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Neutrophil-to-lymphocyte-to-albumin ratio as a prognostic marker for mortality in sepsis and septic shock in Vietnam

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Background: Sepsis and septic shock are life-threatening global health challenges associated with high mortality rates. Early identification of high-risk patients is critical for improving outcomes. In the present study, the association between the neutrophil-to-lymphocyte-to-albumin ratio (NLAR) and mortality in septic patients was evaluated.

Methods: A retrospective study was performed at a tertiary hospital in Vietnam. Patients ≥18 years of age diagnosed with sepsis or septic shock based on the Sepsis-3 criteria were included. Exclusion criteria included recent corticosteroid use within 7 days, autoimmune diseases, hematological disorders, and active cancer within 5 years. NLAR was calculated from complete blood counts and albumin levels within the first 24 hours of intensive care unit admission. Receiver operating characteristic (ROC) curves were used to determine the predictive ability of NLAR for in-hospital mortality.

Results: The present study included 141 patients with a mean age of 72 years. Non-survivors were significantly older with higher rates of mechanical ventilation. NLAR was significantly elevated in non-survivors compared with survivors (median [interquartile range]: 0.88 [0.57–1.24] vs. 0.44 [0.28–0.77], P<0.001). In ROC analysis, the area under the curve for NLAR was 0.70 (P<0.001). Using a cutoff value of 0.56, NLAR showed a sensitivity of 77.8% and a specificity of 61.5% for predicting in-hospital mortality.

Conclusions: Elevated NLAR on admission was associated with a higher mortality rate in sepsis patients. NLAR could be used as an early prognostic marker for sepsis mortality.

Key Words: mortality; neutrophil-to-lymphocyte-to-albumin ratio; sepsis; septic shock

Original Article

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INTRODUCTION

Sepsis is a life-threatening condition and a public health challenge globally. The prevalence of sepsis and septic shock has been steadily increasing, reaching around 49 million cases of sepsis and 11 million sepsis-related deaths worldwide in 2017 [1]. Although significantly developed for the management of patients, sepsis remains a leading cause of death across the world, with a mortality rate of 34.7% in a meta-analysis in 2020 [2]. One critical principle for the management of sepsis is early and accurate detection of patients at high risk of death [3].

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Although many biomarkers, such as interleukin 6, procalcitonin, lactate, presepsin, and neutrophil-to-white blood cell ratio (NWR), have been investigated to predict 28-day mortality in patients with sepsis, future research is needed to discover useful markers for sepsis prognosis [4].

The complete blood count has been an indispensable laboratory test for the initial evaluation of sepsis and sepsis shock patients. Based on the complete blood count, the neutrophil-to-lymphocyte ratio (NLR) can be easily calculated. Although the mechanism of NLR elevation is unclear, the explanation may be based on the pathophysiology of neutrophilia and lymphopenia with systemic inflammation and stress [5]. In several studies, neutrophils were elevated in response to the increase in proinflammatory mediators and lymphocytes decreased due to sepsis-induced apoptosis in systemic inflammatory conditions similar to sepsis [6-8]. Some authors have validated the predictive value of NLR in the prognosis of sepsis severity and outcomes [9,10]. Albumin, a key protein in the human body, plays a critical role in modulating inflammation, maintaining oncotic pressure, and neutralizing oxidative stress [11]. Hypoalbuminemia was associated with short- and long-term outcomes in septic patients, including increased mortality [12,13]. Serum albumin was shown to have a predictive value in 30-day mortality in septic patients, especially in patients with low-to-medium Sequential Organ Failure Assessment (SOFA) scores [14]. In addition, biomarkers incorporating albumin, such as the lactate-to-albumin ratio, have demonstrated prognostic value in sepsis [15]. Based on the heavy burden of sepsis, septic shock, and the prognostic value of the NLR and albumin, the neutrophil-to-lymphocyte-to-albumin ratio (NLAR) was evaluated in the present study as a novel biomarker for predicting in-hospital mortality in patients with sepsis and septic shock.

KEY MESSAGES

- Elevated neutrophil-to-lymphocyte-to-albumin ratio (NLAR) was associated with significantly higher mortality rates in septic patients.
- NLAR demonstrated moderate predictive ability for in-hospital mortality, with area under the curve of 0.70 in receiver operating characteristic analysis.
- Elevated NLAR could potentially serve as an early prognostic marker for identifying high-risk septic patients.

MATERIALS AND METHODS

The Ethics Committee of the 108 Military Central Hospital approved this study (No. 488/GCN- BV) and waived the need for informed consent due to the retrospective study design.

Study Population

This was a retrospective observational study conducted at the intensive care unit (ICU) of a tertiary hospital in Vietnam, focusing on patients admitted for sepsis or septic shock between January 2021 and December 2022. Inclusion criteria included all patients >18 years of age diagnosed with sepsis or septic shock according to the Sepsis-3 criteria. Patients were excluded if they had used corticosteroids within the past 7 days, had a history of autoimmune diseases or hematological disorders, or had active cancer within the past 5 years (Figure 1).

Data Collection

Data were collected from patient medical records. Information included demographic details (age, sex), medical history (comorbidities), vital signs, source of infection, mechanical ventilator requirement, continuous renal replacement therapy, and in-hospital mortality. Laboratory test results including complete blood count (white blood cell [WBC] count, neutrophil count, lymphocyte count, red blood cell count, hemoglobin, hematocrit, platelet), biochemistry panel (urea, creatinine,

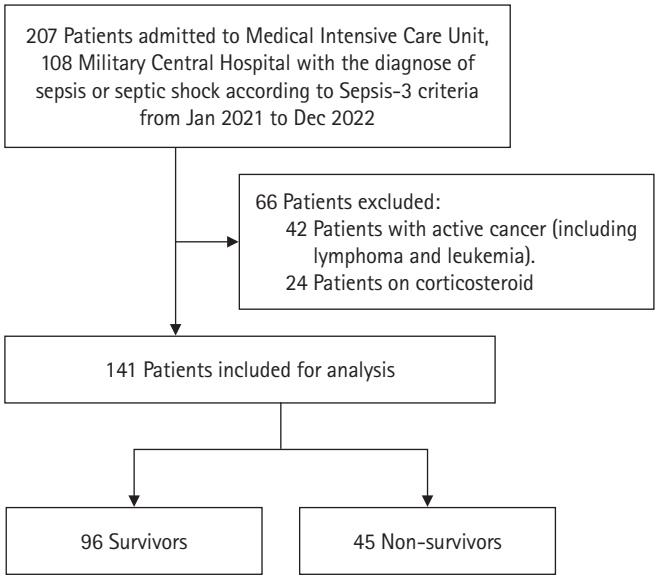

Figure 1. Flowchart of patient selection process.

aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, procalcitonin, electrolytes), lactate, and blood culture within the first 24 hours of ICU admission were collected. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The NLAR was defined as the ratio of the NLR to the albumin level. SOFA, Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, and modified Nutrition Risk in the Critically Ill (mNUTRIC) scores were calculated within 24 hours of ICU admission.

Statistical Analysis

Epi Info version 7.6.0.2, SPSS Statistics 29 (IBM Corp.) was used for data analysis. Categorical variables were described as frequencies (percentages). Continuous variables were introduced as mean±standard deviation for parametric variables or median (interquartile range) for nonparametric variables. Categorical variables were analyzed using the appropriate chi-square test or Fisher's exact test. Normally distributed data were analyzed using the Student t-test and non-normally distributed data analyzed using the Mann-Whitney U-test. The receiver operating characteristic (ROC) curve was performed to calculate the area under the curve (AUC) for NLR and NLAR to predict in-hospital mortality. The best cutoff value was chosen as the maximum value of the sum of sensitivity and specificity. Univariable and multivariable logistic regression analyses were used to confirm independent predictors of in-hospital mortality. Results were considered statistically significant when the P-value was <0.05.

RESULTS

A total of 141 patients were included in the study after screening for exclusion criteria. The study population had a mean age of 72 years, with non-survivors being significantly older (mean age, 76.8 vs. 69.8 years; P<0.01). Males represented 70.2% of the population with no significant sex difference between survivors and non-survivors. Hypertension (53.2%) and diabetes mellitus (35.5%) were common comorbidities, showing similar prevalence among survivors and non-survivors. The proportion of septic shock was 80.1%. Non-survivors had higher rates of mechanical ventilation (80.0% vs. 43.8%) and continuous renal replacement therapy (64.4% vs. 31.3%) compared with survivors. Respiratory tract infections accounted for the majority of cases at 44.7%. Pneumonia was significantly more prevalent among non-survivors than survivors (68.9% vs. 33.3%, P<0.001) and urinary tract infections were more common among survivors than non-survivors (26% vs. 2.2%). Non-survivors had significantly higher median SOFA, APACHE II, SAPS II, and mNUTRIC scores than survivors (P<0.01) (Table 1).

The median WBC and neutrophil counts in the study population were 14.7 G/L and 13.4 G/L, respectively, with similar values observed between survivors and non-survivors. However, non-survivors exhibited lower absolute lymphocyte counts than survivors (0.55 G/L vs. 0.91 G/L; P<0.001). The NLR and NLAR were notably elevated in non-survivors compared with survivors: NLR (median [interquartile range]: 23.0 [13.0–35.9] vs. 12.1 [8.4–20.4], P<0.001) and NLAR (0.88 [0.57–1.24] vs. 0.44 [0.28–0.77], P<0.001). Albumin level was lower in non-survivors than in survivors (28.3 [24.3–31.0] vs. 29.6 [26.9–32.7], P=0.01) (Table 2).

The NLR and NLAR demonstrated statistically significant predictive ability for mortality with AUCs of 0.68 and 0.70, respectively (Figure 2). The optimal cutoff value for NLR was 22.9, showing 51.1% sensitivity and 81.3% specificity. Similarly, the optimal cutoff for NLAR was 0.56 with 77.8% sensitivity and 61.5% specificity (Table 3). In multivariable logistic regression, factors significantly associated with increased mortality included the requirement for mechanical ventilation, higher SOFA score, and elevated NLAR. Mechanical ventilation was associated with a 4.23-fold increase in mortality risk. In addition, each point increase in SOFA score and NLAR was associated with substantial increases in mortality risk (1.16-fold and 3.17-fold, respectively) (Table 4).

DISCUSSION

Sepsis is a complex infectious condition with high prevalence and mortality [1]. In the present study, non-survivors had significantly higher NLR and NLAR compared with survivors of sepsis. After adjusting for potential covariates, NLAR maintained its correlation with in-hospital mortality (odds ratio [OR], 3.17; 95% CI, 1.58–6.36). The AUCs in ROC curve analysis for NLR and NLAR were 0.68 (95% CI, 0.60–0.76) and 0.70 (95% CI, 0.62–0.78), respectively. With a cutoff of 0.56, NLAR had a sensitivity of 77.8% and specificity of 61.5% for in-hospital mortality. To the best of our knowledge, this was the first study in which NLAR was investigated as a novel predictor of mortality in patients with sepsis.

Patients who suffer from sepsis have to take into account the short-term high mortality rate and long-term sequelae. In a

Table 1. Baseline characteristics of the study population

Variable	Total (n=141)	Survivor (n=96)	Non-survivor (n=45)	P-value
Age (yr)	72±14	70±14	77±13	0.006
Male	99 (70.2)	62 (64.6)	34 (82.2)	0.033
Comorbidity				
Hypertension	75 (53.2)	48 (50.0)	27 (60.0)	0.267
Diabetes mellitus	50 (35.5)	32 (33.3)	18 (40.0)	0.440
Stroke	28 (19.9)	17 (17.7)	11 (24.4)	0.350
Chronic coronary disease	8 (5.7)	5 (5.2)	3 (6.7)	0.727
Heart failure	12 (8.5)	5 (5.2)	7 (15.6)	0.040
COPD	6 (4.3)	2 (2.1)	4 (8.9)	0.062
Liver cirrhosis	3 (2.1)	1 (1.0)	2 (4.4)	0.192
Chronic kidney disease	19 (13.5)	8 (8.3)	11 (24.4)	0.009
Clinical features of severity				
Septic shock	113 (80.1)	73 (76.0)	23 (88.9)	0.075
Positive blood culture	48 (34.0)	33 (34.4)	15 (34.1)	0.974
Mechanical ventilation	78 (55.3)	42 (43.8)	36 (80.0)	<0.001
CRRT	59 (41.8)	30 (31.3)	29 (64.4)	<0.001
Site of infection				
Pulmonary	63 (44.7)	32 (33.3)	31 (68.9)	<0.001
Gastrointestinal	28 (19.9)	22 (22.9)	6 (13.3)	0.184
Urinary	26 (18.4)	25 (26.0)	1 (2.2)	0.001
Skin and soft tissue	7 (5.0)	4 (4.2)	3 (6.7)	0.524
Hemodynamics				
SBP (mm Hg)	107 (94–120)	110 (95–120)	100 (93–120)	0.875
DBP (mm Hg)	60 (50–70)	60 (50–70)	60 (50–70)	0.632
MAP (mm Hg)	77 (70–86)	77 (69–87)	73 (70–83)	0.832
HR (bpm)	110 (95–129)	110 (90–125)	118 (100–130)	0.296
Severity score				
SOFA	10 (8–13)	9 (7–12)	12 (10–14)	<0.001
APACHE II	20 (16–24)	19 (15–23)	22 (20–24)	0.003
SAPS II	45 (37–57)	42 (33–52)	52 (43–64)	<0.001
mNUTRIC	5 (4–6)	5 (3–6)	6 (6–7)	<0.001

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
COPD: chronic obstructive pulmonary disease; CRRT: continuous renal replacement therapy; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; mNUTRIC: modified Nutrition Risk in the Critically Ill.

nationwide population-based study from Taiwan, an increased all-cause mortality in sepsis survivors was observed compared with the overall population, which persisted for up to 5 years [16]. In developing countries, a good prognostication tool can help healthcare providers allocate resources more quickly to sicker patients, leading to better patient outcomes and reducing post-sepsis complications. The SOFA score has been used both as a diagnostic tool and a prognostic tool for sepsis. The SOFA score was validated in many studies with different populations, including the Vietnamese population [17,18]. However, calculation of the score includes six complicated parameters that require results from arterial blood gas. Thus, NLR and NLAR could be simpler alternatives for predicting sepsis prognosis, particularly in resource-limited settings.

NLR has been suggested a novel marker that reflects two key immune systems including innate immunity and adaptive immunity [19]. NLR increases in various situations where physiological stress rises, including sepsis [20]. In the hyperinflammatory phase, a surge in neutrophils occurs, driven by pro-inflammatory mediators as a process of the innate immunity, leading to an elevated NLR [21]. Dysfunction of the adaptive immunity, represented by significant lymphopenia, is a

Table 2. Laboratory features of the study population

Variable	Total (n=141)	Survivor (n=96)	Non-survivor (n=45)	P-value
WBC count (G/L)	14.7 (9.1–20.8)	14.6 (8.6–20.8)	15.2 (11.0–20.5)	0.739
Neutrophil (G/L)	13.4 (8.0–18.9)	13.3 (7.3–18.9)	14.4 (9.3–18.6)	0.957
Lymphocyte (G/L)	0.78 (0.45–1.26)	0.91 (0.53–1.33)	0.55 (0.30–0.79)	<0.001
NLR	15.2 (9.0–25.5)	12.1 (8.4–20.4)	23.0 (13.0–35.9)	<0.001
NLAR	0.57 (0.31–0.93)	0.44 (0.28–0.77)	0.88 (0.57–1.24)	<0.001
RBC count (T/L)	4.0 (3.3–4.5)	4.3 (3.5–4.7)	3.6 (3.1–4.0)	<0.001
Hemoglobin (g/L)	118 (96–132)	124 (106–136)	101 (93–116)	<0.001
HCT (%)	36.5 (30.2–40.7)	38.2 (32.6–41.8)	31.9 (27.2–37.0)	<0.001
Platelet count (G/L)	199 (113–270)	198 (123–260)	212 (86–303)	0.915
Urea (mmol/L)	13.1 (9.5–19.9)	12.6 (9.0–17.9)	15.0 (11.7–23.1)	0.194
Creatinine (μmol/L)	173 (113–270)	168 (109–255)	187 (137–279)	0.619
AST (U/L)	49 (30–173)	49 (30–160)	56 (37–250)	0.361
ALT (U/L)	41 (20–121)	41 (20–115)	47 (22–168)	0.452
Total bilirubin (μmol/L)	19.4 (12.1–30.6)	18.4 (12.1–30.3)	22.0 (12.1–31.7)	0.569
Albumin (g/L)	28.9 (26.0–32.0)	29.6 (26.9–32.7)	28.3 (24.3–31.0)	0.010
Procalcitonin (ng/mL)	20.7 (4.8–98.9)	36.9 (5.7–114.6)	11.8 (4.4–38.3)	0.022
Sodium (mmol/L)	136 (132–140)	136 (132–140)	136 (132–140)	0.614
Potassium (mmol/L)	3.8 (3.3–4.5)	3.7 (3.3–4.2)	4.2 (3.6–4.7)	0.115
Bicarbonate (mmol/L)	18.9 (15.2–22.5)	19.2 (15.6–22.4)	17.8 (15.0–22.6)	0.598
Lactate (mmol/L)	3.5 (2.1–6.1)	3.1 (1.9–5.4)	4.0 (2.8–7.1)	0.020

Values are presented as median (interquartile range).
WBC: white blood cell; NLR: neutrophil-lymphocyte ratio; NLAR: neutrophil-to-lymphocyte-to-albumin ratio; RBC: red blood cell; HCT: hematocrit; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

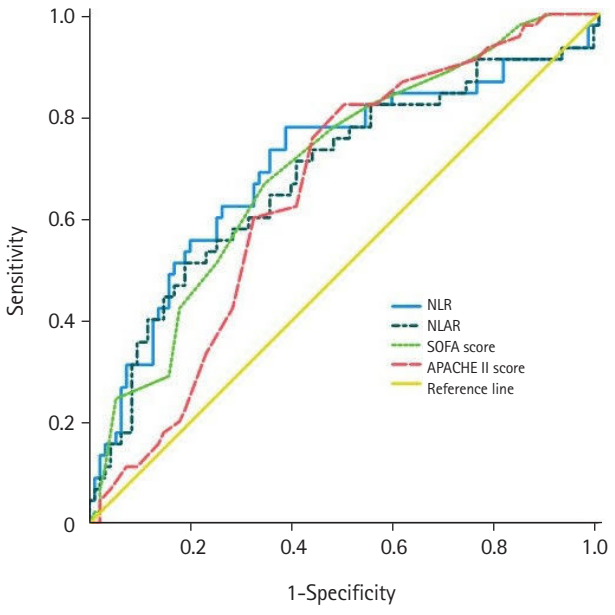

Figure 2. Receiver operating characteristic curves of the neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-lymphocyte-to-albumin ratio (NLAR), and severity scores as predictors for in-hospital mortality. SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

hallmark of sepsis [7]. A marked increase in lymphocyte apoptosis was observed in septic shock patients when compared with healthy controls [8]. As sepsis progresses and the immune system becomes exhausted, lymphopenia may worsen, further contributing to a high NLR. However, in the later stages of immunoparalysis, both neutrophil production and function may be impaired, potentially leading to a decrease in NLR. This highlights the complex relationship between NLR and the different immune phases of sepsis. Although in the present study NLR was measured at a single time point after admission and cannot fully capture these dynamic changes, it provides valuable insights into the prognostic value of NLR at the initial presentation of sepsis.

NLR was significantly higher in non-survivors compared with survivors of sepsis in a 2019 meta-analysis [9]. However, a significant heterogeneity existed between studies. We hypothesized that incorporating albumin into NLR could enhance its prognostic value. Albumin, which accounts for more than half of human plasma proteins, plays a vital role in the body. Albumin is essential during the inflammatory process for expanding volume, transporting important substances, and protecting from oxidative stress [11]. Hypoalbuminemia in sepsis

Table 3. ROC analysis of NLR, NLAR, SOFA score, and APACHE II score as predictors for in-hospital mortality

Variable	Cutoff	Sensitivity (%)	Specificity (%)	AUC	95% CI	P-value
NLR	22.9	51.1	81.3	0.68	0.60–0.76	<0.001
NLAR	0.56	77.8	61.5	0.70	0.62–0.78	<0.001
SOFA score	10	65.6	66.7	0.70	0.62–0.78	<0.001
APACHE II score	18	50.0	82.2	0.65	0.57–0.73	0.001

ROC: receiver operating characteristic; NLR: neutrophil-lymphocyte ratio; NLAR: neutrophil-to-lymphocyte-to-albumin ratio; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; AUC: area under the curve.

Table 4. Multivariable logistic regression of NLAR and in-hospital mortality

Variable	In-hospital mortality		
	OR	95% CI	P-value
Age	1.03	0.99–1.06	0.134
History of heart failure	1.76	0.44–7.01	0.422
Mechanical ventilation	4.23	1.44–12.44	0.009
SOFA score	1.16	1.01–1.33	0.039
NLAR	3.17	1.59–6.36	0.001

NLAR: neutrophil-to-lymphocyte-to-albumin ratio; OR: odds ratio; SOFA: Sequential Organ Failure Assessment.

can reflect the severity of inflammation, nutritional status, and the interplay between liver function and gut microbiota, all of which are associated with worse outcomes [12,22,23]. By combining NLR with albumin, NLAR may offer a more comprehensive assessment of the patient's physiological state and immune response. Although both NLR and NLAR can be elevated in various inflammatory conditions, the potential to reflect both immune dysregulation and nutritional status renders NLAR a promising prognostic marker in sepsis. Compared with other similar indices, such as the delta neutrophil index, which focuses solely on neutrophil changes, and the neutrophil percentage-to-albumin ratio (NPAR), which does not include lymphocyte counts, NLAR may offer a broader perspective on sepsis pathophysiology [24,25].

In a study in China, an association was found between elevated NPAR and mortality in sepsis patients [25]. Although both NLAR and NPAR incorporate neutrophils and albumin, NLAR also includes lymphocyte count which reflects the adaptive immunity and is significantly affected in sepsis. Thus, the inclusion of lymphocytes in NLAR could provide a more comprehensive overview of the host's immune response to infection.

In infection, neutrophils are the first line of defense because they are rapidly mobilized from the bone marrow and migrate to the infection site, leading to neutrophilia. However, in sepsis, spontaneous apoptosis of neutrophils was found inhibited and the lifespan of neutrophils was extended. In addition, all four stages of neutrophil margination were found affected during sepsis [21]. In the present study, a difference was not observed in neutrophil count between survivors and non-survivors (13.3 G/L vs. 14.4 G/L, P=0.957). Conversely, extensive lymphocyte apoptosis and T-cell anergy were described in sepsis [8]. These processes lead to lymphopenia and sepsis-induced immunosuppression. In the present study, a significantly lower lymphocyte count was observed in non-survivors (0.55 G/L vs. 0.91 G/L, P<0.001). In addition, the albumin level in non-survivors was lower than in survivors (28.3 g/L vs. 29.6 g/L, P=0.010). NLAR incorporates three variables, neutrophils, lymphocytes, and albumin, representing different aspects of sepsis pathophysiology. Despite the similar AUC for NLAR compared with NLR, NLAR could more adequately capture the complexity of sepsis pathogenesis.

The present study had several limitations. First, this was a single-center, retrospective study inherently prone to biases. Second, the study population was small and the baseline characteristics do not represent the overall population of Vietnam. Third, although many variables were included in the analyses, possible confounders may still exist that can alter the relationship between independent and dependent variables, possibly leading to bias. Finally, the NLAR was recorded only on admission and changes in NLAR could not be monitored during hospitalization. The results of the present study should be validated in future studies including larger, multicenter cohorts and the dynamic changes in NLAR explored during the course of sepsis treatment.

In conclusion, elevated NLAR level on admission was associated with poor outcomes in patients with sepsis. Due to the simplicity of NLAR and ability to reflect complex pathogenesis, NLAR can be considered a rapid and effective tool for sepsis prognostication. However, further research is needed to confirm the robustness of NLAR in predicting sepsis severity.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: NVVT, PDH. Methodology: NVVT, PDH. Formal analysis: NVVT. Data curation: NVVT. Visualization: NVVT. Project administration: PDH. Writing - original draft: NVVT, LTL, NTTV. Writing - review & editing: PDH. All authors read and agreed to the published version of the manuscript.

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