Using the lactate-to-albumin ratio to predict mortality in patients with sepsis or septic shock: a systematic review and meta-analysis

S.H. YOON1, B. CHOI2, S. EUN1, G.E. BAE3, C.M. KOO1, M.K. KIM1

1Department of Pediatrics, Severance Children’s Hospital, Yonsei University College of Medicine, Seoul, Korea
2Yonsei University College of Medicine, Seoul, Korea
3Department of Emergency Medicine, Yonsei University College of Medicine, Seoul, Korea

Abstract. – OBJECTIVE: This study aimed to investigate whether the lactate-to-albumin ratio (LAR) can predict mortality in patients with sepsis or septic shock.

PATIENTS AND METHODS: A systematic search of the PubMed, EMBASE, Web of Science, and Google Scholar databases was conducted on December 16, 2021, for relevant articles that provided the predictive performance of LAR for mortality in patients with sepsis or septic shock.

RESULTS: Eight studies encompassing a total of 4,723 patients were included in this paper. The pooled sensitivity, specificity, and diagnostic odds ratio of the LAR for predicting mortality were 0.71 (95% confidence interval [CI]: 0.54-0.84), 0.68 (95% CI: 0.58-0.76) and 5.23 (95% CI: 2.62-10.45), respectively. The area under the summary receiver operating characteristic curve was 0.74 (95% CI: 0.70-0.78).

CONCLUSIONS: The current evidence suggests that LAR is moderately predictive of mortality among patients with sepsis or septic shock and may be beneficial to identify high-risk patients.

Key Words: Lactate-to-albumin ratio, Sepsis, Septic shock, Prognosis, Prediction, Meta-analysis.

Introduction

Sepsis is a leading cause of morbidity and mortality globally. Mortality rates vary between 20% and 30% and may increase to over 40% among patients with severe sepsis or septic shock. Before identifying the causative organisms, prompt, and adequate administration of antibiotics with careful hemodynamic resuscitation is recommended for the management of sepsis. It is particularly crucial to identify patients who are at a high risk of death from sepsis in order to improve their clinical outcomes.

The risk classification of sepsis is based on clinical signs and/or laboratory findings. Biomarkers derived from laboratory tests are relatively simple and objective auxiliary indicators for predicting prognosis. In patients with sepsis or septic shock, hyperlactatemia is an indicator of the disease severity and is also a powerful predictor of mortality. Elevated lactate levels result from cellular dysfunction, tissue hypoperfusion, and increased aerobic glycolysis in patients with sepsis and because blood lactate levels can be determined easily and rapidly, their measurement is widely used for diagnosing sepsis as well as for risk classification and guiding treatment. Albumin is another prognostic biomarker in critically ill patients; it is secreted by the liver and plays a role in producing plasma colloid osmotic pressure. Albumin also transports and ligates many endogenous and exogenous compounds and participates in acid-base balancing. It has anti-inflammatory and antioxidative characteristics and plays a role in effective host immune response. In contrast to lactate, hypoalbuminemia is associated with an increased risk of mortality and can serve as a prognostic biomarker in patients with severe sepsis.

Several recent studies investigated the value of an increase in the lactate-to-albumin ratio (LAR) in sepsis; this measure considers both the elevated lactate and decreased albumin. The LAR has shown promising results as a predictive marker of mortality in patients with sepsis or septic shock; this is potentially important for identifying high-risk patients and preventing death. However, these studies have not been systematically reviewed or validated. Thus, we aimed to determine the prognostic value of LAR in patients with sepsis or septic shock by conducting a meta-analysis and systematic review.
Patients and Methods

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) guidelines\(^\text{21}\) when performing this meta-analysis.

Search Strategy, Inclusion and Exclusion Criteria, and Data Extraction

Two authors (SHY and BC) searched the PubMed, EMBASE, and Web of Science electronic databases on December 16, 2021, using the following terms: (“lactate albumin ratio”) AND (“sepsis” OR “septic shock” OR “bacteremia” OR “septicemia” OR “systemic inflammatory response syndrome”) without any date or language restrictions. Furthermore, we manually searched Google Scholar to identify additional suitable studies. The inclusion criteria were as follows: (1) studies that evaluated the performance of LAR as a predictor of mortality in patients with sepsis or septic shock and (2) studies that reported sufficient data to construct 2 × 2 contingency tables. Papers were excluded if they were reviews, case reports, editorials, or animal/laboratory experiments.

The following data were extracted from each report: name of the first author, year of publication, country, study period, the total number of samples, patient source, study outcome, cutoff values, time of LAR measurement, reference standards (definition of sepsis/septic shock), true positives, false positives, true negatives, and false negatives in terms of the LAR’s prediction of mortality. If any article provided insufficient data, we contacted the corresponding authors by email to obtain the missing information about the study. For studies with more than two datasets derived from the same population, we chose only one dataset to avoid double-counting bias in our pooled analysis.

Quality Assessment

Methodological quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 tool\(^\text{22}\).

Statistical Analysis

We calculated summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–), and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CI). The area under the summary receiver operating curve (AUC) was used to summarize the overall test performance; an AUC above 0.7 was considered useful\(^\text{23,24}\). Cochran’s Q test (where a p-value <0.05 was deemed significant) and the I\(^2\) statistic (where an I\(^2\) >50% was deemed significant) with 95% CI were calculated to evaluate heterogeneity. We also used a forest plot to summarize the information from each study graphically and to provide a visual assessment of heterogeneity\(^\text{25}\). Meta-regression analysis was conducted to explore the causes of heterogeneity using the following covariates: patient source (emergency department vs. intensive care unit [ICU]); sample size (<600 vs. ≥600); outcome (in-hospital mortality vs. 28-day mortality); definition for sepsis [the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) vs. others]; LAR cutoff value (≥1.2 vs. <1.2). We excluded studies in which the endpoint was neither in-hospital mortality nor 28-day mortality (e.g., in-ICU mortality) when conducting meta-regression analysis. Deeks’ funnel plot was used to assess publication bias with p<0.1 indicating the presence of such bias. Data analysis was performed using the STA¬TA software version 17.0 (StataCorp, College Station, TX, USA) with the MIDAS and Metandi modules. A p-value <0.05 was considered statistically significant.

Results

The electronic literature search yielded 98 articles. After applying our inclusion and exclusion criteria, eight studies\(^\text{26-33}\) involving 4,723 patients were ultimately included in our meta-analysis. The study selection process is presented in Figure 1.

Study Characteristics and Quality Assessment

The included studies were published between 2015 and 2021 and conducted across the following seven countries: China (n=1)\(^\text{26}\), Egypt (n=1)\(^\text{27}\), Indonesia (n=1)\(^\text{28}\), Lebanon (n=2)\(^\text{29,31}\), South Korea (n=2)\(^\text{28,33}\), and Turkey (n=1)\(^\text{32}\). Half of the studies\(^\text{26,27,30,31}\) was prospective, and the remaining\(^\text{28,29,32,33}\) was retrospective. Seven studies (87.5%)\(^\text{26,27,29-33}\) were conducted at a single institution. The endpoints were in-hospital mortality in three studies (37.5%)\(^\text{29-31}\); 28-day mortality in three (37.5%)\(^\text{27,28,33}\); in-ICU mortality in two (25%)\(^\text{26,32}\). There were 1,457 patients in ICUs included from five studies\(^\text{26,27,30,32,33}\) as well as 3,266 patients in emergency departments included from three of them\(^\text{28,29,31}\). Six of the studies (75%)\(^\text{26,28-32}\) reported data of adult patients while the remaining two (25%)\(^\text{27,33}\) of pediatric patients. Four of the studies (50%)\(^\text{29-32}\) adopted the Sepsis-3 for defining sepsis or septic shock. The LAR cutoff val-
Lactate-to-albumin ratio as a predictor of sepsis-induced mortality

The sensitivity (0.35-1.00) and specificities (0.47-0.85) of the included studies varied widely (Figure 3). The pooled sensitivity and specificity of the LAR in predicting mortality were 0.71 (95% CI: 0.54-0.84) and 0.68 (95% CI: 0.58-0.76), respectively. The pooled LR+, LR−, and DOR were 2.22 (95% CI: 1.69-2.91), 0.42 (95% CI: 0.26-0.70), and 5.23 (95% CI: 2.62-10.45), respectively. The AUC was found to be 0.74 (95% CI: 0.70-0.78) (Figure 4). Significant heterogeneity was noted in terms of sensitivity ($I^2=97.1\%$) and specificity ($I^2=94.2\%$) (Figure 3). No evidence of publication bias was observed based on Deeks’ funnel plot ($p=0.99$) (Figure 5). Univariate meta-regression analysis revealed that patient outcome significantly affected heterogeneity (Table II). When we compared the pooled estimates with covariates, the pooled sensitivity

![Figure 1. Flow chart of the study selection process.](image)
Table 1. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Study period</th>
<th>Patient source</th>
<th>Outcome</th>
<th>Time of LAR measurement</th>
<th>LAR cutoff</th>
<th>Patients</th>
<th>Reference standard</th>
<th>Sample size (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015 Wang et al²⁶</td>
<td>China</td>
<td>Oct 1, 2012-Sep 30, 2013</td>
<td>ICU</td>
<td>In-ICU mortality</td>
<td>On the first day of ICU admission</td>
<td>1.735</td>
<td>Severe sepsis and septic shock</td>
<td>Surviving Sepsis Campaign guidelines 2012</td>
<td>54</td>
</tr>
<tr>
<td>2018 Moustafa et al²⁷</td>
<td>Egypt</td>
<td>Jan 2016-Apr 2017</td>
<td>ICU’</td>
<td>28-day mortality</td>
<td>At ED presentation¹</td>
<td>1.17</td>
<td>Severe sepsis and septic shock</td>
<td>IPSCC</td>
<td>119</td>
</tr>
<tr>
<td>2018 Shin et al²⁸</td>
<td>South Korea</td>
<td>Oct 2015-Feb 2017</td>
<td>ED</td>
<td>28-day mortality</td>
<td>Immediately after ED arrival</td>
<td>1.32</td>
<td>Septic shock</td>
<td>ACCP/SCCM 1992</td>
<td>946</td>
</tr>
<tr>
<td>2020 Bou Chebl et al²⁹</td>
<td>Lebanon</td>
<td>Jan 1, 2014-Jun 30, 2019</td>
<td>ED</td>
<td>In-hospital mortality</td>
<td>At ED presentation¹</td>
<td>1.22</td>
<td>Sepsis and septic shock</td>
<td>Sepsis-3</td>
<td>1,381</td>
</tr>
<tr>
<td>2021 Iskandar et al³⁰</td>
<td>Indonesia</td>
<td>Jan-May 2019</td>
<td>ICU</td>
<td>In-hospital mortality</td>
<td>On the first day of admission</td>
<td>1.32</td>
<td>Sepsis</td>
<td>Sepsis-3</td>
<td>58</td>
</tr>
<tr>
<td>2021 Bou Chebl et al³¹</td>
<td>Lebanon</td>
<td>Sep 2018-Feb 2021</td>
<td>ED</td>
<td>In-hospital mortality</td>
<td>At ED presentation</td>
<td>0.115</td>
<td>Sepsis and septic shock</td>
<td>Sepsis-3</td>
<td>939</td>
</tr>
<tr>
<td>2021 Cakir et al³²</td>
<td>Turkey</td>
<td>Jan 2016-Jan 2019</td>
<td>ICU</td>
<td>In-ICU mortality</td>
<td>At the time of ICU admission</td>
<td>0.71</td>
<td>Sepsis</td>
<td>Sepsis-3</td>
<td>1,136</td>
</tr>
<tr>
<td>2021 Choi et al³³</td>
<td>South Korea</td>
<td>Feb 2012-May 2015</td>
<td>ICU’</td>
<td>28-day mortality</td>
<td>Immediately after ICU admission</td>
<td>1.016</td>
<td>Septic shock</td>
<td>IPSCC</td>
<td>90</td>
</tr>
</tbody>
</table>

ACCP/SCCM, American College of Chest Physicians/Society of Critical Care Medicine Consensus definition; ED, emergency department; ICU, intensive care unit; IPSCC, International Pediatric Sepsis Consensus Conference definition; LAR, lactate-to-albumin ratio; Sepsis-3, the Third International Consensus Definitions for Sepsis and Septic Shock. *Pediatric intensive care unit. †Although this study was conducted on patients admitted to the intensive care unit, initial lactate and albumin levels were measured in the emergency department. ‡Lactate levels were measured at ED presentation, while albumin level was measured in the ED or during the hospital admission.
was significantly higher in studies with 28-day mortality as the primary outcome, while the pooled specificity was significantly higher in studies with a cutoff value <1.2 (Table II).

Discussion

Our meta-analysis revealed that the LAR had moderate sensitivity (0.71) and low specificity.
### Table II. Stratified meta-regression analyses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>No. of Studies</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LRT chi-square</th>
<th>p-value (joint model)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled value [95% CI]</td>
<td>p-value</td>
<td>Pooled value [95% CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>Patient source</td>
<td>ICU</td>
<td>5</td>
<td>0.82 [0.70-0.95]</td>
<td>0.18</td>
<td>0.70 [0.56-0.83]</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>ED</td>
<td>3</td>
<td>0.54 [0.31-0.76]</td>
<td>0.69</td>
<td>0.54 [0.40-0.84]</td>
<td>0.40</td>
</tr>
<tr>
<td>Size (n)</td>
<td>≥600</td>
<td>4</td>
<td>0.65 [0.43-0.87]</td>
<td>0.32</td>
<td>0.72 [0.62-0.82]</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>&lt;600</td>
<td>4</td>
<td>0.77 [0.57-0.97]</td>
<td>0.62</td>
<td>0.62 [0.48-0.76]</td>
<td>0.72</td>
</tr>
<tr>
<td>Outcome</td>
<td>In-hospital mortality</td>
<td>3</td>
<td>0.46 [0.34-0.58]</td>
<td>0.01</td>
<td>0.74 [0.64-0.83]</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>28-day mortality</td>
<td>3</td>
<td>0.71 [0.60-0.82]</td>
<td>0.59</td>
<td>0.47 [0.63-0.87]</td>
<td>0.97</td>
</tr>
<tr>
<td>Sepsis/septic shock definition</td>
<td>Sepsis-3</td>
<td>4</td>
<td>0.60 [0.39-0.81]</td>
<td>0.10</td>
<td>0.76 [0.68-0.83]</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>4</td>
<td>0.81 [0.64-0.97]</td>
<td>0.58</td>
<td>0.68 [0.48-0.69]</td>
<td>0.97</td>
</tr>
<tr>
<td>Cutoff</td>
<td>≥1.2</td>
<td>4</td>
<td>0.65 [0.42-0.88]</td>
<td>0.33</td>
<td>0.63 [0.50-0.75]</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2</td>
<td>4</td>
<td>0.76 [0.58-0.94]</td>
<td>0.72</td>
<td>0.62 [0.50-0.82]</td>
<td>0.04</td>
</tr>
</tbody>
</table>

CI, confidence interval; ED, emergency department; ICU, intensive care unit; LRT, likelihood-ratio test; Sepsis-3, the Third International Consensus Definitions for Sepsis and Septic Shock.
Lactate-to-albumin ratio as a predictor of sepsis-induced mortality

(0.68) for predicting mortality in patients with sepsis or septic shock, with an AUC of 0.74. Following previous studies23,34,35, we used the AUC to determine the discriminative power of a prognostic biomarker (in our case, the LAR) in terms of identifying high-risk patients. This value was 0.74 in our study, which indicated that the LAR is a suitable biomarker for discriminating patients with sepsis or septic shock who are at higher risk of mortality. Likewise, our calculated DOR (which is a single, prevalence-independent indicator of test performance)36 was 5.23; this indicated that the odds of a positive test (i.e., an LAR above the cutoff value) in patients who were at a high-risk of mortality was approximately five times higher than those in low-risk patients. Since early diagnosis and adequate management are critical to improving outcomes in patients with sepsis, the LAR may be invaluable in identifying those with a high risk of death and helping clinicians determine which patients should receive intensive care versus monitoring.

Although a number of biomarkers and clinical scoring systems that can assist in predicting the prognosis of patients with sepsis have been identified37, there is no prognostic gold-standard biomarker or clinical scoring system to date. The most commonly used prognostic biomarkers in patients with sepsis include lactate (AUC, 0.70-0.868)38-40, procalcitonin (AUC, 0.57-0.732)39,41-43, and C-reactive protein (AUC, 0.51-0.56)39,41,42; clinical scoring systems include the sequential organ failure assessment score (AUC, 0.59-0.943)39,42,44-46 and the acute physiology and chronic health evaluation II (AUC, 0.740-0.856)39,42,45. We could not compare the overall prognostic value of the LAR with other biomarkers or clinical scores due to the limited information available in the included publications. However, the LAR represents a more simplified approach than determining clinical scores, and its performance was similar to or higher than that of conventional inflammatory biomarkers, such as procalcitonin and C-reactive protein when comparing our results with exiting literature39,41-43. Cakir et al32 also reported that LAR was superior to lactate or albumin alone in terms of mortality prediction of patients with sepsis (AUC was 0.816 for lactate; 0.812 for albumin; 0.869 for LAR, respectively).

We conducted a meta-regression analysis because considerable heterogeneity existed in our data, with outcomes (i.e., the study endpoints) being the only significant source of this heterogeneity. Studies aimed at assessing the performance of the LAR in predicting 28-day mortality showed higher sensitivity than did those assessing this value for in-hospital mortality (0.71 vs. 0.46, \(p=0.01\)). According to our results, therefore, it is reasonable to use the LAR for predicting 28-day mortality in patients with sepsis or septic shock.

The reported optimal LAR cutoffs for predicting mortality range from 0.115 to 1.735 (Table I). A possible explanation for this wide range is that biomarker cutoff values can vary depending on assay type, the time and method of specimen collection, and patient characteristics such as age, sex, life stage, race, clinical settings, and the reference standard used47. In our study, we found higher pooled sensitivities and specificities in studies using cutoff values <1.2 (range, 0.115-1.17) than in those using cutoffs \(\geq1.2\) (range, 1.22-1.735); however, the difference was only significant for specificity (sensitivity, 0.76 vs. 0.65, \(p=0.33\); specificity 0.72 vs. 0.63, \(p=0.04\)). Future well-designed prospective studies are needed to identify and validate the optimal LAR cutoff value for predicting mortality.

To our knowledge, our meta-analysis is the first to assess the value of the LAR for predicting mortality in patients with sepsis or septic shock. However, several limitations in this study should be considered. First, half of the included...
studies were retrospective and carried a high risk of patient selection bias. Second, substantial heterogeneity existed across the included studies. Various clinical settings, patient characteristics, and accompanying treatment can be the source of heterogeneity, however, we failed to find any factors contributing to heterogeneity except for the specific outcome. Finally, most included studies were conducted outside of Europe and the American continent. Thus, when applying our results to clinical practice these limitations should be taken into account.

Conclusions

Our results indicate that the LAR is of moderate prognostic value in patients with sepsis or septic shock. The LAR may be useful for identifying patients who are at a high risk of death and to optimize clinical decision-making. However, additional studies are required to determine the optimal LAR cutoff value and identify prognostic biomarkers with higher predictive performance for mortality.

Conflict of Interest

The authors declared no conflict of interest.

Funding

Neither financial support nor any sort of sponsorship was received for this study.

Acknowledgments

We deeply appreciate Professor Ralphe Bou Chebl for his encouragement and assistance in fixing problems during data extraction.

References


2) Filho RR, Rocha LL, Corrêa TD, Pessoa CM, Colombo G, Assuncao MS. Blood lactate levels cu-
Lactate-to-albumin ratio as a predictor of sepsis-induced mortality


