-albumin ratio (LAR) provides a more comprehensive reflection of the host’s physiological state in sepsis [15]. High lactate combined with low albumin amplifies the prognostic signal, identifying patients with both metabolic and inflammatory dysregulation. In this context, LAR has been proposed as a more stable and reliable biomarker compared to lactate alone, as it reduces the confounding effects of conditions that independently alter lactate or albumin [16]. This pathophysiological synergy underpins the growing clinical interest in LAR as a prognostic tool.

### **Early clinical investigations**

Initial investigations into the prognostic role of the lactate-to-albumin ratio (LAR) emerged from retrospective cohort studies in critically ill patients with sepsis and septic shock. Shin et al. demonstrated in a multicenter study that LAR at admission had a stronger predictive value for 28-day mortality compared to lactate alone, particularly in patients with hypoalbuminemia [17]. Similarly, Kim and colleagues confirmed that LAR was independently associated with hospital mortality and had superior prognostic accuracy over lactate or albumin when analyzed separately [18]. These early findings laid the groundwork for considering LAR as a composite marker capable of enhancing risk stratification in sepsis.

### **Validation across diverse populations**

Subsequent studies extended these findings to different populations and clinical scenarios. For example, in elderly patients admitted with sepsis, LAR showed consistent association with in-hospital and long-term mortality, suggesting that it could be especially valuable in populations with inherently higher risk [19]. In surgical intensive care cohorts, elevated LAR predicted higher mortality following abdominal sepsis, underscoring its generalizability across medical and surgical cases [20]. Notably, the predictive value of LAR was also observed in patients with sepsis secondary to community-acquired infections, where conventional scoring systems are often difficult to apply in resource-limited emergency settings [21].

### **Comparison with established severity scores**

Another important stream of evidence comes from studies comparing LAR to established scoring systems. Wang et al. found that LAR correlated strongly with both SOFA and APACHE II scores, yet was simpler and faster to obtain, making it practical in urgent care scenarios [22]. In some analyses, LAR demonstrated comparable predictive performance to these complex scoring systems, raising the possibility of using it as a quick screening biomarker while awaiting more comprehensive assessments [23]. Furthermore, integrating LAR into existing models improved prognostic discrimination, suggesting that LAR may serve as a valuable adjunct rather than a replacement.

### **Meta-analyses and pooled evidence**

The robustness of LAR as a prognostic biomarker has been supported by systematic reviews and meta-analyses. Li et al. performed a pooled analysis of multiple cohort studies and concluded that higher LAR values were significantly associated with increased mortality across various subgroups, including patients with septic shock and different infection sources [24]. Importantly, the association remained consistent across sensitivity analyses, highlighting the reliability of LAR in diverse clinical contexts. These pooled data strengthen the argument for considering LAR in sepsis prognostication guidelines, although heterogeneity in cut-off thresholds remains a major limitation.

### **LAR versus lactate alone**

Lactate has long been a cornerstone biomarker in sepsis evaluation due to its ability to reflect tissue hypoperfusion and metabolic stress. However, its specificity is limited, as elevations can result from non-hypoxic mechanisms such as  $\beta$ -adrenergic stimulation, hepatic dysfunction, or mitochondrial impairment [25]. Several studies have shown that LAR provides superior prognostic accuracy compared to lactate alone, as the inclusion of albumin adjusts for systemic inflammation and nutritional reserve [26]. For instance, in patients with septic shock, LAR demonstrated a higher area under the receiver operating characteristic curve (AUROC) for mortality prediction than lactate alone, particularly in those with borderline lactate elevations [27].

### **LAR versus albumin**

Although hypoalbuminemia is consistently associated with worse outcomes in sepsis, albumin alone lacks dynamic sensitivity as its levels change gradually and are influenced by chronic comorbidities such as liver disease or malnutrition [28]. In contrast, LAR accounts for the acute stress-related increase in lactate, thereby improving real-time prognostic value. Comparative studies have confirmed that while hypoalbuminemia is an independent risk factor for mortality, the discriminative ability of albumin alone is weaker than that of LAR [29]. Thus, LAR synergizes the long-term prognostic implications of hypoalbuminemia with the acute predictive capacity of lactate.

### **LAR compared to lactate clearance**

Lactate clearance, defined as the percentage reduction in lactate levels over time, is widely used as a dynamic marker of resuscitation effectiveness and has been incorporated into sepsis management guidelines [30]. However, its calculation requires serial lactate measurements, which may not always be feasible in resource-limited settings. LAR, on the other hand, requires only a single measurement of lactate and albumin, making it more practical at admission [31]. Interestingly, some studies have suggested that LAR at admission has prognostic value comparable to lactate clearance, particularly for early mortality prediction [32]. This makes LAR a potentially attractive alternative when repeated lactate testing is not possible.

### **LAR versus inflammatory biomarkers (CRP and procalcitonin)**

C-reactive protein (CRP) and procalcitonin (PCT) are commonly used inflammatory biomarkers in sepsis. CRP rises in response to cytokine release, while PCT correlates more specifically with bacterial infections [33]. Although both have utility in infection diagnosis and antibiotic stewardship, their predictive value for sepsis mortality is limited compared to LAR [34]. Head-to-head comparisons revealed that LAR showed superior prognostic accuracy for both short-term and long-term mortality, while CRP and PCT were more useful for infection identification rather than outcome prediction [35]. This highlights LAR's unique advantage as a combined metabolic-inflammatory biomarker rather than a purely inflammatory one.

### **Variability in reported thresholds**

One of the most debated aspects of LAR is the absence of a universally accepted cut-off value for predicting sepsis outcomes. Reported thresholds vary widely across studies, ranging from as low as 0.1 to values above 1.8, depending on methodology, patient population, and the units used to measure albumin. For example, Bou Chebl et al. reported an optimal threshold of 0.115 when albumin was expressed in g/L, whereas other cohorts using g/dL found clinically meaningful cut-offs closer to 1.0 [36]. This inconsistency complicates clinical application, as differences in reporting units may lead to misinterpretation of results. Thus, standardization in measurement and reporting is urgently required. [36]

### **Population-specific differences**

Beyond technical issues, population characteristics also influence optimal LAR thresholds. In elderly patients with sepsis, cut-offs as low as 0.9 have been shown to predict 28-day mortality with high sensitivity [37]. In contrast, younger and post-surgical populations demonstrated higher discriminatory values, closer to 1.2–1.4 [38]. Ethnic and regional variations may also play a role, reflecting differences in baseline albumin levels, comorbidity burden, and nutritional status. These findings emphasize the need for individualized threshold determination rather than a “one-size-fits-all” approach, particularly when applying LAR across diverse clinical settings. [37,38]

### **Outcome-specific considerations**

The choice of outcome measure—whether in-hospital, 28-day, or long-term mortality—further affects LAR cut-off selection. Studies focusing on early outcomes, such as ICU or 28-day mortality, often identify lower thresholds around 0.9–1.2, whereas those assessing long-term survival suggest higher thresholds, sometimes exceeding 1.5 [39]. This may be explained by the dynamic interaction between acute metabolic stress and chronic inflammation. Patients with persistently high LAR beyond the acute phase often exhibit poor long-term prognosis, reflecting unresolved systemic dysfunction. Therefore, clinicians must consider the intended prognostic horizon when applying LAR thresholds. [39]

### **Clinical implications of threshold variability**

Despite the variability, a consistent trend emerges: higher LAR values reliably indicate worse outcomes. Even without absolute consensus on the precise cut-off, LAR stratifies patients into low-, intermediate-, and high-risk categories with reasonable accuracy. In practice, this means that clinicians can use relative increases in LAR rather than a rigid threshold to guide prognostic assessment. Moreover, combining LAR with dynamic monitoring—such as lactate clearance—may further refine its predictive capacity. Future research should focus on deriving population-adjusted, outcome-specific cut-offs, ideally through large, prospective, multicenter studies. [40]

### **LAR in initial risk stratification**

Rapid and accurate risk assessment is essential in sepsis to guide early resuscitation and therapeutic interventions. LAR offers a simple, easily obtainable biomarker that can be calculated immediately upon admission using routine laboratory values. Studies have shown that incorporating LAR into emergency department triage improves the early identification of patients at high risk of deterioration compared to lactate alone [41]. Unlike complex scoring systems that require multiple parameters and may not be readily available, LAR can serve as a pragmatic first-line stratification tool, especially in resource-constrained settings. [41]

### **Guiding resuscitation strategies**

Beyond risk stratification, LAR may have utility in guiding hemodynamic resuscitation. Persistently elevated LAR values, or failure to decline within the first 24 hours, have been associated with inadequate resuscitation and higher mortality [42]. Clinicians may use serial LAR assessments to evaluate treatment response alongside established markers such as lactate clearance and mean arterial pressure. Some investigators suggest that integrating LAR into resuscitation protocols could identify patients who require more aggressive interventions, such as vasopressors, fluids, or albumin supplementation. However, this role remains investigational and requires prospective validation. [42]

### **LAR as a complement to severity scoring systems**

While severity scores such as SOFA and APACHE II remain gold standards for prognostication, they are not always practical for bedside decision-making. Integrating LAR with these systems has been shown to enhance predictive accuracy without adding significant complexity [43]. For example, a hybrid model combining LAR with SOFA yielded higher AUROC values than SOFA alone in predicting 28-day mortality [44]. This suggests that LAR may serve as a complementary biomarker, augmenting the performance of existing prognostic frameworks rather than replacing them. [43,44]

### **Potential for individualized therapy and precision medicine**

One of the most promising applications of LAR lies in its potential role within precision medicine. By identifying patients at particularly high risk of poor outcomes, clinicians could tailor interventions more aggressively, such as early initiation of renal replacement therapy, immunomodulatory treatments, or albumin supplementation [45]. Conversely, patients with low LAR values may be spared unnecessary invasive procedures or prolonged ICU stays. As the field of sepsis management evolves toward individualized therapy, LAR could become a cornerstone biomarker in guiding clinical decision-making. [45]

### **A. Conclusion**

Sepsis remains a major global health burden with persistently high mortality despite advances in critical care. Accurate prognostication is crucial for optimizing resource allocation, guiding therapeutic decisions, and identifying high-risk patients early in the disease course. The lactate-to-albumin ratio (LAR) has emerged as a promising prognostic biomarker that integrates two complementary physiological signals: lactate, reflecting metabolic stress and tissue hypoperfusion, and albumin, indicating systemic inflammation, nutritional reserve, and microcirculatory stability. By combining these factors, LAR provides a more comprehensive measure of illness severity than either biomarker alone.

Evidence from retrospective and prospective studies, as well as meta-analyses, consistently demonstrates that elevated LAR is independently associated with short- and long-term mortality in patients with sepsis and septic shock. Moreover, LAR correlates with established severity scores such

as SOFA and APACHE II while offering the advantage of being simple, inexpensive, and readily available in clinical practice. Its prognostic accuracy often exceeds that of lactate, albumin, or inflammatory markers like CRP and procalcitonin, and in some cases approaches that of traditional severity scoring systems.

Despite its strengths, important limitations remain. There is no universally accepted cut-off value for LAR, with thresholds varying according to population demographics, comorbidities, and outcomes studied. In addition, much of the current evidence comes from retrospective cohorts, and few studies have rigorously examined how LAR-guided interventions may impact patient outcomes. Standardization of reporting units, prospective multicenter trials, and mechanistic research into the biological interplay between lactate metabolism and albumin depletion are urgently needed.

Looking forward, the integration of LAR into sepsis management holds considerable promise. Its role in initial triage, dynamic monitoring, and as a complement to established prognostic scores highlights its clinical versatility. Furthermore, LAR may serve as a stepping stone toward precision medicine in sepsis, helping to identify patients who might benefit from targeted therapies, such as albumin supplementation or advanced hemodynamic support.

In conclusion, LAR is an inexpensive, accessible, and powerful biomarker with strong potential to refine sepsis prognostication. While current evidence supports its use as an adjunct to traditional scoring systems, future large-scale prospective studies are necessary to establish standardized thresholds and confirm its role in guiding individualized therapy. As the field of sepsis care evolves, LAR may prove to be an essential component of biomarker-driven management strategies, ultimately improving outcomes for critically ill patients worldwide.

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