Original Article

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Prognostic Value of a Novel Lactate-shock Index for 28-day Mortality in Adult Sepsis Patients

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Abstract

Aim: Early and accurate diagnosis of sepsis allows for the timely initiation of appropriate treatment, which can improve clinical outcomes. Studies have shown that the shock index (SI) and high lactate levels are successful in predicting mortality and adverse outcomes in various clinical situations. However, the variability in lactate levels due to various factors limits its usability when used alone. Considering these limitations, we aimed to evaluate the performance of a combined lactate SI (LSI) in predicting 28-day mortality in patients with sepsis.

Methods: Patients aged 18 and over who were diagnosed with sepsis between 15.02.2023 and 15.12.2023 and presented to the emergency department (ED) were included in the study. Sepsis diagnosis was evaluated according to the criteria in the sepsis-3 guidelines. Data collection for patients presenting to the ED with suspected sepsis included demographic findings such as age and gender. Glasgow coma scale score; vital signs including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), body temperature (°C), and respiratory rate (breaths/min). The SI, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, and LSI values were calculated and recorded in the data collection form.

Results: The study included a total of 77 patients, with 28-day mortality occurring in 31 patients (40.3%). Multivariate logistic regression analysis identified SI [Odds ratio (OR), 9.623, p=0.023] and LSI (OR: 1.333, p=0.029) as independent prognostic indicators of 28-day mortality. In the receiver operating characteristic analysis, LSI [area under the curve (AUC): 0.710] outperformed both SI (AUC: 0.690) and lactate (AUC: 0.681).

Conclusion: This study demonstrates that LSI is an independent predictor of 28-day mortality in patients with sepsis. Lactate shock index showed better performance than both lactate and SI in predicting 28-day mortality.

Keywords: Emergency medicine, lactate, mortality, sepsis, shock index

Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction due to an inappropriate host response secondary to infection (1). It is among the common causes of infection-related deaths and is associated with high morbidity and mortality. Sepsis affects approximately 30 million people globally each year, resulting in death in about 6 million of these patients (2,3). Despite current advancements in diagnosis and treatment, mortality rates remain high in sepsis, particularly in septic shock (1,4).

Early and accurate diagnosis of sepsis allows for the timely initiation of appropriate treatment, which can improve clinical outcomes (3,5). Emergency departments (EDs) are often the first point of contact for patients suspected of sepsis. However, due to the nature of EDs, there is limited time for evaluating and initiating treatment for these patients. Early identification of high-risk patients in ED is important due to the benefits of early initiation of appropriate treatment, identification of patients with critical care needs, and improvement in patient survival outcomes (1,5). Due to limited resources and time

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constraints in ED, practical and rapid risk stratification tools are needed (6).

The shock index (SI), defined as the ratio of heart rate (HR) to systolic blood pressure (SBP), is an easily calculable index at the bedside (6). The literature has demonstrated the success of SI in predicting mortality and adverse outcomes in various clinical situations such as sepsis, trauma, and pulmonary embolism (4,7-10). Lactate, a product of anaerobic metabolism, is an indicator of hypoperfusion and tissue hypoxia. Studies in critically ill patient groups have shown that elevated lactate levels are associated with mortality (11,12). Serum lactate levels above 2 mmol/L have been proposed as a new criterion for defining septic shock in the sepsis-3 guidelines. While studies have shown that high lactate levels are strong predictors of disease severity and mortality, low lactate levels are associated with improved clinical outcomes (11,13,14). However, lactate levels can also rise due to metformin use, liver and kidney failure, and malignancies, limiting their usability when used alone (15). Considering the limitations of lactate levels, we developed a combined lactate SI (LSI) obtained by multiplying lactate by SI and aimed to evaluate the performance of this new index in predicting 28-day mortality in patients with sepsis.

Materials and Methods

Compliance with Ethical Standards

This study was conducted prospectively in the ED of a tertiary hospital following approval from the Ordu University Clinical Research Ethics Committee (approval no.: 2023/41, date: 03.02.2023). The study was conducted in accordance with the ethical rules and principles of the Helsinki Declaration at all stages. Written and verbal consent was obtained from the participants.

Study Design and Selection of Participants

Patients aged 18 and over who were diagnosed with sepsis between 15.02.2023 and 15.12.2023, presented to the ED, and who read and accepted the consent form were included in the study. Sepsis diagnosis was evaluated according to the criteria in the sepsis-3 guidelines.

Exclusion criteria included pregnant women, patients under 18 years of age, patients presenting to the ED with cardiac arrest, those with chronic liver failure, chronic kidney failure, a history of chronic heart failure affecting SBP, bedridden immobile patients, patients diagnosed with epilepsy and presenting post-epileptic seizure, trauma patients, those who withdrew consent, and those with incomplete data in their records.

Data Collection and Measurements

Data collection for patients presenting to the ED with suspected sepsis included demographic findings such as age and gender. Glasgow coma scale score; vital signs including SBP (mmHg), diastolic blood pressure (DBP, mmHg), HR (bpm), body temperature (°C), and respiratory rate (breaths/min).

Blood samples taken according to sepsis guidelines were analyzed for white blood cells, hemoglobin (mg/dL), platelets, neutrophil count, lymphocyte count, monocyte count, alanine aminotransferase (IU/L), aspartate aminotransferase (IU/L), C-reactive protein (CRP), and blood gas samples including pH, partial pressure of carbon dioxide ($PaCO_2$, mmHg), bicarbonate (mEq/L), and lactate (mmol/L).

The SI, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and LSI values were calculated and recorded in the data collection form. The calculations for these parameters are as follows:

SI=HR (bpm)/SBP (mmHg)
NLR=Neutrophil count/Lymphocyte count
PLR=Platelet count/Lymphocyte count
LMR=Lymphocyte count/Monocyte count
LSI=Lactate (mmol/L) x SI

In the ED, blood samples are collected in standardized tubes containing dipotassium ethylenediaminetetraacetic acid for complete blood counts. Plasma CRP levels are measured using a turbidimetric immunological test. Lactate levels are determined from blood gas samples collected in heparinized tubes.

The primary outcome was 28-day mortality, defined as death within 28 days from the time of ED presentation. Patients were classified as alive or deceased based on the 28-day mortality data.

Statistical Analysis

Statistical analysis was performed using SPSS v.26 and Jamovi v2.5.3. The normality of the data was assessed using visual and analytical methods. Descriptive statistics were presented as mean ± standard deviation, median (25^{th} and 75^{th} percentiles), and frequency (n and %). Based on the continuous and categorical characteristics of the variables, as well as the results of the normality analysis, appropriate analyses were performed using the independent samples t-test, Mann-Whitney U test, and chi-square test.

Multivariate logistic regression analysis was conducted to evaluate whether lactate, SI, and LSI were independent predictors of 28-day mortality. The odds ratios (ORs) of the variables were calculated with a 95% confidence interval (CI). Receiver operating characteristics (ROC) analysis was applied to evaluate the diagnostic performance of the variables. Cut-off points were calculated using the Youden index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated based on

the cut-off points for predicting 28-day mortality. A p-value of <0.05 was considered statistically significant.

Results

The study included a total of 77 patients, aged 43-94 years, who met the inclusion and exclusion criteria. The mean age of the patients was 72.01±10.86 years, and the majority were male (63.6%). Twenty-eight-day mortality was observed in 31 patients (40.3%). Table 1 shows the relationship between the patients' demographic, clinical, and laboratory findings and 28-day mortality. No statistical difference was found between the deceased and surviving patient groups in terms of gender and age (p=0.272 and p=0.174). Deceased patients had lower SBP (p=0.020) and higher HR (p=0.049). Lactate, SI, and LSI were higher in deceased patients (p-values of 0.005, 0.005, and 0.001, respectively).

Univariate logistic regression analysis revealed that lactate (OR: 1.707, 95% CI 1.195-2.438, p=0.003), SI (OR: 6.447, 95% CI 1.568-26.51, p=0.010), and LSI (OR: 1.448, 95% CI 1.157-1.814, p=0.001) were positively and statistically significantly associated with 28-day mortality. Multivariate logistic regression analysis was performed to assess the independent effects of these variables on

Table 1. Relationship with 28-day mortality and patient's demographic characteristics, clinic and laboratory findings

	28 day mortality		
	Alive (n=46)	**Deceased (n=31)**	**p-values**
Sex; n (%)			
Male	27 (55.1%)	22 (44.9%)	0.272
Female	19 (67.9%)	9 (32.1%)	
Age (year)	71 (62-78)	75 (65-81)	0.134
SBP (mmHg)	100 (88.75-110)	80 (80-100)	**0.020**
DBP (mmHg)	60 (50-70)	50 (50-68)	0.217
Pulse rate (beats/min)	102.72±20.65	113.1±24.51	**0.049**
Body temperature (°C)	37.5 (36.78-38.35)	37.5 (36.5-38.6)	0.901
Respiratory rate	20 (17-26)	23 (20-30)	0.117
GCS	15 (14-15)	13 (10-15)	**<0.001**
WBC count (cells/mm^3)	16.35 (10.59-21.84)	11.68 (7.01-18)	**0.014**
Hemoglobin (mg/dL)	11.9±2.35	11.87±2.2	0.964
Platelet count (cells/mm^3)	179 (140.25-282.75)	190 (106-304)	0.827
Neutrophil count (cells/mm^3)	14.05±7.88	10.84±6.35	0.063
Lymphocyte count (cells/µL)	1.17 (0.65-2.04)	0.81 (0.38-1.2)	**0.029**
Monocyte count	0.95±0.6	0.55±0.33	**<0.001**
IGG	0.13 (0.06-0.27)	0.09 (0.03-0.19)	0.138
NLR	11.48 (4.43-21.25)	11.38 (7.58-18.84)	0.732
PLR	159.47 (100.05-263)	285.19 (101.67-447.96)	0.101
LMR	1.63 (0.79-2.75)	1.79 (1.02-3.14)	0.506
ALT (IU/L)	19 (10-29.25)	18 (11-28)	0.872
AST (IU/L)	23 (14-34.5)	23 (19-49)	0.339
CRP	133 (39.25-275)	125 (60-188)	0.516
pH	7.36±0.08	7.4±0.08	**0.025**
PCO_2	42.54±9.52	38.06±10.82	0.059
Bicarbonate	22.4 (20.15-26.3)	23.1 (21.2-28.4)	0.403
Lactate (mmol/L)	2.2 (1.55-3.275)	3.1 (2.1-4.9)	**0.005**
SI	1.1±0.31	1.34±0.42	**0.005**
LSI	2.88±1.72	5.02±3.12	**0.001**

Values are presented as mean ± SD, median (25^{th} and 75^{th} quartile), or n (%)
ALT: Alanine transaminoferase, AST: Aspartate transaminoferase, CRP: C-reactive protein, DBP: Diastolic blood pressure, GCS: Glasgow coma scale, IGG: Immature granulocytes, LMR: Lymphocyte-monocyte ratio, LSI: Lactate-shock index, NLR: Neutrophil-lymphocyte ratio, PCO_2: Partial pressure of carbon dioxide, PLR: Platelet-lymphocyte ratio, SBP: Systolic blood pressure, SI: Shock index, WBC: White blood cells

28-day mortality. Shock index (OR: 9.623, 95% CI 1.358-68.16, p=0.023) and LSI (OR: 1.333, 95% CI 1.031-1.723, p=0.029) were identified as independent prognostic indicators of 28-day mortality. The analysis of multivariate logistic regression is shown in Table 2.

Receiver operating characteristics analysis was performed on all patients to predict 28-day mortality. Lactate shock index [area under the curve (AUC): 0.710] showed better performance than both SI (AUC: 0.690) and lactate (AUC: 0.681). The ROC curve graph is shown in Figure 1, and Table 3 contains statistics on the performance characteristics of the variables in predicting 28-day mortality.

Discussion

This study demonstrated that LSI, a combined index of lactate and SI, is an independent predictor of 28-day mortality in patients with sepsis. Lactate shock index (AUC: 0.710) performed better than lactate (AUC: 0.690) and SI (AUC: 0.681) in predicting 28-day mortality.

Sepsis is a significant public health problem worldwide, being one of the leading causes of hospital admission and death (16). In-hospital mortality due to sepsis occurs in approximately 20% of patients, with rates even higher in those with septic shock. Additionally, patients treated for sepsis remain at risk for mortality and morbidity after discharge (17). Due to this high mortality risk, identifying critically ill patients through risk stratification is crucial. Effective risk classification tools are needed to successfully predict patient outcomes in sepsis and guide treatment and management strategies in the initial hours (1,4).

Neutrophil-lymphocyte ratio, an inflammatory marker obtained by dividing the neutrophil count by the lymphocyte count, is an indicator of systemic inflammation (16). Sepsis is characterized by an inappropriate inflammatory response to infection by the host. Physiological stress due to sepsis causes an increase in neutrophil count while inducing lymphopenia by promoting lymphocyte apoptosis (18,19). However, neutrophil values may be normal or low in septic patients, limiting the prognostic value of neutrophil and lymphocyte counts. Studies have shown that NLR is more reliable than neutrophil and lymphocyte counts alone (20,21). Liu et al. (22) found that increasing NLR values predicted 28-day mortality in septic patients. Similarly, another study demonstrated that NLR is an independent predictor of 28-day mortality (18). In our study, we found that low lymphocyte count was associated with mortality, consistent with the literature. However, neutrophil count was lower in deceased patients compared to survivors, with no statistical relationship with mortality. This discrepancy may be due to the patient population and sample size included in the study. Consequently, the failure of NLR to predict mortality may be explained by the difference in neutrophil counts between deceased and surviving patients.

Shock index is a reliable indicator of hemodynamic status and has the advantage of being easily calculable at the bedside. It is a more sensitive indicator of hemodynamic status than HR and SBP alone (9). Previous studies have shown the success of SI in predicting adverse clinical outcomes in various conditions such as trauma, myocardial infarction, sepsis, and pneumonia (4,8,9,23). The inappropriate inflammatory response seen in sepsis leads to increased vascular permeability and suppression of vascular tone. This results in decreased arterial blood pressure and impaired tissue perfusion. Compensatory mechanisms activate the alpha and beta adrenergic systems, increasing HR and cardiac contractility (24). The hemodynamic effects of sepsis are associated with an increase in SI. Al Aseri et al. (10) found that SI was a successful predictor of hemodynamic collapse in septic patients, and similarly, Devendra Prasad et al. (9) showed that SI predicted the need for mechanical ventilation. Studies have also investigated the relationship between SI and short- and long-term mortality in septic patients (4). Zhang et al. (1) investigated the performance of SI in predicting 3-day and in-hospital mortality in patients with septic shock; they found an AUC of 0.746 for 3-day mortality and 0.654 for in-hospital mortality. Multivariate logistic regression analysis in the same study found SI to be an independent predictor of 3-day mortality (1). Another study investigating the prognostic performance of SI in

Table 2. ORs of the prognostic factors for predicting 28-day mortality in patients with sepsis

Parameters	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Lactate	1.707 (1.195-2.438)	**0.003**	1.712 (1.188-2.468)	**0.004**	1.467 (0.979-2.199)	0.064
SI	6.447 (1.568-26.51)	**0.010**	6.424 (1.467-28.138)	**0.014**	9.623 (1.358-68.16)	**0.023**
LSI	1.448 (1.157-1.814)	**0.001**	1.446 (1.151-1.816)	**0.002**	1.333 (1.031-1.723)	**0.029**

Model 1: Unadjusted model
Model 2: Adjusted for age and sex
Model 3: Each variable was adjusted for age, sex, GCS, WBC, lymphocyte and monocyte
CI: Confidence interval, GCS: Glasgow coma scale, LSI: Lactate-shock index, OR: Odds ratio, SI: Shock index, WBC: White blood cells, PPV: Positive predictive value, NPV: Negative predictive value

predicting 28-day mortality identified sensitivities of 0.71 and specificities of 0.41 for two different cut-off points (≥0.7 and ≥1.0) and a sensitivity of 0.37 and specificity of 0.80 for a cut-off point of >1.0 (25). Another study reported a sensitivity of 0.731, a specificity of 0.458 and an AUC of 0.708 for short-term mortality at an SI cut-off of ≥1.2 (8). In our study, consistent with previous studies, we found an AUC of 0.681, sensitivity of 0.71, and specificity of 0.652 in predicting 28-day mortality for an SI cut-off of ≥1.144. Logistic regression analysis demonstrated that SI is an independent predictor of 28-day mortality.

High lactate levels have been shown to be associated with increased mortality and adverse clinical outcomes in various conditions, including sepsis (15,26). Sepsis leads to increased lactate levels due to impaired tissue perfusion and cellular hypoxia (27). Current sepsis guidelines emphasize the central role of lactate levels in patient management (26,28). Filho et al. (29) investigated the relationship between initial lactate levels and mortality in septic patients, finding an AUC of 0.70, sensitivity of 0.674, and specificity of 0.617 for a cut-off of >2.5 in predicting 28-day mortality. Another study examining the performance of lactate in predicting 28-day mortality in elderly septic patients reported a cut-off value of >2.4 with an AUC of 0.618, a sensitivity of 0.483, and a specificity of 0.687 (28). Consistent with the literature, our study showed that increased lactate levels were associated with increased mortality. For predicting 28-day mortality, the AUC of lactate was 0.690, with a sensitivity of 0.71 and specificity of 0.63 at a cut-off of >2.65. We recommend a cut-off of 2.5 for lactate, in line with previous clinical studies (26,30), despite studies suggesting a cut-off of 4.0. Choosing a higher cut-off could lead to the misclassification of patients with moderate hyperlactatemia, who are at risk of morbidity and mortality, as low-risk, thus missing a patient group that could benefit from aggressive treatment and intensive monitoring (29).

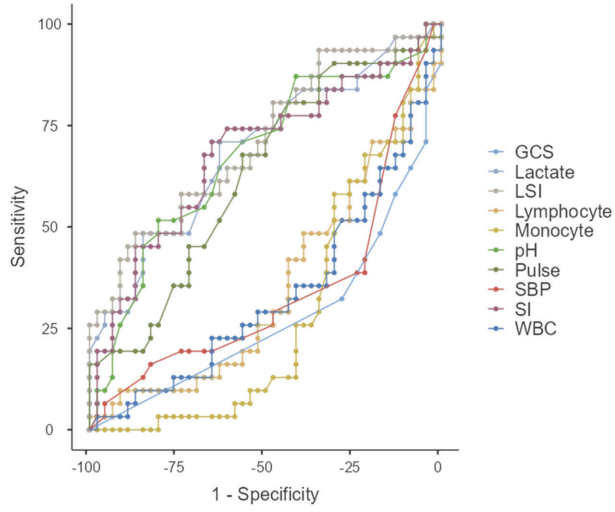

Figure 1. ROC curve analysis for predicting 28-days mortality
GCS: Glasgow coma scale, LSI: Lactate-shock index, ROC: Receiver operating characteristic, SBP: Systolic blood pressure, SI: Shock index, WBC: White blood cells

Considering the performance of lactate and SI in predicting adverse outcomes, including mortality, in septic patients, we developed LSI. Lactate shock index is a practical, low-cost index obtained by multiplying lactate and SI and can be quickly calculated at the bedside. We compared the performance of this new index with the already established and proven performance of lactate and SI in predicting mortality in septic patients (1,8,25,28,29). In ROC curve analysis, LSI showed better performance in predicting 28-day mortality than lactate and SI (AUC 0.710 vs. 0.690 and 0.681, respectively). Additionally, LSI had the highest specificity (0.870) and PPV (0.720) among the predictors of 28-day mortality. Multivariate logistic regression analysis also identified LSI as an independent predictor of 28-day mortality in septic patients.

Table 3. Cut-off points and performance characteristics of prognostic factors in predicting 28-day mortality

Parameters	AUC	95% CI	Cut-off	Sensitivity	Specificity	PPV	NPV	p-value
SBP	0.656	(0.525-0.786)	83	0.613	0.783	0.66	0.75	0.021
Pulse rate	0.628	(0.501-0.755)	105	0.677	0.565	0.51	0.72	0.049
GCS	0.723	(0.603-0.843)	14.5	0.677	0.717	0.62	0.77	0.001
WBC	0.666	(0.541-0.791)	12.325	0.645	0.674	0.57	0.74	0.014
Lymphocyte	0.647	(0.521-0.773)	1.28	0.806	0.478	0.51	0.79	0.029
Monocyte	0.713	(0.599-0.827)	0.835	0.871	0.587	0.59	0.87	0.002
pH	0.673	(0.547-0.798)	7.415	0.516	0.804	0.64	0.71	0.011
Lactate	0.690	(0.567-0.813)	2.65	0.71	0.63	0.56	0.76	0.005
SI	0.681	(0.555-0.808)	1.144	0.71	0.652	0.58	0.77	0.007
LSI	0.710	(0.591-0.83)	5.236	0.484	0.870	0.72	0.71	0.002

AUC: Area under the curve, CI: Confidence interval, GCS: Glasgow coma scale, LR: Likehood ratio, LSI: Lactate-shock index, SBP: Systolic blood pressure, SI: Shock index, WBC: White blood cells, PPV: Positive predictive value, NPV: Negative predictive value

Study Limitations

This study has several limitations. The study was conducted at a single center, and the small number of patients included constitutes the main limitation. This affects the generalizability of the study results.

Conclusion

This study demonstrates that LSI is an independent predictor of 28-day mortality in patients with sepsis. Lactate shock index showed better performance than both lactate and SI in predicting 28-day mortality. The findings suggest that LSI could be a valuable tool for early risk stratification of sepsis patients in the ED due to its superior prognostic performance. Incorporating LSI into clinical practice could facilitate the timely implementation of appropriate therapeutic interventions, thereby improving the clinical outcomes of patients with sepsis. Multicenter studies with larger patient cohorts are needed to validate the utility of LSI in different clinical settings.

Ethics

Ethics Committee Approval: This study was conducted prospectively in the ED of a tertiary hospital following approval from the Ordu University Clinical Research Ethics Committee (approval no.: 2023/41, date: 03.02.2023).

Informed Consent: Written and verbal consent was obtained from the participants.

Footnotes

Authorship Contributions

Concept: I.C., A.A., Design: I.C., A.A., A.K., Data Collection or Processing: A.K., M.T., Analysis or Interpretation: I.C., M.S.S., Literature Search: I.C., M.S.S., M.T., Writing: I.C., A.A., A.K., M.S.S., M.T.

Conflict of Interest: No conflicts of interest were declared by the authors.

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