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ORIGINAL ARTICLE

Validity of Neutrophils to Lymphocyte and Platelet to Lymphocyte Ratios as Diagnostic and Prognostic Markers in Patients with Sepsis at Pediatric Intensive Care Unit

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ABSTRACT

Background: Sepsis is a systemic syndrome induced by infection and results in extensive inflammation, septic shock, multiple organ failure, and even death. The blood neutrophil-to-lymphocyte ratio (NLR) has been proposed as a marker of systemic inflammation since sepsis is characterized by an increase in neutrophils and a reduction in lymphocytes in the blood. This study aimed to evaluate the value of the neutrophil-to-lymphocyte and platelet-to-lymphocyteratio as early diagnostic markers of sepsis and predict patient outcomes in thePediatric Intensive Care Unit. **Patients and methods:** Sixty-six children aged 1 month to 16 years were admitted to the pediatric intensive care unit for early diagnosis of sepsis and prediction of patient outcomes at the Pediatric Intensive Care Unit, Zagazig University Hospital. **Results:** All patients in thenon survivorsgroup had positive blood cultures, and a greater percentage of patients had growth: denoting *Staphylococcus aureus* (57.6%), followed by Klebsiella (21.2%). The best cut-off of the NLR for the prediction of mortality among patients with sepsis was ≥6.8521, with a sensitivity of 78.6% and specificity of 78.9%. The best cut-off of the PLR for the prediction of mortality among patients with sepsis was ≥126.7365, with a sensitivity of 78.6% and specificity of 73.7%. **Conclusion:** PLR and NLR are dependable predictive indicators that are inexpensive and rapidly obtainable in the early detection of sepsis onset. They assist in identifying children at high risk for sepsis, predicting their mortality, and objectively monitoring clinical improvement.

Keywords: Sepsis; Neutrophil/ lymphocyte ratio;Pediatric intensive care

INTRODUCTION

A systemic syndrome known as sepsis is caused by infection and results in extensive inflammation, septic shock, multiple organ failure, and even death. Admissions to the pediatric intensive care unit (PICU) are still frequently caused by pediatric sepsis and septic shock, which have been linked to high rates of juvenile death and medical expenses **[1].**

Numerous biomarkers have been evaluated to distinguish sepsis from noninfectious causes of the systemic inflammatory response. The most commonly used sepsis biomarker at present is procalcitonin (PCT), which is elevated during sepsis and the systemic inflammatory response, particularly in patients with systemic bacterial, parasitic, or fungal infections. Nevertheless, PCT testing is costly and time-consuming. As a result, physicians must create instruments that are quick, cheap, and simple to measure **[1].**

Researchers have evaluated the neutrophil/ lymphocyte ratio (NLR) in an effort to simplify the diagnosis of sepsis. The absolute and relative numbers of both neutrophils and lymphocytes can be used to compute this ratio. This report is important because it shows that physiological stress results in a decrease in thelymphocyte count and an increase in the neutrophil count. Because sepsis induces lymphocyte apoptosis, the ratio is greater in these situations. Because of the sharp decreasein lymphocyte numbers induced by septic shock, the NLR increases dramatically**[2].**

The main cellular defences the neutrophils and lymphocytes of the human host against an infection. In light of the patient's immune system, the etiology of the infection, and the stage of sepsis, the quantity of white blood cells can change during the course of the illness. A clinician is alerted to an infection by a decreasein lymphocytes and an increase in neutrophils. A greater NLR could be a sign of severe inflammatory development **[3].**

By releasing inflammatory cytokines and interacting with T cells, macrophages, neutrophils, and other immune cell types ((monocytes and Platelets) may be essential for both immunomodulatory and inflammatory processes because they are progenitors of macrophages that can initiate or intensify the inflammatory process **[4].**Reduced lymphocyte counts may indicate an inflammatory disease-related immunological and inflammatory response that has been repressed. Therefore, the PLR was suggested to function as a novel systematic inflammatory marker**[5].**

According to current research, platelets and lymphocytesplay important roles in the inflammatory process. The PLR is a measure of how well thrombosis and inflammation are balanced. Consequently, the inflammatory state causes megakaryocyte growth to accelerate and thrombocytosis to follow**[6].**

There are a number of indicators that can indicate the severity of inflammation in PICU patients with a severe clinical course, but these indicators are useful and challenging to use. The PLR represents the platelet-to- lymphocyte ratio: a novel indicator of inflammation. The PLR can serve as a useful indicator for early disease identification and treatment **[7]**.Instead of serving only as a sign of acute medical issues, an elevated platelet– lymphocyte ratio (PLR) also serves as a predictor of long-term mortality**[8].**

A popular physiologically based scoring system for predicting mortality in critically ill children is called the Pediatric Risk of Mortality (PRISM). It was originally created in 1988 in PICUs across North America by Pollack et al., and it was later upgraded to become the Pediatric Risk of Mortality III (PRISM III). With 17 routinely measured physiologic variables and their ranges, PRISM is a widely used physiologically based severity of illness assessment**[9].**

In PICUs, the Sequential Organ Failure Assessment (SOFA) scale is frequently utilized to assess the condition and prognosis of patients suffering from multiple organ failure. The rapid sequential evaluation of organ failure, or q-SOFA, is a scale that uses heart rate, systolic blood pressure, and consciousness to measure changes in a patient's condition rapidly; a respiratory rate ≥22/min, a systolic blood pressure ≤100 mmHg, and an altered mental state are the criteriafor failure**[10].**

This research aimed to assess the value of platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios as early diagnostic indicators of sepsis and prognostic factors in the pediatric intensive care unit.

METHODS

This comparative cross-sectionalstudy was conducted in the PediatricsDepartment, Faculty of Medicine, at Zagazig University Hospital for 66 children for early diagnosis of sepsis and prediction of its outcome at the Pediatric Intensive Care Unit from January through June 2023. All of the children's parents or guardians provided written informed consent, and the research ethics committee of Zagazig University's Faculty of Medicine (International Review Board) authorized the study ZU-IRB 10889-13/6-2023. The work was completed in compliance with the Declaration of Helsinki, the World Medical Association's code of ethics for human subjects' research.

The inclusion criterion was age between 1 month and 16 years, admission to the PICU of Zagazig University Children Hospital and diagnosis of septic shock or severe sepsis. The Surviving Sepsis Campaign international recommendations for the management of septic shock and sepsis-associated organ dysfunction in children published in 2020 and the 2005 International Pediatric Sepsis Consensus Conference criteria (IPSCC) served as the foundation for the definitions of severe sepsis and septic shock **[11,12].** The exclusion criteria were age>18 years;hematological malignancies; splenectomy; platelet disorders; immunosuppressive medication use; or immunosuppressive illnesses, such as cancer and HIV infection.

The mother provided a complete history to each participant, covering the following: name, age, sex, place of residence, complaint (including the start and duration of related symptoms), and a thorough clinical examination. The investigation included complete blood count (CBC) analysis. C-reactive protein (CRP) was measured using the immunoturbidimetric technique. Blood culture was performed using the BACT/ALERT (bioMérieux, France) instrument.Inpediatricpatients, 1-3 ml was collected in a yellow tube and then incubated at 37°C for 7-10 days under septic conditions; a positive signal indicated the presence of microbial infection, and a negative signal indicated the absence of microbial infection. Liver profile tests were also performed(total protein, serum albumin, serum aspartate transaminase, serum alanine transaminase, total bilirubin and direct

bilirubin). Kidney function tests were also performed (serum creatinine andblood urea). Urine and stool analysis. Coagulation profile (INR, prothrombin time and concentration).

Assessment of the neutrophil/ lymphocyte ratio (NLR) and platelet– lymphocyte ratio (PLR)

All blood samples were taken at the time of admission for initial diagnosis using a Sysmex XN30 (include 5 parts) or Sysmex XP300 (include 5 parts) instrument under a septic technique.We collected samples up to the mark (approximately 2 cm) in an EDTA tube. The NLR and PLR were computed using the numbers of neutrophils, platelets, and lymphocytes found in these blood samples. The NLR was calculated by dividing the total neutrophil count by the total lymphocyte count, while the PLR was calculated by dividing the total platelet count by the total lymphocyte count. Receiver operating characteristic (ROC) curves were used to assess the cut-off values, sensitivity, and specificity of the NLR and PLR **[13].**

Assessment Pediatric Risk of Mortality (PRISM) score:

The 14 parameters of the PRISM III scoring system were evaluated. The PRISM III score was evaluatedbythe advice of Pollock et al. Throughout a 12-hour clinical assessment, the most anomalous values were taken into account for assigning a score. The patients were monitored during their PICU stay, and on discharge from ICU stay, the outcome was recorded as "survived" or "died"**[14].**

Assessment of Sequential Organ Failure Assessment (SOFA) score:

The sofa score is a quantitative scoring indicator that represents the dynamic state of organ dysfunction due to sepsis and encompasses the central nervous system, liver function, cardiovascular system, respiratory system, coagulation system, and kidneys. The scores ranged from 0 to 24. The higher the score is, the more severe the organ dysfunction linked to sepsis **[10].** The patients were followed up during the PICU stay, and the outcome was recorded as "survived" or "died" at the end of their ICU stay **[14].**

STATISTICAL ANALYSIS

The IBM PC running SPSS version 23 statistical software was used to construct, graph, and analyze the data. The standard deviation (SD), mean, and percentage [%] were used to display descriptive data. Two quantitative variables were studied for statistical significance using the Mann–Whitney test or Student's t-test. Chi-square analysis [x^2] was used to investigate the statistical significance of the relationship between two qualitative variables. The effectiveness of classification techniques that use a single variable to divide patients into two categories was assessed using the receiver operating characteristic (ROC) curve. A p-value of less than 0.05 was considered to indicate statistical significance.

Results

Table 1shows that there were statistically nonsignificant differences between the studied groups regarding sex, age, weight, height, BMI, and residence.Therewere statistically nonsignificant differences between the studied groups regarding comorbidities, cause of admission, GCS score, or history of ICU admission. However, there were statistically significant differences between the groups in terms of PRISM III (range of PRISMIII among survivors ranged from 2 to 12) and sofa scores**.** All patients in thenon-survivors group had positive blood cultures, and a greater percentage of patients had growthdenoting *Staphylococcus aureus* (57.6%), followed by

Klebsiella (21.2%), as shown in Table1.

Table 2shows that there were statistically significant positive correlations between the NLR and the PLR, sofa score, and PRISM III score. On the other hand, there was a statistically significant negative correlation between the NLR and Glasgow coma scale score. There were statistically significant positive correlations between the PLR and the NLR, sofa score, and PRISM III score. On the other hand, there was a statistically nonsignificant negative correlation between the PLR and Glasgow coma scale score.

A low BMI significantly decreased the risk of sepsis (AOR=0.328). ANLR ≥4.163 and a PLR≥85.8571 significantly and independently increased the risk of mortality by 224.5- and 40.179-fold, respectively, as shown in Table3.

Table 4 shows that the best cut-off of the NLR for the prediction of mortality among patients with sepsis was ≥6.8521, with a sensitivity of 78.6% and specificity of 78.9%. The best cut-off of the PLR for the prediction of mortality among patients with sepsis was ≥126.7365, with a sensitivity of 78.6% and specificity of 73.7% (Table 4, Figure 1).

Table (1): Comparison between the studied groups regarding baseline data:

	Non survivors group	**Survivors group**	χ^2	**p**
	N=33 (%)	**N=33 (%)**		
Gender: • **Male** • **Female**	20 (60.6%) 13 (39.4%)	23 (69.7%) 10 (30.3%)	0.601	0.438
Residence: • **Rural** • **Urban**	24 (72.7%) 9 (27.3%)	22 (66.7%) 11 (33.3%)	0.287	0.592
	Median (IQR)	**Median (IQR)**	**Z**	**p**
Age (year)	2(0.83 – 7.25)	3(0.92 – 10)	0.212	0.832
Weight (kg)	11(7 – 15)	10.5(7 – 17)	-0.52	0.603
	Mean ± SD	**Mean ± SD**	t	p
length (cm)	87.3 ± 26.43	85.58 ± 26.43	0.281	0.779
BMI	14.34 ± 3.3	16.99 ± 8.19	-1.727	0.091
Comorbidity • **Absent** • **Present**	6 (18.2%) 27 (81.8%)	7 (21.1%) 26 (78.9%)	0.096	0.757

	Non survivors group	Survivors group	χ^2	p
	N=33 (%)	N=33 (%)		
Type:	N=27	N =26		
• **Epilepsy**	6 (22.2%)	7 (26.9%)		
• **CHD**	5 (18.5%)	4 (15.4%)		
• **CP**	5 (18.5%)	6 (23.1%)		
• **Down syndrome**	2 (7.4%)	0 (0%)		
• **SMA**	2 (7.4%)	3 (11.5%)		
• **Epidermolysis bullosa**	1 (3.7%)	0 (0%)	MC	0.999
• **CKD**	1 (3.7%)	3 (11.5%)		
• **HIE**	1 (3.7%)	2 (7.7%)		
• **Hydrocephalus**	1 (3.7%)	0 (0%)		
• **VSD**	1 (3.7%)	0 (0%)		
• **DM**	2 (7.4%)	0 (0%)		
Cause of admission				
• **Apnea**	1 (3%)	2 (6%)		
• **Severe dehydration**	1 (3%)	3 (9.1%)		
• **DCL**	1 (3%)	0 (0%)		
• **DKA**	2 (6%)	0 (0%)	MC	0.969
• **GBS**	3 (9.1%)	4 12.1%)		
• **RD IV**	6 (18.2%)	8 (24.2%)		
• **RD III**	8 (24.2%)	10 (18.2%)		
• **Status epilepticus**	11 (33.3%)	6 (30.3%)		
Glasgow coma score	5.24 ± 1.35	6.11 ± 2.89	-1.528	0.132
	Median (IQR)	**Median (IQR)**	**Z**	**p**
sofa score	13(11 – 15)	7(3.5 – 10)	-5.194	<0.001**
PRISM III score	14(12.5 – 16)	2(2 – 3)	-7.11	<0.001**
			N=33	**%**
Blood culture of non survivors group				
• **Negative**			0	0%
• **Positive**			33	100%
Type:				
• **Staphylococcus aureus**			19	57.6%
• **Klebsiella**			7	21.2%
• **Coagulase negative staph aureus (CONS)**			3	9.1%
• **Acinetobacter**			2	6.1%
• **Streptococcihemolyticus**			1	3.0%
• **Candida, E. coli**			1	3.0%

BMI= body mass index.

CHD = Congenital Heart disease. CP = Cerebral palsy. SMA = Spinal muscular atrophy. CKD = Chronic Kidney disease. HIE = Hypoxic ischemic encephalopathy. VSD =Ventricular septal defect. DM = Diabetes mellitus. DCL = Disturbed conscious level. DKA = Diabetes Keto acidosis. GBS = Gullian barre syndrome. RDIV =Respiratory distress grade IV. RD III = Respiratory distress grade III. sofa = Sequential organ failure assessment. Prism= Pediatric risk of mortality. χ^2 = Chi square

test. Z= Mann Whitney test. t= independent sample t test. *p<0.05 is statistically significant **p≤0.001 is statistically highly significant.

Table (2): Correlation between PLR, NLR and all of GCS, SOFA and PRISM III scores among studied participants:

	PLR		NLR	
	r	p	r	p
PLR	1		0.492	<0.001**
NLR	0.492	<0.001**	1	
Sofa	0.276	0.025*	0.543	<0.001**
PRISM III	0.318	0.009*	0.644	<0.001**
GCS	-0.178	0.153	-0.636	<0.001**

NLR = Neutrophil lymphocyte ratio. PLR = Platelet lymphocyte ratio. GCS = Glasscow coma scale. Sofa = Sequential organ failure assessment. POISM = Pediatric Risk of mortality. r = Spearman rank correlation coefficient **p≤0.001 is statistically highly significant.

Table (3): Multivariate regression analysis of factors associated with mortality:

	β	p	AOR	95% CI	
BMI (kg/m^2)	-1.115	0.008*	0.328	0.144	0.746
NLR≥4.163	5.414	0.002*	224.5	7.524	6698.23
PLR≥85.8571	3.693	0.041*	40.179	1.165	1386.232

BMI= body mass index. NLR = Neutrophil lymphocyte ratio. PLR = Platelet lymphocyte ratio. AOR = adjusted odds ratio. CI = Confidence interval. *p<0.505is statistically significant

Table (4): Performance of NLR and PLR in prediction of mortality among studied patients with sepsis:

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
NLR	≥6.8521	0.902	78.6%	78.9%	73.3%	83.3%	78.8%	<0.001**
PLR	≥126.7365	0.868	78.6%	73.7%	68.8%	82.4%	75.8%	<0.001**

NLR = Neutrophil lymphocyte ratio. PLR = Platelet lymphocyte ratio. AUC = area under curve. PPV = positive predictive value. NPV= negative predictive value. *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

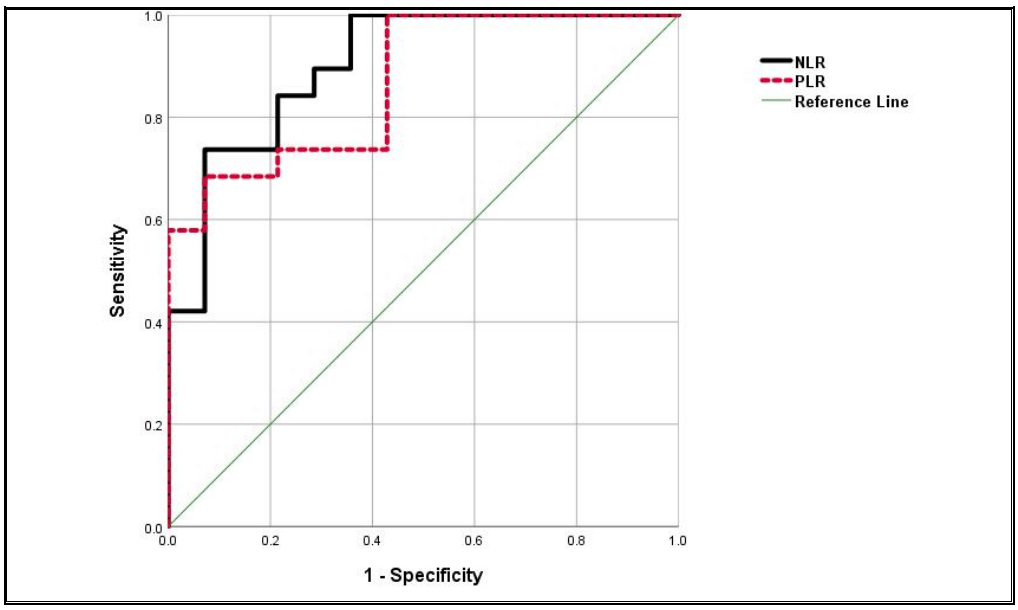

Fig. (1): ROC curve showing performance of NLR and PLR in the prediction of mortality among studied patients with sepsis."NLR = Neutrophil lymphocyte ratio. PLR = Platelet lymphocyte ratio

DISCUSSION

According to the current study, there were no statistically significant differences in sex, residency, age, weight, height, or BMI between the analyzed groups.

According to the current study, there was no statistically significant difference in comorbidities between the non-survivorsand survivors groups or in the cause of admission or GCS score. Another study by**Karamouzoset al. [15]** reported that upon study completion, 28 patients (65.6%) were successfully discharged from the hospital, and 15 (34.9%) passed away.

Karamouzoset al. [15] reported that numerous indicators and ratings have been used throughout the disease, but their sensitivity and specificity vary since there is no single "gold standard" for diagnosing sepsis. Patients with poor outcomes reported higher scores on clinical practice-wide scales such as the sofa, APACHE II, and SAPS II.

However, there were statistically significant differences between the non-survivors and survivors groups in terms of PRISM III and sofa scores. By these findings, **Baloch et al.[16]** reported that the p-SOFA and PRISM scores were significantly high among critically ill children. Additionally, **El-Mashad et al.[17]** reported that the sofa score was greater in critically ill children with sepsis.

Blood analysis is a quick and accessible test where common clinical signs include the neutrophil count, lymphocyte count, and platelet count **[18]**.

According to the current study, there was a statistically significant positive relationship between the NLR and the PLR, sofa score, and PRISM III score. However, the Glasgow Coma Scale (GCS) score and NLR were significantly negatively related. A statistically significant positive association was observed between the PLR and the NLR, SOFA score, and PRISM III score.Conversely, a statistically insignificant negative correlation was observed between the PLR and Glasgow coma scale score.

Similarly, according to the Spearman correlation test, **Mira et al. [19]** reported that the NLR and sepsis score were significantly positively related [Spearman rho=0.23, p=0.02].

In regard to predicting bacterial infection, the NLR is starting to show greater value as an inflammatory marker than is neutrophilia or lymphocytopenia alone. Inflammatory indicators for sepsis, such as the PLR and NLR, have been linked to alterations in neutrophil, platelet, and lymphocyte counts **[20].**

The current study showed that all patients within the non-survivorsgroup had positive blood cultures, and a greater percentage of patients had growth, as indicated by*Staphylococcus aureus* (57.6%) followed by Klebsiella (21.2%). Similarly,**Wilar et al. [21]**reported that in forty-four blood cultures, the most common organism was *Klebsiella pneumoniae,*followed by *Candida albicans*.

The primary cause of infection in critical-care environments, *Staphylococcus aureus*, is responsible for a considerable amount of morbidity and mortality. It can cause a wide variety of infections in humans, ranging from nosocomial infections that impede the clinical course of patients with other primary medical or surgical disease processes to potentially fatal infections in otherwise healthy persons**[22].**

According to the results of the present study, there was a significant difference in the NLR between the studied groups (with the non survivors group showing a substantially greater difference), which is consistent with the findings of**Pasaribu et al. [23],** who reported an increase in the NLR in patients with sepsis compared to patients without sepsis.

In reaction to systemic inflammation, the body's immune system naturally increases the number of circulating leukocytes, with a decrease in lymphocyte count and an increase in neutrophil count. Proinflammatory cytokines released by macrophages, such as interleukin (IL)-6, IL-1, and TNF-α, cause a rise in neutrophils, whereas increased secretion of glucocorticoid hormones, which repress lymphocyte synthesis, causes a decrease in lymphocytes **[24].** Additionally, either direct or indirect activation of the bone marrow results in an increase in the NLR and an increase in the quantity of neutrophils in the blood **[10]**. The NLR may therefore be a helpful indicator and forecaster of inflammation induced by the inflammatory process itself. Completing complete blood counts, which are frequently performed on patients with suspected sepsis, makes it simple to compute the NLR and PLR**[21].**

The mechanism underlying the sepsis-related lymphocytopenia process, which involves the speeding up of the apoptotic process and the marginalization and redistribution of lymphocytesthroughout the lymphatic

system, is what causes an increase in the NLR.

When germs or products cause macrophages to release proapoptotic chemicals such as glucocorticoids, nitric oxide (NO), and tumor necrosis factor (TNF)-a, the apoptotic process takes place. After that, this state inhibits the formation of lymphocytes**[25]**.

According to the results of the present study, there was a statistically significant difference in the PLR among the studied groups (significantly greater among the patient groups), which is in agreement with the findings of **Pasaribu et al.[23],** who reported that the PLR is a valuable biomarker for predicting the severity of an inflammatory process because it is positively correlated with the occurrence of inflammation.

In contrast, **Aygün et al.[26]** reported that a statistically significant difference in platelet count and sepsis incidence were related. The platelet count was noticeably lower in the sepsis group. There was no connection found between sepsis and the PLR.

In contrast to the results obtained in this study**, Aydemir et al. [27]**reported that the PLR values did not significantly differ between patients with and without sepsis. When there is a disparity in the diagnosis of sepsis, this discrepancy may be caused by the timing of blood draws. There was a statistically significant decrease in the PLT during the first three days of sepsis in gram-positive sepsis patients, during the first four days in gram-negative sepsis patients, and during the first five days in fungal sepsis patients.

The current study showed that the best cut-off of the NLR for the prediction of mortality among patients with sepsis was ≥6.8521, with an area under the curve of 0.902, sensitivity of 78.6%, specificity of 78.9%, positive predictive value of 73.3%, negative predictive value of 83.3% and overall accuracy of 78.8% ($p<0.001$). The best cut-off of PLR in prediction of mortality among patients with sepsis is ≥126.7365, with area under curve 0.868, sensitivity 78.6%, specificity 73.7%, positive predictive value 68.8%, negative predictive value 82.4% and overall accuracy 75.8% ($p<0.001$). Like our results, **Mathews et al.[8]** reported that a 61.1% increase in the NLR was the expected result and that increased survival was associated with a decreased NLR. A sensitivity of 89.2% and specificity of 61.1% may predict mortality when the NLR increases to >0.2. **Yoldas et al. [28]**reported that the NLRs for patients who survived and died were 2.06 (1.18-21.68) and 10.42 (2.85-48.2), respectively. When the NLR of deceased patients was compared to that of living patients, there was a considerable increase ($p<0.001$). The NLR can predict mortality in critically ill patients.

Shenoy and Patil [29]reported that the area under the curve (AUC) for the NLR and PLR in predicting mortality was 0.617 (95% CI=0.535–0.7) and 0.609 (95% CI=0.521–0.696), respectively. The NLR had a threshold value of 2.18, a sensitivity of 54%, and a specificity of 67% for predicting death. The risk of death was 2.2 times greater for those with a high NLR (95% CI=1.3–3.6, $p=0.003$). The cut-off point for the PLR was 34.1, with a sensitivity of 68% and specificity of 55%. A high PLR was associated with a 2.4-fold greater risk of mortality (95% CI=1.3–4.2, $p=0.002$).

This study is limited by itssingle-centernature and the small sample size.

CONCLUSIONS

PLR and NLR are dependable predictive indicators that are inexpensive and rapidly

obtainable in the early detection of sepsis onset. They assist in identifying children at high risk for sepsis, predicting their mortality, and objectively monitoring clinical improvement. Further prospective multicentre studies involving serial monitoring of PLR and NLR could provide additional insights into their usefulness in pediatric critical illness. More research is necessary to determine whether these ratios can be utilized to identify individuals who require critical care

Declaration of interest

The authors report no conflicts of interest.
The authors are responsible for the content and writing of the paper.

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