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Neutrophil-lymphocyte ratio versus lactate-albumin ratio as a predictor of morbidity and mortality in patients with sepsis and septic shock

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Abstract
Background: Sepsis is a severe inflammatory reaction throughout the body triggered by an infection, which may result in life-threatening malfunction of several organs. This study aims to assess the effectiveness of the neutrophil lymphocyte ratio (NLR) and lactate albumin ratio (L/A) as predictive markers for illness progression and death in patients diagnosed with sepsis and septic shock.
Methods: A cohort research was undertaken on a sample of 50 septic patients, ranging in age from 18 to 60 years, including both males and females, who were thought to be infected. The patients were classified into two groups: those who did not survive and those who survived. The NLR, lactate-to-albumin ratio, and SOFA score were assessed in all patients.
Results: The group of individuals who did not survive had markedly greater NLR and LA ratio. The L/A ratio, NLR and the Sequential Organ Failure Assessment Score (SOFA) exhibited strong correlation upon admission (p<0.05). An L/A ratio>0.58 is a reliable indicator of death. The sensitivity of the test is 88.46%, meaning it correctly identifies 88.46% of the true positive cases. The study demonstrated that NLR, L/A ratio, and SOFA score were significant independent predictors of death in patients with sepsis and septic shock.
Conclusions: NLR and L/A ratio were independent significant predictors for mortality in sepsis and septic shock. But lactate/albumin ratio is more accurate than neutrophil/lymphocyte (AUC=0.885).

Keywords: Neutrophil lymphocyte ratio, lactate albumin ratio, sepsis, septic shock, morbidity and mortality

Introduction

Sepsis is a severe inflammatory reaction throughout the body induced by an infection that may result in life-threatening malfunction of several organs [1].

Septic shock causes disruptions in both the circulatory system and metabolic processes, leading to increased mortality rates in hospitalized patients, especially those in the intensive care unit (ICU) [2] .

Only a few numbers of indicators are considered suitable for diagnosing sepsis. Novel biomarkers may enhance the monitoring of the patient's status and maybe lead to a more precise determination of the illness prognosis [3].

The quantity and function of immune cells including monocytes, lymphocytes, and neutrophils may be affected by sepsis [4].

Neutrophils are vital constituents of the innate cellular immune system. Increased neutrophil numbers in the early stages were correlated with worse severity of sepsis [5].

In sepsis, lymphocyte levels fall due to apoptosis induced by the innate immune response. [4]. Neutrophil count exhibits a substantial rise in direct proportion to the severity of inflammation. The neutrophil-to-lymphocyte ratio (NLR) is a recently discovered biomarker for inflammation that may be assessed by routine blood tests. It is affordable and readily available, and it helps quickly identify negative results in individuals with sepsis [6].

Albumin is the primary protein found in plasma. Albumin serves several physiological functions such as acting as a primary buffer, extracellular antioxidant, immunological modulator, antidote, and transporter in plasma due to its various physiological processes [7].

One characteristic of SIRS is the heightened permeability of capillaries leading to albumin leakage. Reduced albumin levels are linked to substantial systemic inflammation and organ dysfunction [8].

Hypoxia and decreased tissue blood flow in sepsis play a crucial role in causing multiple organ failure in people with sepsis [9].

Lactic acidosis is a strong sign of inadequate blood flow or the onset of anaerobic metabolism in septic shock [10]. Reduced hepatic perfusion causes the liver to be unable to metabolize lactate, resulting in increased lactate levels [11]. Measuring blood lactate levels to assess tissue hypoxia is quick, cost-effective, and simple [12].

Examining the lactate albumin ratio (L/A) instead of examining L/A in isolation might provide a new and perhaps more efficient prognostic indicator for sepsis patients because of their unique progression patterns [9].

The objective of this research is to evaluate the prognostic significance of the NLR and the L/A ratio in predicting the likelihood of complications and mortality in patients diagnosed with sepsis and septic shock.

Material and Methods:

The observational study included 50 septic patients aged 18 to 60, of both sexes. Individuals met at least two QSOFA requirements: impaired cognitive function (GCS < 15), systolic blood pressure < 100 mmHg, and respiration rate > 22 breaths per minute. The presence of certain criteria showed that the organs were dysfunctional. The criteria included the following: Infection-related changes in SOFA score variables of more than 2 points, a PaO2/FiO2 ratio below 300, a Glasgow Coma Scale score below 15, a mean arterial blood pressure less than 70 mmHg, a serum creatinine level exceeding 1.2 mg/dl, a urine output less than 0.5 ml/kg/hr, a serum bilirubin level higher than 1.2 mg/dl, a platelet count below 150 X 103/µl, septic shock with persistent hypotension requiring vasopressors to maintain MAP above 65 mmHg, and a serum lactate level > 2 mmol/L despite adequate volume resuscitation.

The research took place at Tanta University Hospital's Surgical Intensive Care Unit (SICU) from May 2022 to May 2023. The Tanta University Hospitals Ethical Committee in Tanta, Egypt approved the research (approval code: 35280/2/22) and it was filed on clinicaltrials.gov (ID: NCT05825118). Patients or their families supplied informed written consent.

The exclusion criteria included the presence of cancer and recent chemotherapy within the past 90 days, recent use of steroids within 3 months prior to admission, confirmed liver dysfunction, kidney failure, and conditions requiring the use of albumin supplementation such as liver cirrhosis with ascites, nephrotic syndrome, and burn injuries.

Patients were divided into 2 groups: non survivors' group and survivors' group.

All patients had a series of procedures, including gathering medical history, conducting a physical examination, and performing standard laboratory tests. These tests included a complete blood count (CBC) which measured the total number of white blood cells (neutrophils and lymphocytes) using the Dirui BCC-3600 cell counter. Additionally, arterial blood gases (ABG), liver and kidney function tests, coagulation profile, serum lactate levels using a blood Gas Analyser, and blood inflammation markers such as C-reactive protein (CRP) were also assessed. Upon admission, blood culture and cultures from any suspected source of infection, such as sputum, wound, or urine, were collected.

NLR and L/A ratio

Measurements were taken in all patients identified with sepsis by clinical examination and tests and were documented upon admission. Peripheral venous, artery, or central catheter was used to obtain blood samples for the assessment of complete blood count (neutrophil and lymphocyte), serum lactate, and serum albumin levels. The samples were not stored, and the investigations were reported within 1.5 hours.

Follow up: All patients followed for 28 days, and Length of ICU were recorded then patients were categorized to 2 groups non-survivors and survivors according to 28 days mortality. Survivors were followed up at ward or by telephone after discharge until 28 days completed.

Correlation of NLR and LA ratio with 28-day mortality. NLR and L/A ratio on admission. Hemodynamic measurements (MAP, HR, RR) were assessed in 0 hr, 6 hrs, 24 hrs. Length of ICU stay. SOFA score and assessment of organ dysfunction in 0 hrs, 6 hrs, 24 hrs.

The main result was the correlation of NLR and LA ratios with 28-day mortality. Secondary outcomes were the duration of ICU stay and the amount of organ failure in patients with sepsis and septic shock.

Sample Size Calculation

Worldwide Health Organization and Centers for Disease Control and Prevention software, version 2002, in Atlanta, Georgia, USA, was used to determine the sample size and power analysis. The following is the process that was used to determine the sample size: Carry out the research using an 80% power level and a 95% confidence level. Patients with sepsis and septic shock who get effective care have a 90% predicted sensitivity for mortality prediction, while those in the group that receives the least favorable treatment have a 65% forecast sensitivity. The sample size, as determined by the conditions specified above, is more than 44 (N > 44). The researcher enlarged the sample size to 50 to address the incomplete data.

Statistics

The data analysis was conducted using IBM SPSS software program, namely version 20.0. This information is sourced from the publication of IBM Corp. in Armonk, NY. The two groups were compared using an unpaired Student's t-test, which entails computing the average and standard deviation (SD) of quantitative parametric variables. The median and interquartile range (IQR) were used to present the quantitative non-parametric data, which were then examined using the Mann Whitney-test. The frequency and percentage of qualitative variables were shown, and if applicable, they were analyzed using either the Chi-square test or Fisher's exact test. The Pearson correlation coefficient was used to evaluate the linear relationships between many variables. It was believed that the data followed a normal distribution. The test's diagnostic accuracy is quantified by the area under the ROC curve. The study analyzed the relationship between a single dependent variable and a single independent variable using both univariate and multivariate regression. A two-tailed P value below 0.05 was deemed statistically significant for the purpose of statistical analysis.

Results

Among the total of 65 patients that were evaluated, nine were found to be ineligible based on the criteria, and six chose not to take part in the study. Among the original 50 patients, 26 were randomly assigned to the non-survivors' group and 24 were assigned to the survivors' group. Statistical approaches were used to track and evaluate all 50 patients. Figure 1

When comparing the two groups according to sex, body mass index (BMI), and cause of sepsis, no statistically significant differences were found (p>0.05). Compared to survivors, non-survivors had noticeably greater age and SOFA scores (p<0.05). Compared to patients who survived, those who did not had a considerably shorter period of stay in the critical care unit (p<0.05). The non-survivor's group had a much greater NLR and LA ratio than in survivor's group (p<0.001). Table 1

The heart rate exhibited a significant increase in the group of individuals who did not survive as compared to the group of individuals who did survive at 0, 6, and 24 hours (p<0.05). When comparing the two groups' respiratory rate (RR), no statistically significant difference was found (p>0.05). At 0 hours, 6 hours, and 24 hours, the non-survivor group had a significantly lower MAP than the survivor group (p<0.05). Figure 2

There was a significant positive correlation between NLR with SOFA score on admission (rs = 0.490, p<0.05). There was a strong positive correlation between L/A ratio with SOFA score on admission (rs= 0.571, p<0.05). Figure 3

Neutrophil/lymphocyte ratio can significantly predict mortality at cut-off value > 5.7 with sensitivity 76.92%, specificity 54.17%, PPV 64.5% and NPV 68.4% with area under the curve 0.801and (95% C.I: 0.670-0.932) with P value <0.001. L/A can significantly predict mortality at cut-off value > 0.58 with sensitivity 88.46%, specificity 58.33%, PPV 69.7% and NPV 82.4% with area under the curve 0.885 and (95% C.I: 0.796-0.975) with p<0.001. Figure 4

As far as mortality in sepsis and septic shock is concerned, the NLR, L/A ratio, and SOFA score were shown to be significant predictors independently (P value <0.05). The parameters that had the greatest impact on mortality were the SOFA score and the lactate/albumin ratio (p<0.05) Table 2

Table 1: Comparison between the two studied groups according to demographic data, SOFA score, cause of sepsis, ICU stay and NLR and LA ratio on admission

		Survivor		p
		No (n = 26)	**Yes (n = 24)**	
Age (years)		49.23 ± 11.52	37.29 ± 14.02	0.002*
Sex	Male	15(57.7%)	17(70.8%)	0.333
	Female	11(42.3%)	7(29.2%)	
BMI (kg/m^2)		31.67 ± 6.88	29.21 ± 4.33	0.137
SOFA score	0 hr	14.0 (11.0-15.0)	8.0(6.0-8.50)	<0.001*
	6 hr	13.0(11.0-14.0)	6.50(6.0-8.0)	
	24 hr	12.0(11.0-14.0)	6.0(5.0-8.0)	
Cause of sepsis	Abdominal infection	8(30.8%)	5(20.8%)	0.424
	Chest infection	6(23.1%)	5(20.8%)	0.848
	Infected wound	2(7.7%)	6(25%)	0.610
	Cervical abscess	1(3.8%)	0(0.0%)	1.000
	Central line infection	0(0.0%)	3(12.5%)	0.103
	Infected bed sores	2(7.7%)	0(0.0%)	0.491
	L.L gangrene	5(19.2%)	1(4.2%)	0.192
	Septic hip	1(3.8%)	2(8.3%)	0.602
	UTI	1(3.8%)	2(8.3%)	0.602
ICU stay (days)		10.04 ± 2.97	18.04 ± 5.01	<0.001*
NLR		9.65 (6.70-11.60)	5.70 (4.85-6.57)	<0.001*
LA ratio		0.80(0.65-0.99)	0.55(0.39-0.62)	<0.001*

Data are presented as mean ± SD or frequency (%), SD: Stander Deviation. BMI: Body mass index,
* Significant p value <0.05, UTI: urinary tract infection, ICU: Intensive Care Unit, NLR: Neutrophil lymphocyte ratio, LA ratio: Lactate albumin ratio.

Table 2: Univariate and multivariate Logistic regression analysis for the parameters affecting mortality

	Univariate		#Multivariate	
	p	**OR (LL-UL 95%C. I)**	**p**	**OR (LL-UL 95%C. I)**
NLR	<0.001*	1.731(1.276-2.348)	0.582	1.148(0.702-1.876)
L/A	0.002*	3.035(1.487-6.194)	0.039*	2.545(1.048-6.181)
SOFA Score at 0hr.	<0.001*	1.931(1.380-2.704)	0.009*	1.638(1.132-2.369)

Data are presented as Number, * Significant p value <0.05, NLR: Neutrophil/Lymphocyte ratio, L/A: Lactate/albumin

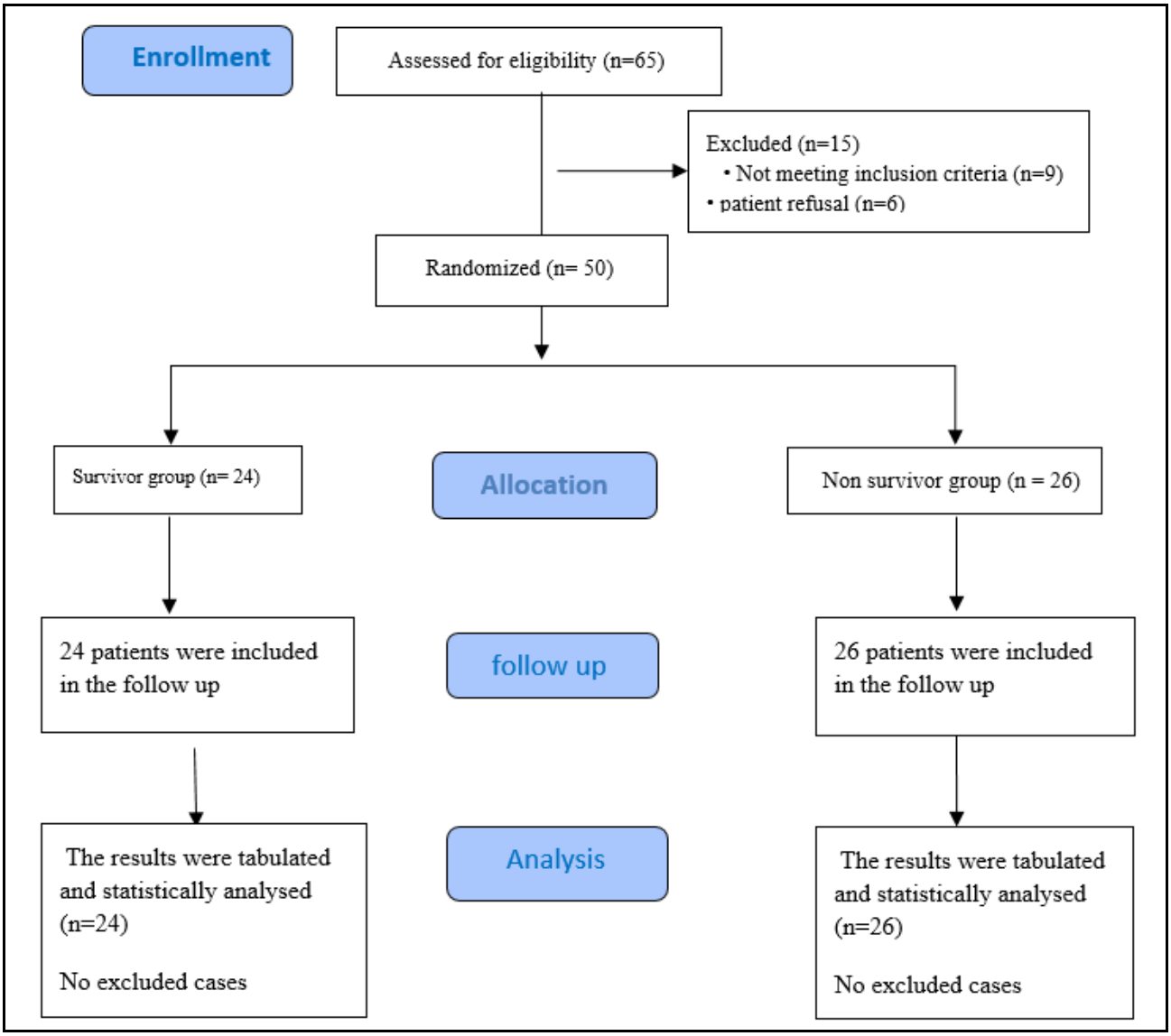
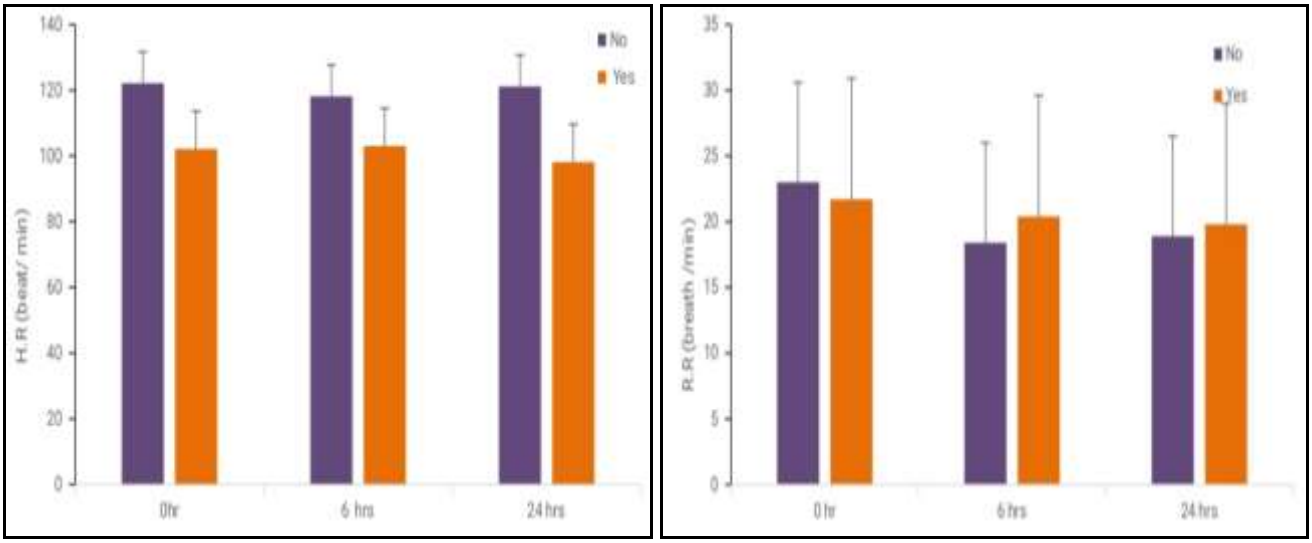
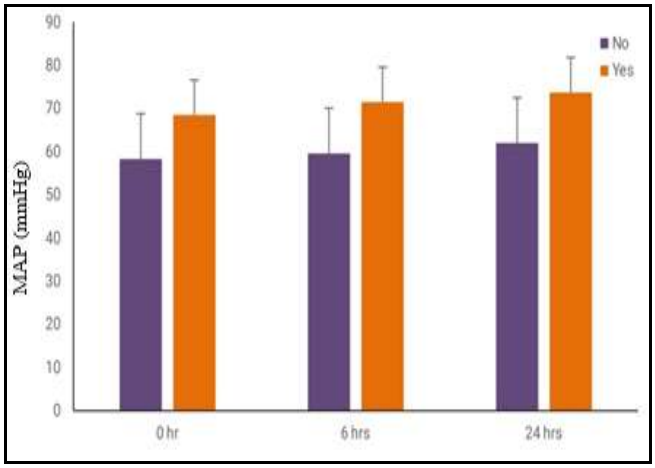


Fig 1: Consort flowchart of the enrolled patient

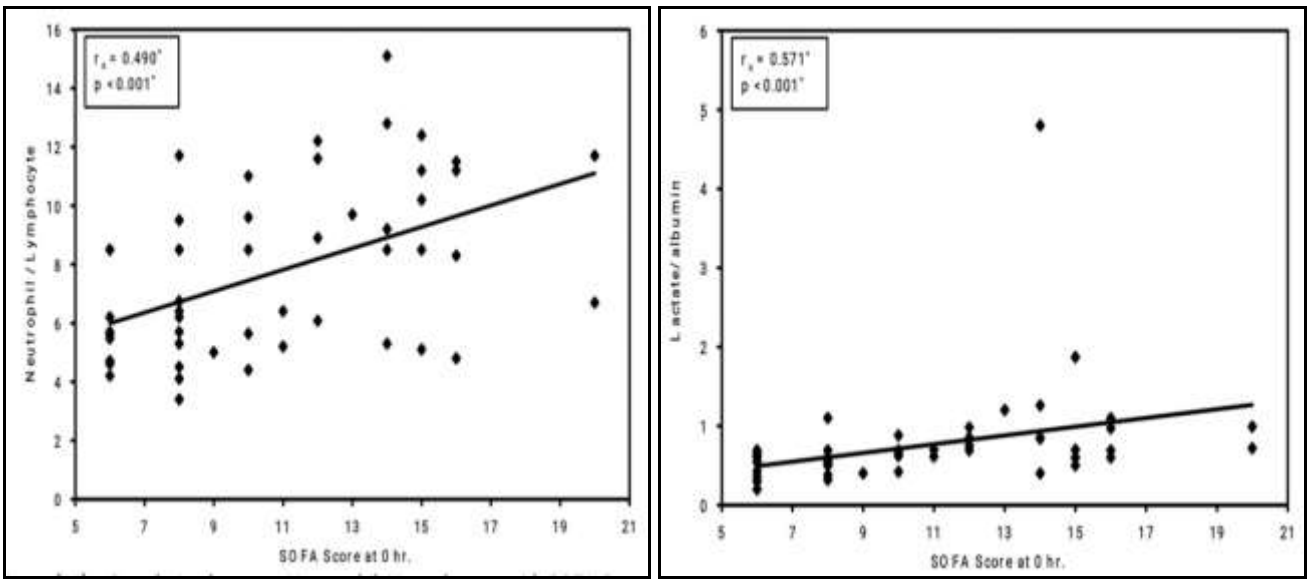


(a) (b)



(c)

Fig 2: Comparison between the two studied groups according to (a) heart rate (HR), (b) respiratory rate (RR) and (c) mean arterial blood pressure (MAP)



(A) (B)

Fig 3: Correlation between (A) Neutrophil/Lymphocyte ratio (NLR), (B) Lactate/albumin ratio (L\A) with SOFA score at 0 hr

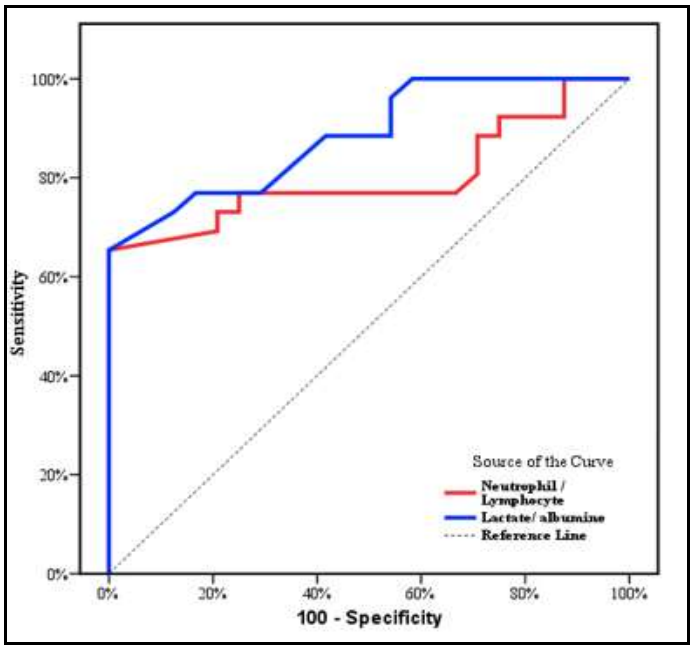


Fig 4: ROC curve for Lactate/albumin (L/A) ratio and Neutrophil/Lymphocyte ratio (NLR) to predict mortality

Discussion

Sepsis is a medical illness that arises from an infection and is marked by physiological, pathological, and metabolic disturbances [13]. A recently discovered inflammatory biomarker, the Neutrophil-to-Lymphocyte Ratio (NLR), may be determined using routine blood testing. Its use in predicting the severity or prognosis of systemic inflammation, sepsis, ischemia events, cancer, and other medical situations is on the rise [14].

Both univariate and multivariate regression analysis demonstrated that the admission SOFA score was a significant predictor of death. Consistent with the findings of the present investigation, Lorente *et al*. [15] demonstrated that the group of individuals who did not survive had substantially elevated SOFA scores at 1, 4, and 8 days after admission, in comparison to the group of those who survived. Also. Ahmed *et al*. [16] showed that A high baseline SOFA was shown to be a significant independent predictor of adverse prognosis among septic patients, according to multivariate logistic regression analysis.

The study revealed a statistically significant decrease in MAP among those who did not survive, as opposed to those who did survive, at 0, 6, and 24 hours. At 0, 6, and 24 hours, the heart rates of the survivors' group were significantly lower than those of the non-survivors' group. In terms of RR, there was no discernible difference between the two groups. Bou Chebl *et al*. [17] demonstrated a notable rise in RR among non-survivors compared to survivors. Survivors exhibited considerably higher SBP, but there was no significant disparity in HR at presentation. Ni *et al*. [6] A recently discovered inflammatory biomarker, the Neutrophil-to-Lymphocyte Ratio (NLR), may be determined using routine blood testing. Its use in predicting the severity or prognosis of systemic inflammation, sepsis, ischemia events, cancer, and other medical situations is on the rise.

According to our findings, the non-survivor's group had a much greater NLR. This comes in agreement with Lorente *et al*. [18] revealed that Non-surviving patients had elevated NLR levels on the 1st, 4th, and 8th day after sepsis diagnosis in comparison to survivors. Sari *et al*. [19] discovered that non-surviving patients had greater NLR than surviving patients on days 1, 3, and the final day of ICU.

In our study, ROC curve analysis was preformed, and revealed that the NLR at cut-off value > 5.7 can predict mortality with sensitivity 76.92%, specificity 54.17%, PPV 64.5% and NPV 68.4% with area under the curve 0.801 and (95% C.I: 0.670-0.932) with $p<0.001$. Higher than our cutoff point Ahmed *et al*. [16] showed that An NLR value greater than 8.9 was suggested as the best cutoff point, with a sensitivity of 75.0% and a specificity of 67.7% in predicting death in sepsis. Wang *et al*. [20] discovered that the NLR was highly predictive of sepsis prognosis, with an AUC of ROC curve of 0.77, a sensitivity of 95.8%, and a specificity of 48.1%. Univariate regression analysis in our study showed that NLR was significant predictor for mortality. But in multivariate regression analysis NLR was non-significant predictor for mortality. In concordance with our study, Liu *et al*. [21] showed that NLR on day 1 was significant predictor for mortality In univariate regression analysis ,but in multivariate regression analysis NLR was non-significant predictor for mortality. In contrast, Zhao *et al*. [22] in multivariate analysis showed that higher NLR was significant independent predictor of mortality in septic patients, this contrast may be due to our small sample size.

Regarding L/A ratio on admission, our study showed that L/A ratio ranged from (0.2-4.8), The findings indicated a statistically significant rise in the L/A ratio in the non-survivors group compared to the survivors' group. Consistent with our findings, Kabra *et al*. [23] shown that the lactate/albumin ratio was notably greater in the group who died compared to the group that was discharged. Our results aligned with Jeong *et al*.'s findings [24], indicating that the lactate/albumin ratio was greater in the non-survivors' group compared to the survivors' group.

ROC curve analysis was preformed and revealed that the lactate/albumin at cut-off value > 0.58 can predict mortality with sensitivity 88.46%, specificity 58.33%, PPV 69.7 and NPV 82.4 with area under the curve 0.885 and (95% C.I: 0.796-0.975) with $p<0.001$**.** However, lower than our cutoff point Bou Chebl *et al*. [25] showed that Researchers determined that an L/A ratio of 0.115 was the ideal value for differentiating septic patients into survivors and non-survivors. There is an 83% negative predictive value, 35% sensitivity, and 81% specificity, with a 39% positive predictive value. Our established criterion was exceeded by Kabra *et al*., who found that a mortality prediction with a sensitivity of 100% and specificity of 88% was achieved with an L/A ratio of 0.96 or higher.

The research found that the L/A ratio was an independent predictor for death based on univariate and multivariate regression analysis. Shin *et al*. [26] found that According to the current analysis, the L/A ratio was shown to be more useful than a single lactate test in predicting 28-day mortality in critically sick septic patients. In their study, Cakir *et al*. [27] found that lactate and albumin were significant indicators of mortality in septic patients in the ICU. Moreover, it has been shown that the lactate/albumin ratio may be used autonomously as a more potent prognosticator of mortality compared to any individual metric.

In our study, the survivors 'group have significantly longer ICU stay compared to non-survivors (18.04 ± 5.01 versus 10.04 ± 2.97days respectively; $p<0.001$). Our results came in line with, Jeong *et al*. [24] found that Survivors of pneumonia had a considerably greater rate of ICU admission compared to non-survivors at 28 days. Bou Chebl *et al*. [25] shown that the non-survivors had notably longer stays in the ICU and overall hospital compared to survivors.

Our data indicated a substantial association between NLR and SOFA upon admission, with a Spearman's correlation coefficient of 0.469 and a P value of 0.001. As per our findings by Rehman *et al*. [28] reported that there is a showed a significant association with the SOFA score ($p<0.05$). Also, Wang *et al*. [20] NLR levels were found to be positively correlated with SOFA score ($r = 0.164$, $p<0.001$).

The current study showed that there is significant correlation between L/A ratio and SOFA score at admission. ($rs= 0.579$, $p<0.001$). In line with our study, Cakir *et al*. [29] reported that there is a positive association between SOFA score and L/A ratio as L/A > 1.27 showed a significant association with patients with SOFA score > 11. Also, Wang *et al*. [30] Analyzed the link between the L/A ratio and multi-organ failure as well as death in 54 sepsis patients in the ICU [31], revealing a significant relationship.

Study limitations: The sample size is quite limited. The research used a single-center prospective design. Absence of a control group. Short duration for follow-up.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

Conclusions

NLR and L/A ratio were independent significant predictors for mortality in sepsis and septic shock. But L/A ratio is more accurate than neutrophil/lymphocyte (AUC=0.885).

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