European Review for Medical and Pharmacological Sciences 2022; 26: 1743-1752

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

S.H. YOON[1], B. CHOI[2], S. EUN[1], G.E. BAE[3], C.M. KOO[1], M.K. KIM[1]

[1]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea
[2]Yonsei University College of Medicine, Seoul, Korea
[3]Department 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[1]. Mortality rates vary between 20% and 30% and may increase to over 40% among patients with severe sepsis or septic shock[2-5]. Before identifying the causative organisms, prompt, and adequate administration of antibiotics with careful hemodynamic resuscitation is recommended for the management of sepsis[6,7]. 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[8]. 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[8,9]. Elevated lactate levels result from cellular dysfunction, tissue hypoperfusion, and increased aerobic glycolysis in patients with sepsis[4,8,10] 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[11,12]. Albumin is another prognostic biomarker in critically ill patients[13]; it is secreted by the liver and plays a role in producing plasma colloid osmotic pressure[14]. Albumin also transports and ligates many endogenous and exogenous compounds and participates in acid-base balancing[15]. It has anti-inflammatory and antioxidative characteristics and plays a role in effective host immune response[15-18]. 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[16,19,20].

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.

Corresponding Author: Seo Hee Yoon, MD; e-mail: yoonsh@yuhs.ac

Patients and Methods

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) guidelines[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 "septic" 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[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[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[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 STATA 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[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)[26], Egypt (n=1)[27], Indonesia (n=1)[30], Lebanon (n=2)[29,31], South Korea (n=2)[28,33], and Turkey (n=1)[32]. Half of the studies[26,27,30,31] was prospective, and the remaining[28,29,32,33] was retrospective. Seven studies (87.5%)[26,27,29-33] were conducted at a single institution. The endpoints were in-hospital mortality in three studies (37.5%)[29-31]; 28-day mortality in three (37.5%)[27,28,33]; in-ICU mortality in two (25%)[26,32]. There were 1,457 patients in ICUs included from five studies[26,27,30,32,33] as well as 3,266 patients in emergency departments included from three of them[28,29,31]. Six of the studies (75%)[26,28-32] reported data of adult patients while the remaining two (25%)[27,33] of pediatric patients. Four of the studies (50%)[29-32] adopted the Sepsis-3 for defining sepsis or septic shock. The LAR cutoff val-

ue for predicting mortality ranged from 0.115 to 1.735. The characteristics of the included studies are summarized in Table I.

The quality assessment of the included studies is shown in Figure 2. Five of the eight studies (62.5%) had a high-risk of patient selection bias because the authors did not state the patient inclusion criteria, nor did they mention whether patients were administered albumin before LAR assessment. Other than the patient selection domain, all studies were rated low risk for bias and had a low concern regarding applicability.

LAR for Predicting Mortality

The sensitivities (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

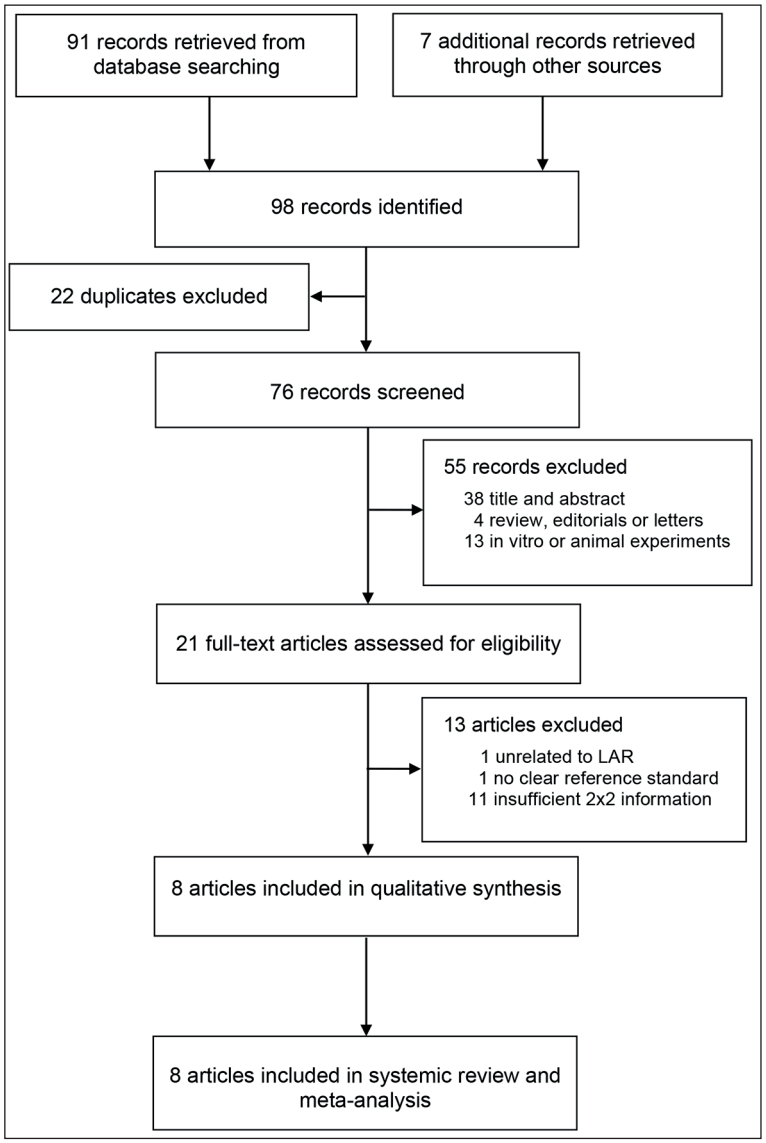

Figure 1. Flow chart of the study selection process.

Table I. Characteristics of the included studies.

Study ID	Country	Study period	Patient source	Outcome	Time of LAR measurement	LAR cutoff	Patients	Reference standard	Sample size (n)
2015 Wang et al[26]	China	Oct 1, 2012-Sep 30, 2013	ICU	In-ICU mortality	On the first day of ICU admission	1.735	Severe sepsis and septic shock	Surviving Sepsis Campaign guidelines 2012	54
2018 Moustafa et al[27]	Egypt	Jan 2016-Apr 2017	ICU*	28-day mortality	At ED presentation†	1.17	Severe sepsis and septic shock	IPSCC	119
2018 Shin et al[28]	South Korea	Oct 2015-Feb 2017	ED	28-day mortality	Immediately after ED arrival	1.32	Septic shock	ACCP/SCCM 1992	946
2020 Bou Chebl et al[29]	Lebanon	Jan 1, 2014-Jun 30, 2019	ED	In-hospital mortality	At ED presentation‡	1.22	Sepsis and septic shock	Sepsis-3	1,381
2021 Iskandar et al[30]	Indonesia	Jan-May 2019	ICU	In-hospital mortality	On the first day of admission	1.32	Sepsis	Sepsis-3	58
2021 Bou Chebl et al[31]	Lebanon	Sep 2018-Feb 2021	ED	In-hospital mortality	At ED presentation	0.115	Sepsis and septic shock	Sepsis-3	939
2021 Cakir et al[32]	Turkey	Jan 2016-Jan 2019	ICU	In-ICU mortality	At the time of ICU admission	0.71	Sepsis	Sepsis-3	1,136
2021 Choi et al[33]	South Korea	Feb 2012-May 2015	ICU*	28-day mortality	Immediately after ICU admission	1.016	Septic shock	IPSCC	90

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.

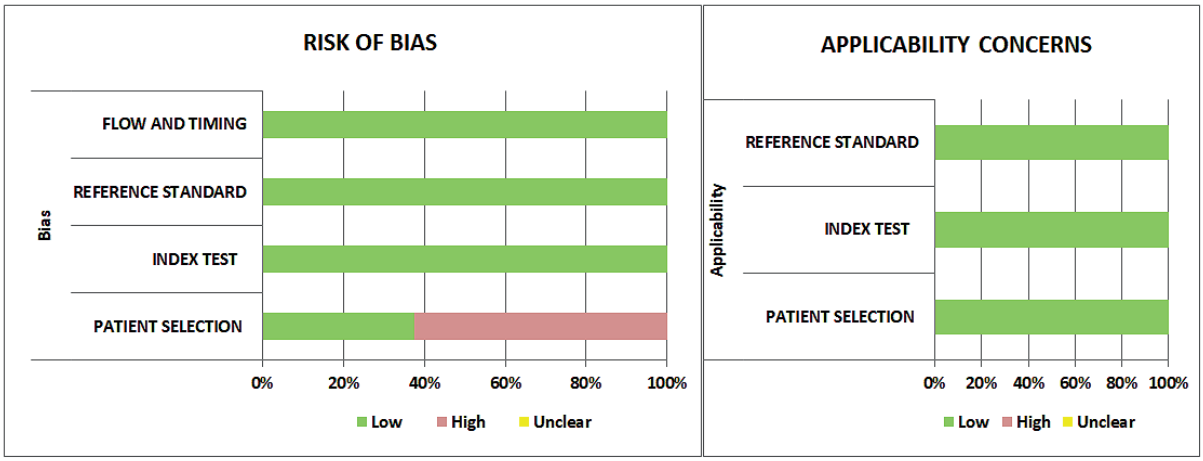

Figure 2. Results of the Quality Assessment of Diagnostic Accuracy Studies-2 tool.

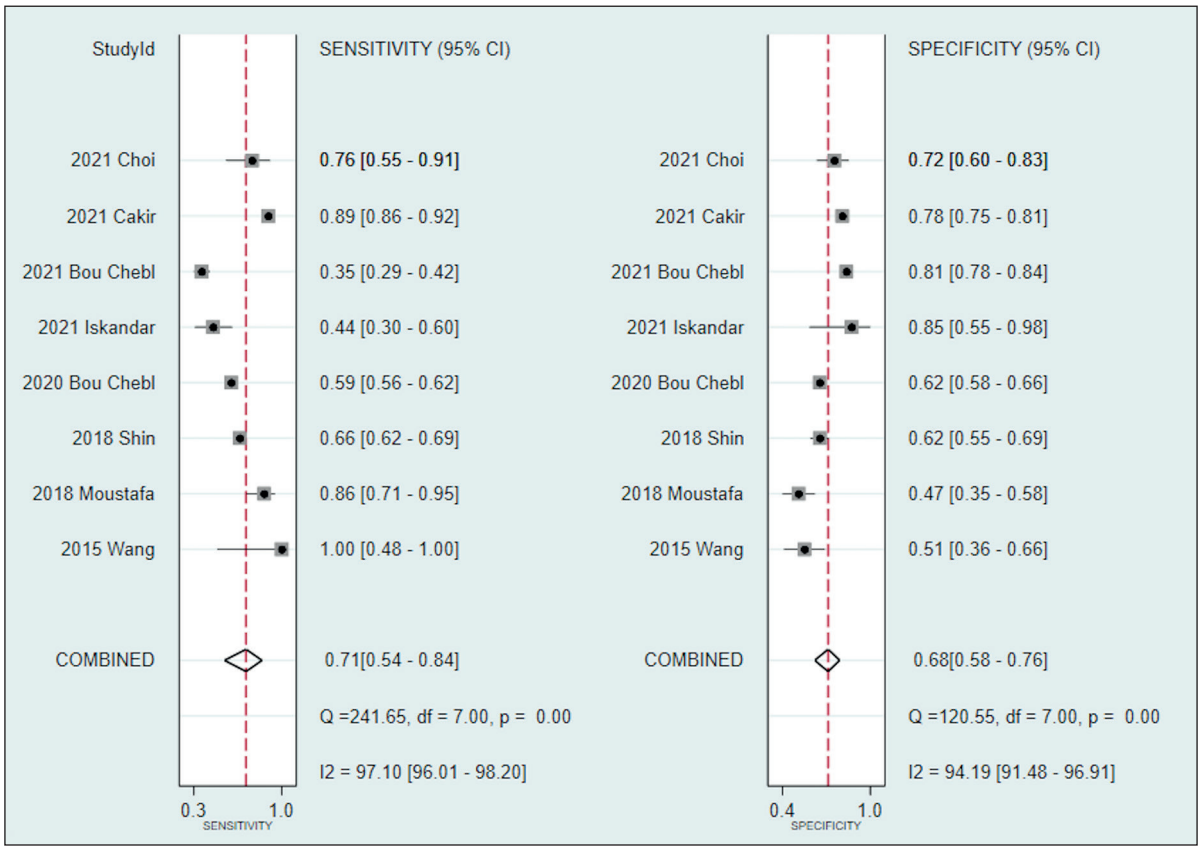

Figure 3. Coupled forest plots of summary sensitivity and specificity. Numbers represent pooled estimates with 95% confidence intervals (CI) in parentheses. Horizontal lines indicate the 95% CI.

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.

Parameter	Category	No. of Studies	Sensitivity		Specificity		LRT chi-square	*p*-value (joint model)
			Pooled value [95% CI]	*p*-value	Pooled value [95% CI]	*p*-value		
Patient source	ICU	5	0.82 [0.70-0.95]	0.18	0.70 [0.56-0.83]	0.40	5.29	0.07
	ED	3	0.54 [0.31-0.76]		0.69 [0.54-0.84]			
Size (n)	≥600	4	0.65 [0.43-0.87]	0.32	0.72 [0.62-0.82]	0.72	1.24	0.54
	<600	4	0.77 [0.57-0.97]		0.62 [0.48-0.76]			
Outcome	In-hospital mortality	3	0.46 [0.34-0.58]	0.01	0.74 [0.64-0.83]	0.99	49.6	<0.01
	28-day mortality	3	0.71 [0.60-0.82]		0.59 [0.47-0.71]			
Sepsis/septic shock definition	Sepsis-3	4	0.60 [0.39-0.81]	0.10	0.76 [0.68-0.83]	0.97	5.56	0.06
	Others	4	0.81 [0.64-0.97]		0.58 [0.48-0.69]			
Cutoff	≥1.2	4	0.65 [0.42-0.88]	0.33	0.63 [0.50-0.75]	0.04	2.8	0.25
	<1.2	4	0.76 [0.58-0.94]		0.72 [0.62-0.82]			

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.

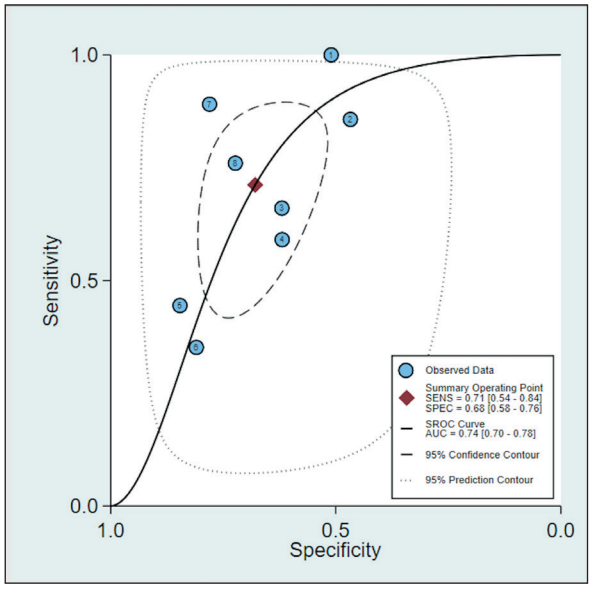

Figure 4. Summary receiver-operating characteristic (SROC) curve for determining the ability of the lactate-to-albumin ratio to predict mortality in patients with sepsis or septic shock. The area under the curve of the SROC was 0.74 (95% confidence interval: 0.70–0.78).

(0.68) for predicting mortality in patients with sepsis or septic shock, with an AUC of 0.74. Following previous studies[23,34,35], 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 identified[37], 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)[40-42,45]. 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 literature[39,41-43]. Cakir et al[32] 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 used[47]. 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 ≥1.2 (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

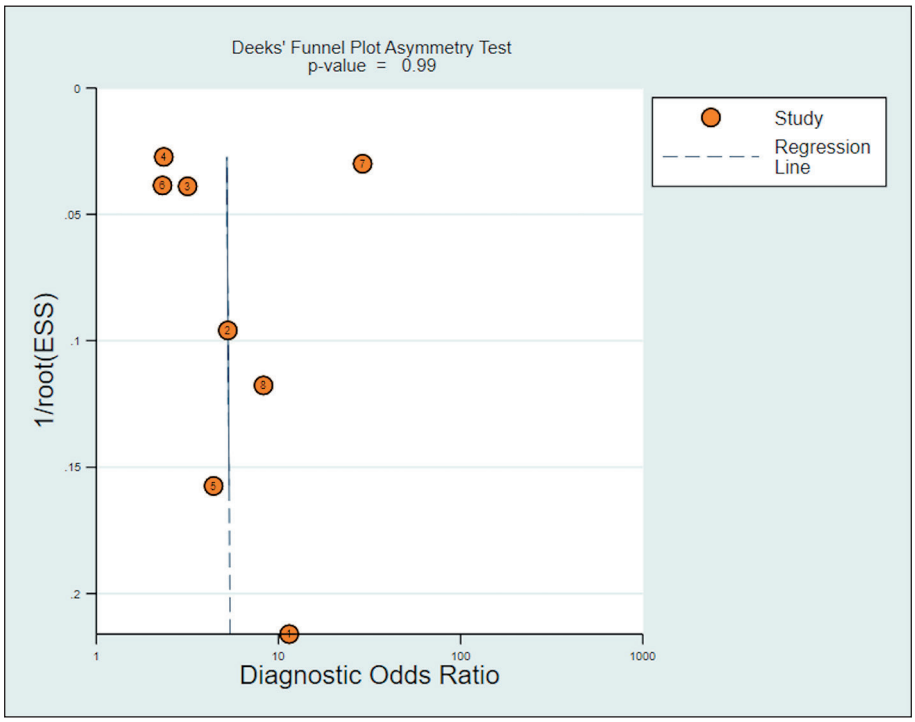

Figure 5. Deeks' funnel plot asymmetry test. ESS = effective sample size.

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

1) Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31: 1250-1256.
2) Filho RR, Rocha LL, Corrêa TD, Pessoa CM, Colombo G, Assuncao MS. Blood lactate levels cu-

toff and mortality prediction in sepsis-time for a reappraisal? A retrospective cohort study. Shock 2016; 46: 480-485.

3) Krau SD. Making sense of multiple organ dysfunction syndrome. Crit Care Nurs Clin North Am 2007; 19: 87-97.
4) Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801-810.
5) Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. Crit Care 2020; 24: 239.
6) Jones AE, Brown MD, Trzeciak S, Shapiro NI, Garrett JS, Heffner AC, Kline JA, Emergency Medicine Shock Research Network investigators. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. Crit Care Med 2008; 36: 2734-2739.
7) Dugar S, Choudhary C, Duggal A. Sepsis and septic shock: Guideline-based management. Cleve Clin J Med 2020; 87: 53-64.
8) Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. Crit Care 2014; 18: 503.
9) Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, Reinhart K, Selvakumar N, Levy MM. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med 2015; 43: 567-573.
10) Kraut JA, Madias NE. Lactic acidosis. N Engl J Med 2014; 371: 2309-2319.
11) Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41: 580-637.
12) Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017; 43: 304-377.
13) Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000; 85: 599-610.
14) Yanni GN, Lubis M, Ali M. The influence of albumin level in critically ill children to length of stay and mortality in paediatric intensive care unit. Open Access Maced J Med Sci 2019; 7: 3455-3458.
15) Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014; 370: 1412-1421.
16) Yin M, Si L, Qin W, Li C, Zhang J, Yang H, Han H, Zhang F, Ding S, Zhou M, Wu D, Chen X, Wang H. Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration: A prospective cohort study. J Intensive Care Med 2018; 33: 687-694.
17) Wiedermann CJ. Hypoalbuminemia as surrogate and culprit of infections. Int J Mol Sci 2021; 22: 4496.
18) Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014; 61: 396-407.
19) Artero A, Zaragoza R, Camarena JJ, Sancho S, González R, Nogueira JM. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. J Crit Care 2010; 25: 276-281.
20) Seo MH, Choa M, You JS, Lee HS, Hong JH, Park YS, Chung SP, Park I. Hypoalbuminemia, low base excess values, and tachypnea predict 28-day mortality in severe sepsis and septic shock patients in the emergency department. Yonsei Med J 2016; 57: 1361-1369.
21) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
22) Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, Quadas-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-536.
23) Altschul DJ, Unda SR, Benton J, de la Garza Ramos R, Cezayirli P, Mehler M, Eskandar EN. A novel severity score to predict inpatient mortality in COVID-19 patients. Sci Rep 2020; 10: 16726.
24) Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010; 5: 1315-1316.

25) Fagerland MW. Chapter 12 - Evidence-Based Medicine and Systematic Reviews. In: Laake P, Benestad HB, Olsen BR, editors. Research in Medical and Biological Sciences (Second Edition). Amsterdam: Academic Press, 2015: 431-461.

26) Wang B, Chen G, Cao Y, Xue J, Li J, Wu Y. Correlation of lactate/albumin ratio level to organ failure and mortality in severe sepsis and septic shock. J Crit Care 2015; 30: 271-275.

27) Moustafa AA, Antonios MA, Abdellatif EM, Hussain AH. Association of lactate/albumin ratio level to organ failure and mortality in severe sepsis in a pediatric intensive care unit in Egypt. Turk J Pediatr 2018; 60: 691-701.

28) Shin J, Hwang SY, Jo IJ, Kim WY, Ryoo SM, Kang GH, Kim K, Jo YH, Chung SP, Joo YS, Beom JH, Yoon YH, Han KS, Lim TH, Choi HS, Kwon WY, Suh GJ, Choi SH, Shin TG. Prognostic Value of The Lactate/Albumin Ratio for Predicting 28-Day Mortality in Critically ILL Sepsis Patients. Shock 2018; 50: 545-550.

29) Bou Chebl R, Jamali S, Sabra M, Safa R, Berbari I, Shami A, Makki M, Tamim H, Abou Dagher G. Lactate/Albumin Ratio as a Predictor of In-Hospital Mortality in Septic Patients Presenting to the Emergency Department. Front Med (Lausanne) 2020; 7: 550182.

30) Iskandar A, Vincentia MI, Jaya W, Aryati A, Pramadhani A, Aprilia A. The profile of lactate, albumin, and lactate/albumin ratio as predictors of mortality in sepsis patients. Russian Journal of Infection and Immunity. 2021; 11(6): 1095-1100.

31) Bou Chebl R, Geha M, Assaf M, Kattouf N, Haidar S, Abdeldaem K, Halawi N, Khamis M, Makki M, Tamim H, Abou Dagher G. The prognostic value of the lactate/albumin ratio for predicting mortality in septic patients presenting to the emergency department: a prospective study. Ann Med 2021; 53: 2268-2277.

32) Cakir E, Turan IO. Lactate/albumin ratio is more effective than lactate or albumin alone in predicting clinical outcomes in intensive care patients with sepsis. Scandinavian Journal of Clinical and Laboratory Investigation 2021; 81: 225-229.

33) Choi SJ, Ha EJ, Jhang WK, Park SJ. Association between the lactate/albumin ratio and mortality in pediatric septic shock patients with underlying chronic disease: retrospective pilot study. Minerva Pediatr (Torino) 2021; 73: 67-72.

34) Ahn C, Kim W, Lim TH, Cho Y, Choi K-S, Jang B-H. The delta neutrophil index (DNI) as a prognostic marker for mortality in adults with sepsis: a systematic review and meta-analysis. Scientific Reports 2018; 8: 6621.

35) Suwanpasu SJJICC. Accuracy of Modified Early Warning Scores for predicting mortality in hospital: a systematic review and meta-analysis. 2016; 2: 29.

36) Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. Journal of clinical epidemiology 2003; 56: 1129-1135.

37) Kim MH, Choi JH. An Update on Sepsis Biomarkers. Infection & chemotherapy 2020; 52: 1-18.

38) Casagranda I, Vendramin C, Callegari T, Vidali M, Calabresi A, Ferrandu G, Cervellin G, Cavazza M, Lippi G, Zanotti I, Negro S, Rocchetti A, Arfini C. Usefulness of suPAR in the risk stratification of patients with sepsis admitted to the emergency department. Intern Emerg Med 2015; 10: 725-730.

39) Andaluz-Ojeda D, Nguyen HB, Meunier-Beillard N, Cicuéndez R, Quenot JP, Calvo D, Dargent A, Zarca E, Andrés C, Nogales L, Eiros JM, Tamayo E, Gandía F, Bermejo-Martín JF, Charles PE. Superior accuracy of mid-regional proadrenomedullin for mortality prediction in sepsis with varying levels of illness severity. Ann Intensive Care 2017; 7: 15.

40) Chen J, He Y, Zhou L, Deng Y, Si L. Long noncoding RNA MALAT1 serves as an independent predictive biomarker for the diagnosis, severity and prognosis of patients with sepsis. Mol Med Rep 2020; 21: 1365-1373.

41) Barre M, Behnes M, Hamed S, Pauly D, Lepiorz D, Lang S, Akin I, Borggrefe M, Bertsch T, Hoffmann U. Revisiting the prognostic value of monocyte chemotactic protein 1 and interleukin-6 in the sepsis-3 era. J Crit Care 2018; 43: 21-28.

42) Kim SB, Lee KH, Lee JU, Ann HW, Ahn JY, Jeon YD, Kim JH, Ku NS, Han SH, Choi JY, Song YG, Kim JM. Long Pentraxin 3 as a Predictive Marker of Mortality in Severe Septic Patients Who Received Successful Early Goal-Directed Therapy. Yonsei Med J 2017; 58: 370-379.

43) Fang Y, Li C, Shao R, Yu H, Zhang Q, Zhao L. Prognostic significance of the angiopoietin-2/angiopoietin-1 and angiopoietin-1/Tie-2 ratios for early sepsis in an emergency department. Crit Care 2015; 19: 367.

44) Seol CH, Yong SH, Shin JH, Lee SH, Leem AY, Park MS, Kim YS, Chung KS. The ratio of plasma angiopoietin-2 to angiopoietin-1 as a prognostic biomarker in patients with sepsis. Cytokine 2020; 129: 155029.

45) Na L, Ding H, Xing E, Gao J, Liu B, Wang H, Yu J, Yu C. Lnc-MEG3 acts as a potential biomarker for predicting increased disease risk, systemic inflammation, disease severity, and poor prognosis of sepsis via interacting with miR-21. J Clin Lab Anal 2020; 34: e23123.

46) Kim H, Hur M, Struck J, Bergmann A, Di Somma S. Circulating Biologically Active Adrenomedullin Predicts Organ Failure and Mortality in Sepsis. Ann Lab Med 2019; 39: 454-463.

47) Raghavan R, Ashour FS, Bailey R. A Review of Cutoffs for Nutritional Biomarkers. Advances in nutrition (Bethesda, Md.) 2016; 7: 112-120