

# Comparing the Prognostic Value of Lactate to the Neutrophil to Lymphocyte Ratio Among Sepsis Patients: A Prospective Cohort Study

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**Background:** Lactate has long been recognized as a key prognostic biomarker in sepsis. Similarly, the prognostic role of the neutrophil-to-lymphocyte ratio (NLR) has been investigated in various conditions, including sepsis. Previous studies have explored the optimal NLR cutoff to differentiate sepsis survivors from nonsurvivors, predict bacteremia, diagnose sepsis, and assess mortality. This study compares the prognostic value of lactate and NLR in septic patients.

**Methods:** This prospective cohort study included 874 adult septic or septic shock patients presenting to a tertiary care center's Emergency Department between September 2018 and February 2021. The primary outcome was to compare the prognostic value of NLR and lactate regarding in-hospital mortality. Secondary outcomes compared their prognostic value in different septic subgroups.

**Results:** Stepwise logistic regression showed NLR was not associated with in-hospital mortality (OR=1.003, p=0.544), while lactate was significantly associated with in-hospital mortality (OR=1.188, p<0.0001). There was no significant difference in the AUCs of NLR and lactate (0.552 vs 0.591, p=0.22). Lactate outperformed NLR in patients with albumin <30, those <65 years old, and those with sepsis from a urinary tract infection. No significant differences were found in AUCs between lactate and NLR in patients with septic shock, Lactate<2, Lactate≥2, diabetes, malignancy, chronic kidney diseases, other sources of infection, albumin ≥30 and age ≥ 65.

**Conclusion:** In this study, lactate but not NLR was associated with in-hospital mortality. There was no significant difference in the AUCs between lactate and NLR among sepsis patients and among most of the subgroups. However, lactate outperformed NLR in the following subgroups: albumin<30 g/L, patients <65 years old and patients with sepsis due to a urinary tract infection. Our results advocate for the continued use of serum lactate rather than NLR, despite its limitations, as a predictor of mortality among septic patients and the different subgroups in this study.

**Keywords:** sepsis, septic shock, lactate, mortality, neutrophil to lymphocyte ratio, prognosis

## Introduction

Sepsis is a life-threatening condition characterized by a dysregulated host response to an infection, resulting in widespread inflammation and organ dysfunction. It is a major cause of morbidity and mortality worldwide, with high mortality rates, especially in severe cases or septic shock.<sup>1-3</sup> During sepsis, the immune system is activated, with lymphocytes and neutrophils playing central roles in the body's defense against pathogens. As a result, neutrophils are rapidly recruited to the site of infection, leading to neutrophilia, which can contribute to tissue damage and exacerbate organ failure.<sup>4</sup>

The neutrophil-to-lymphocyte ratio has emerged as a promising prognostic marker in various clinical conditions, including appendicitis,<sup>5</sup> cardiovascular diseases,<sup>6,7</sup> and malignancies.<sup>8-10</sup> In sepsis, alterations in the NLR reflect the balance between the pro-inflammatory and anti-inflammatory responses, which can be useful for predicting disease

severity and patient outcomes. Indeed, higher NLR values generally correlate with worse prognosis and increased mortality in septic patients. A previous study conducted at our institution found the optimal NLR cut off point that discriminates between survivors and non-survivors in sepsis was 14.20. However, it did not show any significant association with mortality after controlling for confounders.<sup>11</sup> Other studies have shown the NLR to be useful in predicting bacteremia, diagnosing sepsis,<sup>12–15</sup> predicting mortality<sup>16–18</sup> and monitoring response to therapy.<sup>19,20</sup> The evidence thus far supports the use of NLR as a reliable and valuable biomarker for predicting the severity and outcomes of sepsis, with higher values correlating with worse prognosis and increased mortality.

Sepsis and septic shock lead to impaired cellular oxidative phosphorylation due to hypoxia causing elevated lactate levels.<sup>21</sup> In turns, elevated lactate levels reflect tissue hypoperfusion and organ dysfunction. For this reason, lactate has become widely used as a biomarker in diagnosing and risk stratifying patients with sepsis.<sup>22,23</sup>

Given the potential value of both NLR and lactate as prognostic markers, the aim of this study is to compare their ability to predict in-hospital mortality in patients with sepsis and septic shock. By examining these two biomarkers, we seek to better understand their relative prognostic value in guiding clinical decision-making for septic patients.

## Methods

### Setting and Sample Selection

This is a prospective cohort study including adult septic or septic shock patients presenting to the Emergency Department of a tertiary care center, the American University of Beirut Medical Center, between September 2018 and February 2021. Patients who met the diagnosis of sepsis or septic shock were included. Patients below 18 years of age, or pregnant, or presenting with cardiac arrest or trauma or neutropenic were excluded. Sepsis was defined according to the sepsis-3 guidelines<sup>1</sup> as a dysregulated host response to an infection leading to life-threatening organ dysfunction. Organ dysfunction was defined as a variation in total SOFA score  $\geq 2$  points because of an infection.<sup>1</sup> Septic shock was defined as having a lactate greater than or equal to 2mmol/L despite adequate fluid resuscitation or a need for vasopressors to maintain the mean arterial pressure greater or equal to 65mmHg.<sup>1</sup>

### Variables and Outcomes

Patient variables were collected from patient charts using the Electronic Health Record System. The following variables were collected from septic patients: past medical history, vital signs upon arrival to the ED, infection site, blood work (Complete blood count, BUN, Creatinine, Electrolytes, Bilirubin, Lactate, Liver Enzymes, blood cultures, urine analysis and urine cultures). In addition, neutrophil to lymphocyte ratio (NLR), use of vasopressors, antibiotics, steroids as well as patient disposition were retrieved from the medical record.

The primary outcome was to compare the prognostic value of the NLR to lactate with regard to in-hospital mortality. The secondary outcome was to compare the prognostic value of the NLR to lactate in the different septic patient subgroups (Lactate < 2 mmol/L; Lactate  $\geq 2$  mmol/L; diabetes; malignancy; chronic kidney disease; age; source of infection; albumin < 30 g/L; albumin  $\geq 30$  g/L; septic shock).

### Patient Recruitment Process

Patients were recruited by research assistants who monitored the ED dashboard 24 hours a day 7 days a week. Patients who met the inclusion criteria were approached by the research assistants to obtain informed consent. The study was approved by the Institutional Ethics Review Board (BIO-2018-0133).

### Statistical Analysis

Patients were divided into two groups: survivors and non-survivors. In the univariate analysis including all septic patients, continuous variables were presented as mean  $\pm$  standard deviation and categorical variables were presented as absolute numbers with percentages. In the bivariate analysis, Pearson's chi-square test and Student's *t*-test were used to compare the independent categorical or continuous variables between survivors and non-survivors. The significance level was predetermined at an  $\alpha=0.05$ . The magnitude of the relationship between the predictor variables and in-hospital mortality was

determined by calculating the odds ratios and their associated 95% confidence intervals. Stepwise logistic regression including all statistically and clinically significant variables was performed to find the best model that fits the data and that explains the association between mortality and all predictor variables. The variables that were entered in the model included: age; gender; chronic kidney disease; hypertension; dyslipidemia; coronary artery disease; atrial fibrillation; malignancy; history of stroke; history of transient ischemic attack (TIA); diabetes mellitus; chronic obstructive pulmonary disease; systolic blood pressure upon presentation; heart rate upon presentation; oxygen saturation upon presentation; respiratory rate upon presentation; hemoglobin; platelets; lactate at presentation; albumin; BUN; creatinine; bicarbonate; magnesium; calcium.

The prognostic value of both NLR and lactate was determined using receiver operating characteristic curves from which we obtained their AUCs.

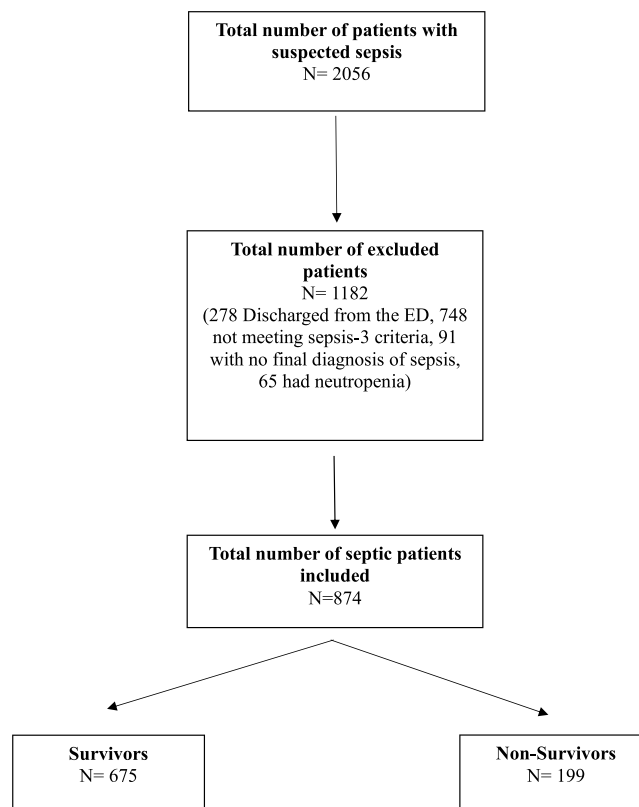
## Sample Size

The number of patients included in this study was obtained from a sample we collected previously to assess the prognostic value of the lactate to albumin ratio in septic patients. On average, 500 septic patients present to the Emergency Department of our tertiary care center annually. A total of 939 septic patients were recruited (between September 2018 and February 2021) from which 65 patients were excluded due to neutropenia.

## Results

A total of 874 septic patients were included in this study. A detailed breakdown of their demographic and clinical characteristics is shown in [Figure 1](#).

22.77% of the patients died during their hospital stay. The average age of the patients was  $73.45 \pm 15.01$  years and 58.9% were males. The most common medical comorbidities were hypertension (65.4%), diabetes (42.4%), dyslipidemia (41.8%) and malignancy (36.2%). The percentage of males was significantly higher in the non-survivor group (69.8% vs 55.7%,  $p$ -value<0.0001). There were no statistically significant differences in age or medical comorbidities between both groups ([Table 1](#)).



**Figure 1** Demographic and clinical characteristics of 874 septic patients.

**Table 1** Baseline Characteristics of the Patients Presenting to the Emergency Department with Sepsis or Septic Shock

	<b>Total (N=874)</b> <b>Mean±SD N(%)</b>	<b>Survivors (N=675)</b> <b>Mean±SD N(%)</b>	<b>Non Survivors (N=199)</b> <b>Mean±SD N(%)</b>	<b>P-value</b>
Age (years)	73.45±15.01	73.30 ±15.36	73.96 ±14.04	0.59
Male	515 (58.9)	376 (55.7)	139 (69.8)	<0.0001
Smoking	382 (43.7)	301 (44.6)	81 (40.7)	0.33
Chronic kidney disease	214 (24.5)	164 (24.3)	50 (25.1)	0.81
Hypertension	572 (65.4)	442 (65.5)	130 (65.3)	0.97
Dyslipidemia	365 (41.8)	287 (42.5)	78 (39.2)	0.40
Atrial fibrillation	179 (20.5)	140 (20.7)	39 (19.6)	0.73
Coronary Artery Disease	303 (34.7)	232 (34.4)	71 (35.7)	0.73
Congestive Heart Failure	221 (25.3)	175 (25.9)	46 (23.1)	0.42
Malignancy	316 (36.2)	235 (34.8)	81 (40.7)	0.13
History of stroke	71 (8.1)	55 (8.1)	16 (8.0)	0.96
History of TIA	11 (1.3)	9 (1.3)	2 (1.0)	0.72
History of Vascular Disease	83 (9.5)	70 (10.4)	13 (6.5)	0.11
Diabetes Mellitus	371 (42.4)	280 (41.5)	91 (45.7)	0.29
Chronic Obstructive Pulmonary Disease	150 (17.2)	124 (18.4)	26 (13.1)	0.08

Systolic blood pressure and oxygen saturation at presentation were significantly higher in the survivor group (116.49 mmHg vs 121.85 mmHg,  $p=0.01$  and 88.48% vs 95.02%,  $p\text{-value}<0.0001$ ). There was no significant difference between both groups with regards to other vital signs (Table 2). The mean lactate level and NLR of the whole population was  $2.95\pm2.27$  mmol/L and  $16.84\pm20.28$ . The NLR and lactate level were significantly higher in the non-survivor group ( $20.53\pm25.18$  vs  $15.77\pm18.52$ ,  $p=0.02$  and  $3.79\pm3.45$  mmol/L vs  $2.70\pm1.71$  mmol/L,  $p\text{-value}<0.0001$ ) (Table 2).

**Table 2** Vital Signs and Laboratory Parameters of Patients in the Emergency Department with Sepsis/Septic Shock

	<b>Total (N=874)</b> <b>Mean±SD</b>	<b>Survivors (N=675)</b> <b>Mean±SD</b>	<b>Non Survivors (N=199)</b> <b>Mean±SD</b>	<b>P value</b>
SBP upon presentation (mmHg)	120.63±26.68	121.85±26.93	116.49±25.41	0.01
DBP upon presentation (mmHg)	67.88±15.70	68.06±15.73	67.27±15.59	0.54
HR upon presentation (Beats/minute)	99.19±25.28	98.34±25.35	102.05±24.89	0.07
O2 saturation upon presentation (%)	93.55±9.52	95.02±7.77	88.48 ± 12.77	<0.0001
Temperature upon presentation (C)	37.39±1.70	37.43±1.75	37.24 ±1.52	0.17
Respiratory rate upon presentation (Breaths/minute)	21.67±7.82	21.17±7.55	23.36±8.47	0.001
WBC (cu.mm)	12486.80±9012.47	12,243.70±7204.38	13,310.19±7204.38	0.28
Absolute Neutrophil Count (cu.mm)	10249.02±7410.61	10,106.92±6468.99	10,730.99±9969	0.41

(Continued)

**Table 2** (Continued).

	<b>Total (N=874) Mean±SD</b>	<b>Survivors (N=675) Mean±SD</b>	<b>Non Survivors (N=199) Mean±SD</b>	<b>P value</b>
Lymphocyte count (cu.mm)	1230.65±2766.68	1196.03±1385.73	1349.07±5231.15	0.69
Hematocrit (%)	35.34±7.08	35.56± 7.10	34.59±6.97	0.09
Platelets (cu.mm)	231648.47±133861.34	236965.28±131523.37	213614.07±140350.23	0.032
Lactate (mmol/L)	2.95±2.27	2.70±1.71	3.79±3.45	<0.0001
CRP (mg/L)	130.27±103.22	118.33±101.12	157.31± 103.13	<0.0001
Albumin (g/L)	33.15±6.89	34.22± 6.51	29.43±6.88	<0.0001
Neutrophil to lymphocyte ratio	16.84±20.28	15.77±18.52	20.53±25.18	0.02
Procalcitonin (ng/mL)	5.47±16.09	5.61±14.95	5.16±18.34	0.78
Glucose (mg/dL)	165.83±92.95	167.05±96.62	161.94± 80.25	0.49
BUN (mg/dL)	34.20±25.13	31.87±23.35	42.13±29.07	<0.0001
Creatinine (mg/dL)	1.56±1.35	1.52±1.41	1.70±1.13	0.11
Bicarbonate (mmol/L)	23.76±9.56	24.42±10.03	21.60±7.44	<0.0001
Calcium (mg/dL)	8.90±0.89	8.99±0.90	8.58±0.77	<0.0001
INR	1.52±1.35	1.40±0.73	1.81±2.24	0.03

**Table 3** Outcomes of Patients Presenting to the Emergency Department with Sepsis or Septic Shock

	<b>Total (N=874) Mean±SD N(%)</b>	<b>Survivors (N=675) Mean±SD N(%)</b>	<b>Non Survivors (N=199) Mean±SD N(%)</b>	<b>P value</b>
Developed septic shock	214 (24.5)	105 (15.6)	109 (54.8)	<0.0001
ICU admission	369 (42.2)	223 (33.0)	146 (73.4)	<0.0001
Required mechanical ventilation	133 (15.2)	63 (9.3)	70 (35.2)	<0.0001
Length of hospital stay (days)	10.36±11.95	8.97±11.07	15.10±13.55	<0.0001

The total number of patients who developed septic shock was 214. The percentages of patients who developed septic shock, required ICU admission or mechanical ventilation during their hospital stay were significantly higher in the non-survivor group (54.8% vs 15.6%; 73.4% vs 33%; 35.25 vs 9.3% respectively with a p-value<0.0001 for all). The average length of hospital stay was significantly higher in the non-survivor group (15.10±13.55 days vs 8.97±11.07 days with a p-value<0.0001) (Table 3).

In the stepwise logistic regression, NLR was not associated with in-hospital mortality (OR=1.003, 95% CI=0.994–1.012, p=0.544), whereas lactate was associated with hospital mortality (OR=1.188, 95% CI=1.086–1.299, p<0.0001) (Table 4).

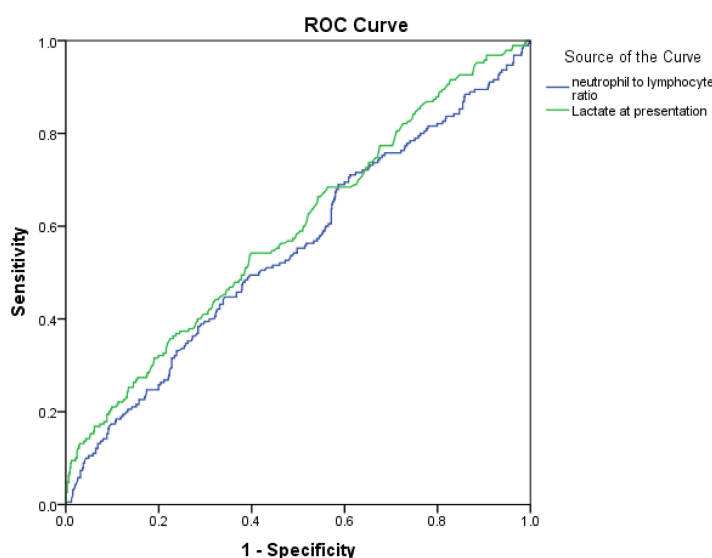
The AUC value of the NLR ratio was 0.552 with a 95% CI=0.504–0.599, whereas that of lactate was 0.591 with a 95% CI=0.544–0.637. There was no significant difference in the AUC between both variables with a p-value=0.22 (Figure 2).

**Table 4** Stepwise Logistic Regression for Mortality

	OR	95% C.I.		P-value
		Lower	Upper	
<b>Neutrophil to lymphocyte ratio</b>	1.003	0.994	1.012	0.544
<b>Lactate at presentation</b>	1.188	1.086	1.299	<0.0001

Variables included in the model:  
**Imposed:** Neutrophil to lymphocyte ratio  
**Stepwise:** age; gender; chronic kidney disease; hypertension; dyslipidemia; coronary artery disease; atrial fibrillation; malignancy history of stroke; history of TIA; diabetes mellitus; chronic obstructive pulmonary disease; SBP upon presentation; HR upon presentation; O<sub>2</sub> saturation upon presentation; respiratory rate upon presentation; hemoglobin; platelets; lactate at presentation; albumin; bun; creatinine; bicarbonate; magnesium; calcium.

Among septic shock patients there was no difference in the AUC values of the NLR and lactate (0.50 95% CI 0.42–0.58 vs 0.49 95% CI 0.42–0.57,  $p=0.83$ ). Lactate outperformed NLR in the following subgroups: albumin<30 g/L, patients less than 65 years of age and patients with sepsis due to a urinary tract infection. There was no statistically



Test Result Variable(s)	AUC	95% CI		P-value (AUCs)
		Lower Bound	Upper Bound	
Neutrophil to lymphocyte ratio	0.552	0.504	0.599	0.22
Lactate at presentation	0.591	0.544	0.637	

**Figure 2** Receiver Operating Characteristic (ROC) curve showing the Area Under the Curve (AUC) values for NLR ratio (AUC=0.552, 95% CI=0.504–0.599) and lactate levels (AUC=0.591, 95% CI=0.544–0.637). There was no significant difference between the two variables ( $p=0.22$ ).

**Table 5** Comparison of the AUCs of Lactate and NLR in Among the Different Sepsis Subgroups

	AUC for in-Hospital Mortality (95% CI)			N/L Ratio Cut-off Threshold				
	Lactate	N/L ratio	p	Cut-off Threshold	Sensitivity	Specificity	PPV	NPV
<b>Overall</b>	0.59 (0.55–0.64)	0.55(0.50–0.60)	0.22	14.15	0.45	0.65	0.27	0.80
<b>Septic shock</b>	0.49(0.42–0.57)	0.50(0.42–0.58)	0.83	17.98	0.40	0.68	0.57	0.53
<b>Lactate levels</b>								
Lactate < 2 mmol/L	0.57(0.50–0.65)	0.54(0.46–0.63)	0.66	14.52	0.43	0.71	0.25	0.85
Lactate ≥ 2 mmol/L	0.59(0.53–0.65)	0.55(0.49–0.60)	0.29	8.07	0.74	0.38	0.28	0.81
<b>Albumin levels</b>								
Albumin < 30 g/L	0.65(0.58–0.72)	0.53(0.45–0.61)	0.03	8.03	0.79	0.32	0.38	0.75
Albumin ≥30 g/L	0.52(0.46–0.59)	0.55(0.48–0.61)	0.55	14.20	0.43	0.68	0.22	0.86
<b>Patient subgroups</b>								
Chronic kidney disease	0.59(0.50–0.69)	0.50(0.41–0.60)	0.16	12.46	0.36	0.58	0.27	0.79
Malignancy	0.61(0.54–0.69)	0.55(0.47–0.62)	0.24	30.61	0.25	0.85	0.36	0.77
<b>Infection site</b>								
Lung	0.60(0.55–0.65)	0.58(0.52–0.63)	0.60	14.51	0.42	0.74	0.43	0.73
Urine	0.70(0.62–0.77)	0.55(0.47–0.63)	0.01	30.92	0.22	0.90	0.35	0.82
Intravascular catheter	0.98(0.92–1.00)	0.71(0.33–1.00)	0.19	28.15	0.60	0.89	0.75	0.80
Gastrointestinal	0.65(0.48–0.83)	0.50(0.32–0.68)	0.11	31.65	0.25	0.86	0.27	0.85
Skin	0.51(0.19–0.84)	0.46(0.07–0.85)	0.89	122.13	0.25	1.00	1.0	0.93
Heart	0.79(0.64–0.94)	0.39(0.17–0.61)	0.27	42.26	0.10	0.97	0.50	0.80
Gall bladder	0.50(0.23–0.76)	0.63(0.35–0.90)	0.41	23.97	0.50	0.85	0.44	0.76
Surgical site	–	–	–	–	–	–	–	–
Bone	–	–	–	–	–	–	–	–
Peritoneum	0.67(0.10–1.00)	0.50(0.00–1.00)	0.87	6.79	0.67	0.70	0.40	0.87
<b>Diabetes Mellitus</b>								
Yes	0.58(0.51–0.65)	0.56(0.49–0.63)	0.66	15.84	0.41	0.72	0.32	0.79
No	0.60(0.55–0.66)	0.54(0.48–0.61)	0.19	14.35	0.43	0.66	0.26	0.81
<b>Age</b>								
<65	0.63(0.53–0.72)	0.49(0.39–0.59)	0.08	19.88	0.31	0.77	0.26	0.82
>65	0.58(0.53–0.63)	0.60(0.52–0.62)	0.81	14.20	0.48	0.66	0.30	0.81

significant difference in the AUCs between lactate and NLR in patients with Lactate<2 mmol/L, Lactate≥2 mmol/L, diabetes, malignancy, chronic kidney diseases, other sources of infection albumin ≥30 g/L and age ≥ 65 years (Table 5).

## Discussion

The results of this prospective study showed that there was no difference in the AUCs of NLR and lactate in sepsis patients. This was also seen among septic shock patients. Lactate outperformed NLR in the following subgroups: albumin<30 g/L, patients less than 65 years of age and patients with sepsis due to a urinary tract infection. Furthermore, NLR was not associated with in-hospital mortality (OR=1.003, 95% CI=0.994–1.012, p=0.544), whereas lactate was (OR=1.188, 95% CI=1.086–1.299, p<0.0001).

Several studies investigated the prognostic role of biomarkers such as lactate, procalcitonin and c-reactive protein (CRP)<sup>24,25</sup> as well as combinations of biomarkers<sup>20</sup> and novel ones such as serum metabolomes in septic patients.<sup>26–28</sup> Lactate remains the most validated and most commonly used biomarker. A single serum lactate is associated with increased mortality and organ failure among patients with sepsis or septic shock.<sup>23,29–31</sup> However, a single serum lactate has its limitations; lactate levels can be elevated by the use of several commonly used medications in the ED setting such as metformin, albuterol or epinephrine.<sup>32,33</sup> Furthermore, impaired lactate clearance can be seen in patients with liver and kidney disease.<sup>34</sup> Lactate can also be elevated in patients with hematologic malignancies with no apparent infection.<sup>35–37</sup> These limit the prognostic ability of lactate prompting research on other prognostic markers in sepsis. One such



biomarker is the neutrophil-to-lymphocyte ratio. Inflammatory states such as sepsis are associated with an increase in absolute neutrophil count as well as a decrease in absolute lymphocyte count. These trends correlate with disease progression.<sup>38,39</sup> Hwang et al showed that among septic or septic shock patients, initial NLR values measured at ED admission at the lowest quintile (adjusted HR: 2.25, 95% CI, 1.63–3.11) or the highest quintile (adjusted HR: 2.65, 95% CI, 1.64–4.29) were independent predictors of 28-day mortality.<sup>17</sup> In addition, an increase in the NLR within the first 5 days of hospital admission was associated with mortality.<sup>18</sup> Liu et al showed a positive correlation between NLR and mortality with an AUC of 0.634 with borderline statistical significance (p-value of 0.049).<sup>40</sup>

However, there is some controversy in the literature regarding the prognostic role of NLR. Saliccioli et al found that there was no statistically significant correlation between NLR and mortality in intensive care unit (ICU) patients.<sup>41</sup> Another study by Xie et al showed no association between NLR and 28-day mortality in patients diagnosed with sepsis.<sup>42</sup> In a study done by Sari et al, the AUC of NLR at the first day of ICU admission in septic shock patients was: 0.515 with a p-value of 0.73.<sup>43</sup> These are similar to the results of our study where NLR was not associated with in-hospital mortality however lactate was.

Considering these mixed findings regarding NLR, our study aligns with recent literature, including findings by Méndez et al (2024), who emphasized the prognostic significance of biomarkers like lactate in sepsis, particularly in the context of COVID-19. Their work highlights how the dynamics of lactate in sepsis, especially with COVID-19 involvement, further enrich the understanding of how biomarkers can aid in the management of septic shock.<sup>44</sup> Our study contributes to this evolving understanding by demonstrating that, despite the utility of NLR in some settings, lactate remains the more reliable marker for predicting mortality in sepsis.

## Limitations

Our study has several limitations. This was a single-center study conducted at a tertiary care center which can limit generalizability. Our study focused on in-hospital mortality and did not include long-term morbidity and mortality after hospital discharge. We only included NLR and lactate levels at presentation and did not examine the relationship between their temporal trend during hospital stay and mortality. Future studies should focus on evaluating the association between NLR and lactate trends during hospital stay and mortality.

## Conclusion

In our study, the prognostic value of both NLR and lactate in predicting in-hospital mortality was determined using receiver operating characteristic curves from which we obtained their AUCs. This is a bivariate analysis that does not take into consideration other variables. It includes lactate or NLR and in-hospital mortality. The AUC value of the NLR ratio was 0.552, whereas that of lactate was 0.591. These values are poor in predicting in-hospital mortality. In addition, there was no significant difference between them with a p-value of 0.22. Moreover, there was no significant difference in the AUCs between lactate and NLR among septic shock patients and most of the septic subgroups. However, lactate outperformed NLR in the following subgroups: albumin<30 g/L, patients less than 65 years of age and patients with sepsis due to a urinary tract infection. Stepwise logistic regression was performed to study the association between NLR or lactate and in-hospital mortality. NLR was not associated with in-hospital mortality (OR=1.003, 95% CI=0.994–1.012, p=0.544), whereas lactate was associated with hospital mortality (OR=1.188, 95% CI=1.086–1.299, p<0.0001). This was a multivariate analysis that included statistically and clinically significant variables (see methods section and Table 4). The variables included in the model could have modified the association between NLR or lactate and in-hospital mortality. This can explain why there was no difference between the AUCs of lactate and NLR, and yet lactate was associated with hospital mortality while NLR was not. Our results advocate for the continued use of serum lactate rather than NLR, despite its limitations, as a predictor of mortality among septic patients and the different subgroups in this study. However, in light of conflicting/variable evidence in the medical literature, we advocate further investigations be done to clearly delineate whether NLR can be a useful biomarker in sepsis, particularly since it has shown to be promising in sepsis diagnosis, monitoring response to therapy, and predicting bacteremia.<sup>12–14,17,19,20</sup>



## Data Sharing Statement

The data that support the findings of this study are available from the author RBC.

## Ethical Approval

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The design of this study ensured that it strongly abided by all ethical considerations according to the American University of Beirut Medical Center's Institutional Review Board (IRB). Reference number: BIO-2018-0133

## Consent to Participate

Written informed consent was obtained from all participants and from a parent and/or legal guardian. The study was approved by the American University of Beirut Medical Center's Institutional Review Board (IRB). Reference number: BIO-2018-0133

## Acknowledgments

Ralphe Bou Chebl and Saadeddine Haidar are co-first authors for this study. This manuscript has been uploaded to a preprint server. The preprint is available at: <https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.researchsquare.com%2Farticle%2Frs-3920988%2Fv1&data=05%7C02%7Cjka20%40mail.aub.edu%7C26b5bf24231649e8821b08dcc6e290de%7Cc7ba5b1a41b643e9a1206ff654ada137%7C1%7C0%7C638603923607461375%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6IklhaWwiLCJXVCi6Mn0%3D%7C0%7C%7C%7C&sdata=klhAMQm4e9b%2FOQHa3YHeZ8Cyc9Rwiocvfz9XnYzQ73M%3D&reserved=0>

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

There is no funding to report.

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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