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To Study the Diagnostic Value of Eosinopenia and Neutrophil to Lymphocyte Ratio in Early Onset Neonatal Sepsis

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Abstract

Early-onset neonatal sepsis (EONS) is a critical condition that occurs within the first 72 hours of life, presenting a significant challenge for early diagnosis. Prompt identification of EONS is essential to initiate timely treatment and reduce neonatal morbidity and mortality. This study evaluates the diagnostic utility of two hematological markers—eosinopenia (reduced eosinophil count) and the neutrophil-to-lymphocyte ratio (NLR)—as potential indicators for early detection of EONS. Eosinopenia and an elevated NLR have been proposed as markers of systemic infection, but their role in neonatal sepsis diagnosis remains underexplored. In this study, a cohort of neonates with suspected EONS was assessed for these markers and compared with traditional diagnostic tools, such as blood cultures and clinical evaluation. The primary objective was to determine the sensitivity, specificity, and predictive value of eosinopenia and NLR for diagnosing EONS. The results showed that both eosinopenia and an elevated NLR were significantly associated with the presence of sepsis. Specifically, eosinopenia demonstrated a strong negative predictive value, while an elevated NLR exhibited high sensitivity. When combined, these markers provided improved diagnostic accuracy compared to either marker alone, highlighting their potential as valuable adjuncts to traditional diagnostic methods. Incorporating eosinopenia and NLR into clinical practice could enhance the early identification of neonates at risk for sepsis, enabling quicker intervention and reducing diagnostic delays. Additionally, these markers offer a cost-effective, rapid, and non-invasive alternative to more conventional diagnostic tests, such as blood culture, which often require longer turnaround times. In conclusion, eosinopenia and NLR are promising biomarkers for EONS, and further large-scale studies are needed to

confirm their clinical effectiveness and integrate them into standard neonatal sepsis diagnostic protocols.

Keywords: early-onset neonatal sepsis, eosinopenia, neutrophil-to-lymphocyte ratio, diagnostic markers, sensitivity, specificity, blood culture, neonatal infection, biomarkers.

Introduction

Neonatal sepsis (NS) is a critical condition in newborns, characterized by the invasion of pathogenic microorganisms into the bloodstream, typically occurring within the first month of life [1]. It remains a major challenge in neonatal care due to its high morbidity and mortality rates. According to the World Health Organization, infections contribute to approximately one million neonatal deaths annually, accounting for 25% of all neonatal deaths and 10% of infant mortality globally [2]. Neonatal sepsis is divided into two categories: early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS), based on the timing of symptom onset. EONS occurs within the first 72 hours of life, often caused by pathogens acquired during delivery, while LONS develops after 72 hours and is typically associated with postnatal infections from the environment [3].

In Indonesia, neonatal sepsis remains a significant cause of neonatal mortality. The 2012 Indonesian Demographic Health Survey reported 32 deaths per 1000 live births due to neonatal infections, highlighting the public health challenge posed by these conditions. At R.D. Kandou General Hospital in Manado, neonatal sepsis contributed to 30.1% of neonatal deaths, further underscoring the need for improved diagnostic and treatment strategies [4]. Diagnosing EONS presents a considerable challenge due to the nonspecific nature of its clinical manifestations, which can overlap with other neonatal conditions [5]. Common clinical signs of EONS include hyper- or hypothermia, apnea or bradycardia, feeding intolerance, abdominal distension, lethargy, hypotonia, hypotension, and skin lesions such as petechial rashes or abscesses. Laboratory tests commonly used to diagnose EONS include abnormal white blood cell (WBC) counts, immature-to-total neutrophil ratio (ITR), platelet counts, and elevated C-reactive protein (CRP) levels [6]. Blood cultures remain the gold standard for confirming NS but are often inconclusive and time-consuming, delaying critical treatment and contributing to poor clinical outcomes. In light of these limitations, there is a growing need for rapid, reliable, and cost-effective diagnostic tools for EONS [7]. Eosinophils, which are involved in type 2 inflammation, may have a significant role in the immune dysregulation observed in neonatal sepsis. Several studies suggest that eosinopenia, a marked reduction in eosinophil count, is closely associated with sepsis. In adults, persistent eosinopenia beyond 48 hours of ICU admission has been linked to increased mortality and complications in septic patients [8]. Although the role of eosinophils in neonatal sepsis is not fully understood, existing research supports their potential as biomarkers for the severity and prognosis of the disease. Investigating the mechanisms behind eosinopenia could lead to enhanced diagnostic accuracy and improved therapeutic strategies for neonates with sepsis [9]. Recent studies have also focused on the neutrophil-to-lymphocyte ratio (NLR) as a potential biomarker for sepsis. NLR, a ratio of neutrophils to lymphocytes in the blood, has been shown to correlate with systemic inflammation and infection in adult populations. However, its diagnostic value in neonatal sepsis, particularly EONS, remains underexplored. While some

research has investigated eosinopenia and NLR in adult sepsis populations, there is a lack of consensus on their applicability to neonates, as most studies used adult-derived cutoff points that may not be directly transferable to neonates [10].

Given the high burden of neonatal sepsis and the limitations of current diagnostic methods, this study aims to evaluate the diagnostic value of eosinopenia and NLR specifically in neonates with EONS [11]. By establishing neonatal-specific cutoff points for these biomarkers, the study seeks to improve the early detection and treatment of EONS, ultimately reducing both morbidity and mortality in affected neonates [12]. The timely diagnosis of EONS remains a significant challenge due to its nonspecific clinical features. Blood cultures, while the gold standard, are often slow to yield results, delaying treatment initiation. In contrast, biomarkers like eosinopenia and NLR provide a rapid, reliable, and cost-effective means of screening neonates for sepsis, potentially leading to earlier intervention and better clinical outcomes [13]. This research aims to address a critical gap in neonatal healthcare by exploring the diagnostic value of eosinopenia and NLR as biomarkers for EONS. The results could offer valuable insights into the clinical utility of these markers, helping clinicians make quicker and more accurate diagnostic decisions, which in turn could reduce the high mortality rates associated with neonatal sepsis [14]. By focusing on the early detection of EONS using these biomarkers, this study has the potential to significantly improve neonatal survival rates and overall health outcomes in the face of a persistent and challenging public health issue [15].

This study aims to evaluate the sensitivity and specificity of two potential biomarkers—eosinopenia and the neutrophil-to-lymphocyte ratio (NLR)—in detecting early-onset neonatal sepsis (EONS). By assessing these markers in neonates with suspected EONS, the research seeks to determine their diagnostic accuracy in comparison to traditional methods. The findings will provide insight into how effectively eosinopenia and NLR can be used for early detection, potentially offering a rapid, cost-effective approach to diagnosing EONS. The results may contribute to improving clinical outcomes by enabling quicker identification and treatment of neonates at risk for sepsis.

Methodology

This is a prospective observational study conducted in the NICU at KIMS Hospital, Bangalore, over an 18-month period (November 2022 to June 2024). The study will include neonates, aged 0-72 hours, who meet specific inclusion criteria, such as risk factors for sepsis and clinical presentations suggestive of infection. An ethical approval has been obtained from the Ethical Approval Committee. Data will be collected through blood samples for septic workup, including complete blood count, CRP levels, and blood cultures. Neonates will be categorized into two groups: Early-Onset Neonatal Sepsis (EONS) and Non-EONS based on clinical and lab criteria. The study will analyze eosinophil count and neutrophil-to-lymphocyte ratio to evaluate their diagnostic value. Statistical analysis will be performed using SPSS, with categorical data analyzed via chi-square test and numerical data using Mann-Whitney U test, considering a p-value <0.05 as statistically significant.

Result

Out of 80 newborns, 63.75% had early onset neonatal sepsis (EONS).65% were premature, with 65.38% of premature babies affected by sepsis. The majority

(47.5%) were born between 32 to 36 weeks, 33.75% were born at or after 37 weeks, and 12.5% were born between 28 to 31 weeks. The smallest group, 6.25%, was born before 28 weeks. Additionally, 71.25% had low birth weight (LBW), and 64.9% of LBW babies had sepsis. Maternal risk factors included 7.5% with foul-smelling liquor, 67% of whom developed sepsis, and 36.25% had prolonged rupture of membranes.

Table 1: Total cases of sepsis (EONS)

	Frequency	Percentage
Non-EONS	29	36.25
EONS	51	63.75
Total	80	100

Out of 80 participants, 63.75% babies had Early onset neonatal sepsis.

Table 2: Distribution based on prematurity

Prematurity	Frequency	Percentage
No	28	35
Yes	52	65
Total	80	100

In the study, out of 80 newborns 65% were premature babies.

Table 3: Showing cross tabulation of sepsis and prematurity

	EONS	Non EONS	Total
Prematurity	34	18	52
	65.38%	34.62%	

In the study, out of 52 premature cases 65.38% had sepsis.

Table 4: Showing cross tabulation of sepsis and gestational age

		EONS	Non EONS	Total
Gestational age	Less than 28 weeks	3	2	5
		60%	40%	
	28 to 32 weeks	7	3	10
		70%	30%	
	32 to 37 weeks	24	14	38
		63.15%	36.85%	
	More than or equal weeks	17	10	27
		63%	37%	

In the study, out of 5 newborns with gestational age Less than 28 weeks- 60% had early onset neonatal sepsis. Newborns with gestational age 28 to 32 weeks-70% had sepsis.63.15% of Newborns with gestational age 32 to 37 weeks had sepsis.

Table 5: Distribution based on low birth weight

Low birth weight	Frequency	Percentage
No	23	28.75
Yes	57	71.25
Total	80	100

Out of 80 newborn babies 71.25% had low birth weight.

Table 6: Showing cross tabulation of Sepsis and LBW

LBW	EONS	Non EONS	Total
Yes	37	20	57
	64.90%	35.08%	

The above table shows, In the LBW group, the majority 64.9% were with sepsis

Table 7: Showing cross tabulation of Sepsis and PROM (>18hrs)

Risk Factor	EONS	Non-EONS	Total	% of Total
PROM (Prolonged Rupture of Membranes)	12	17	29	36.25%

Non-PROM	51	0	51	63.75%

Among PROM cases, 58.6% had no sepsis, while 41.4% were diagnosed with sepsis.

Table 8: Distribution based on secondary Apnea

Secondary Apnea	Frequency	Percentage
No	63	78.75%
Yes	17	21.25%
Total	80	100%

Among the 80 newborn cases,21.25% had secondary apnea as a clinical risk factors of sepsis in this study.

Table 9: Showing cross tabulation of Sepsis and Secondary apnea

Secondary Apnea	EONS	Non-EONS	Total	% of Total
Yes	13	4	17	21.25%
No	50	13	63	78.75%
Total	63	17	80	100%

Among 17 cases of secondary apnea as a risk factor for sepsis majority of 76.5% had sepsis

Table 10: Showing cross tabulation of Sepsis and Refusal of feeds

Refusal of Feeds	EONS	Non-EONS	Total	% of Total
Yes	26	4	30	37.50%
No	37	9	46	62.50%
Total	63	17	80	100%

Among the 30 cases of refusal of food 86.7% had sepsis and 13.3% had no sepsis

Table 11: Showing cross tabulation of Sepsis and Shock

Shock	EONS	Non-EONS	Total	% of Total
Yes	38	6	44	55%
No	25	11	36	45%
Total	63	17	80	100%

Among the 44 shock cases, majority of 86.4% had sepsis and 13.6% had no sepsis.

Table 12: Showing cross tabulation of Sepsis and Lethargy

Lethargy	EONS	Non-EONS	Total	% of Total
Yes	44	6	50	62.50%
No	19	11	30	37.50%
Total	63	17	80	100%

Among the 50 lethargy cases, 88% had sepsis and 12% had no sepsis.

Table 13: Showing distribution based on CRP

CRP	Frequency	Percentage
Negative	28	35%
Positive	52	65%
Total	80	100%

Among the 80 participants, 65% of the newborns had raised C reactive protein more than 0.5mg/dl.

Table 14: Showing cross tabulation of Sepsis and CRP

		No sepsis	sepsis
CRP	Negative	27	1
		93.1%	2.0%
	Positive	2	50
		6.9%	98.0%
Total		29	51
		100.0%	100.0%

The above table shows, In the sepsis group, 1(2.0%) had a negative CRP result, and 50 (98.0%) had a positive result. Among CRP positive cases 96% cases had sepsis.

The above table shows, In the sepsis group, 1(2.0%) had a negative CRP result, and 50 (98.0%) had a positive result. Among CRP positive cases 96% cases had sepsis.

Table 15: Showing frequency of culture positive sepsis and clinical sepsis in EONS group

Type of Sepsis	Frequency	Percent in EONS
Culture Positive Sepsis	15	30%
Clinical Sepsis	36	70%

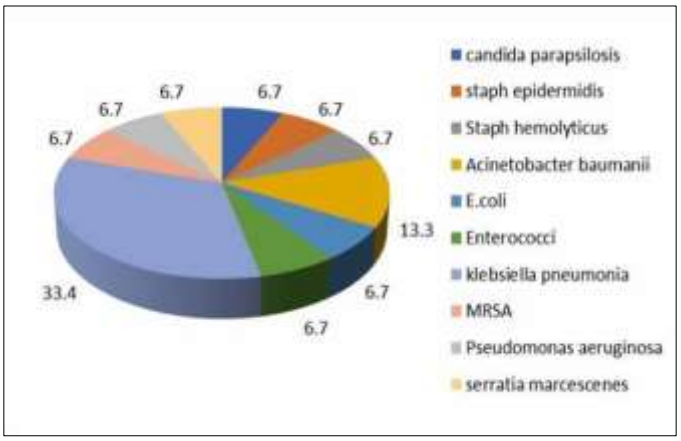
In the study, 30% of the 51 sepsis cases had positive blood cultures, while 70% were diagnosed based on clinical presentation and sepsis risk factors. Among 80 cases 18.75% were with culture-positive sepsis and 45% with clinical sepsis.

Table 16: Distribution of blood cultures in study population

Blood Culture	Frequency	Percent
Culture Positive	15	18.70%
Culture Negative	65	81.30%
Total	80	100%

Majority of 81.3% were culture negative and 18.7% are culture positive.

Graph 1: Representation of organisms isolated in blood cultures



Predominate one is klebsiella pneumonia 5(33.4%)

Table 17: WBC and sepsis

Condition	EONS	Non-EONS	Total	% of Total
Leucopenia	18	0	18	100%
Leucocytosis	10	7	17	58.82% (EONS) / 41.18% (Non-EONS)

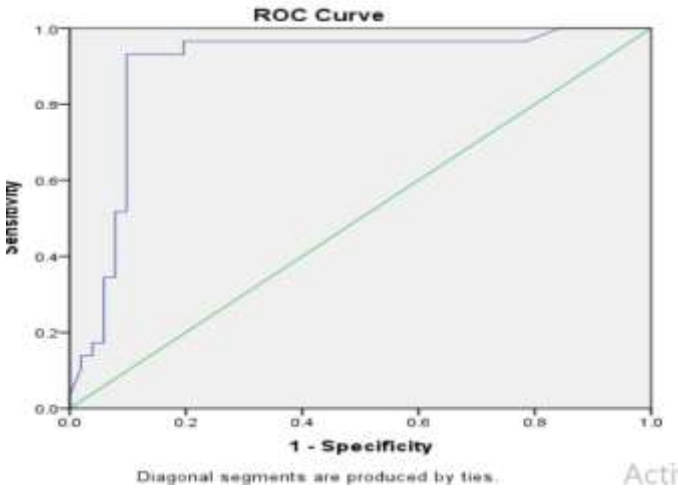
In the study out of 18 babies with leucopenia (WBC <5000), all of them (100%) had sepsis. Leucocytosis (WBC >20,000) was seen in 17 patients ,among them majority of 58.8% had sepsis.

Table 18: Showing comparison of AEC between sepsis and no sepsis group

Parameter	EONS	Non-EONS	U Value	P Value
AEC	Median: 110.000	Median: 300.000	150.5	0.000*
	IQR: (92-156)	IQR: (226-415)		

The table compares AEC between infants with and without sepsis. The sepsis group has an average AEC of 110 (IQR: 92-156), while the no sepsis group has 300 (IQR: 226-415). The U value is 150.500, with a significant p value of 0.000**.**

Graph 2: ROC curve for AEC



This study found that using an AEC cutoff of 140 for early onset neonatal sepsis, the area under the curve was

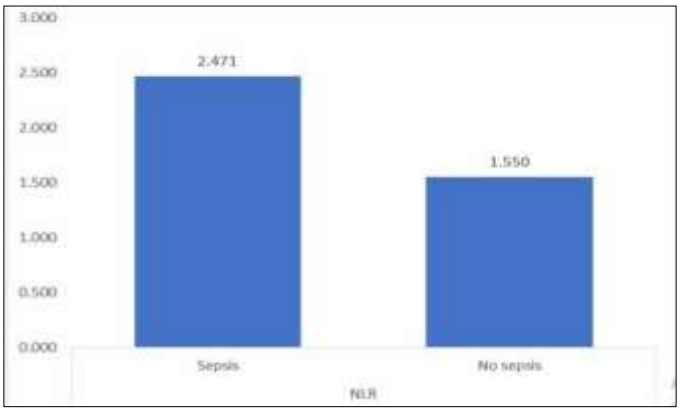
0.898 (p<0.001). Sensitivity was 96.6%, specificity 65%, PPV 90.5%, and NPV 78.1%.

Table 19: Showing comparison of absolute Neutrophil count (ANC) between sepsis and no sepsis group

Parameter	EONS	Non-EONS	U Value	P Value
ANC	Median: 7082.000	Median: 7700.000	563	0.041*
	IQR: (3150-12400)	IQR: (5257-12420)		

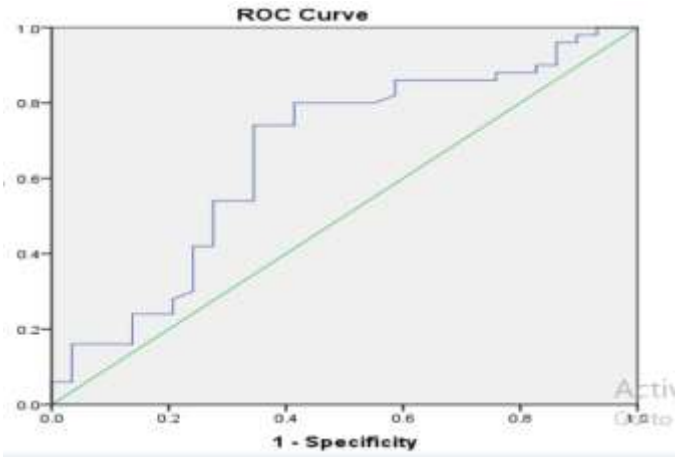
The sepsis group had an average neutrophil count of 7082 (IQR: 3150-12400), while the no sepsis group had 7700 (IQR: 5257-12420). The U statistic was 563.0, with a significant p-value of 0.041.

Graph 3: Representing NLR



The sepsis group had an average NLR of 2.471 (IQR: 1.710-3.650), while the no sepsis group had 1.550 (IQR: 1.010-2.584). The Mann-Whitney U test (U=490.000, p=0.017) showed a significant difference.

Graph 4: ROC curve for NLR



Using a cutoff of 1.57 for NLR in early onset neonatal sepsis, the AUC was 0.662 (p<0.05). Sensitivity was 80.1%, specificity 52.3%, PPV 75.2%, and NPV 89.3%.

Discussion

This study aimed to explore factors associated with early onset neonatal sepsis (EONS) and assess the diagnostic value of biomarkers, specifically eosinophil count (AEC) and neutrophil-to-lymphocyte ratio (NLR). The analysis incorporated chi-square tests for categorical variables and Mann-Whitney U tests for numerical data, considering a p-value of less than 0.05 as statistically significant [16]. The research delves into various risk factors and clinical presentations such as gestational age, prematurity, low birth weight (LBW), foul-smelling liquor, prolonged rupture of membranes (PROM), secondary apnea, refusal of feeds, shock, lethargy, and C-reactive protein (CRP) levels [17]. Among the 80 neonates included in the study, gestational age was a critical factor in the prevalence of EONS. The majority of infants were born between 32 and 36 weeks, which accounted for 47.5% of the total. This finding aligns with other studies, such as Stoll et al. (2011), which reported a higher risk of EONS in preterm infants, especially those born between 32 and 36 weeks. Notably, the prevalence of EONS was significantly higher in infants born at earlier gestational ages. For

instance, 60% of infants born before 28 weeks and 70% of those born between 28 and 32 weeks developed EONS. This aligns with the established fact that preterm infants are more vulnerable to infections due to their immature immune systems [18].

Prematurity was a significant risk factor in this study, with 65% of the neonates being preterm, and 65.38% of these infants developed EONS. These findings are consistent with Schrag et al. (2006), who highlighted the increased risk of sepsis in premature infants due to factors like underdeveloped immune systems and prolonged hospital stays [19]. This underscores the importance of proactive monitoring and infection control measures in neonatal intensive care units (NICUs). Low birth weight (LBW) also emerged as a crucial factor, with 71.25% of the infants in this study being classified as LBW. Among this group, 64.9% developed sepsis. These results corroborate the work of Adams-Chapman (2006), which found that LBW infants are more susceptible to infections due to factors like compromised skin integrity and prolonged exposure to invasive procedures. This highlights the need for targeted interventions in LBW infants to minimize infection risks [20].

The study also examined maternal risk factors, including foul-smelling liquor and prolonged rupture of membranes (PROM). Foul-smelling liquor, which signals a potential intra-amniotic infection, was observed in 7.5% of the cases, with 66.7% of these infants developing sepsis [21]. This finding aligns with Tita et al. (2010), who found a strong association between intra-amniotic infection and neonatal sepsis. Similarly, PROM for over 18 hours was found in 36.25% of the cases, and 41.4% of these infants developed sepsis. PROM increases the risk of ascending infections due to prolonged exposure to the external environment. Several clinical risk factors were also significantly associated with EONS. Secondary apnea was present in 21.25% of the cases, with 76.5% of these infants developing sepsis [22]. Other clinical signs like shock and lethargy were observed in 86.4% and 88% of the infants with EONS, respectively. These findings align with prior studies identifying these symptoms as critical clinical indicators of neonatal infection. For example, Nasser et al. (2015) identified respiratory symptoms as the most common sign, while our study found that lethargy was the most frequent sign of sepsis. CRP levels were measured as part of the diagnostic workup, with 65% of participants showing elevated CRP (>0.5 mg/dl). Among these, 98% developed sepsis, suggesting that CRP is a reliable marker for detecting neonatal infections [23].

The sensitivity of CRP in this study was 96.6%, and specificity was 65%, supporting its utility as a diagnostic tool for EONS. White blood cell (WBC) counts were also assessed, with leukopenia (WBC <5000) present in 18 cases, all of whom had sepsis. In contrast, leucocytosis (WBC >20,000) was seen in 17 cases, of which 58.8% developed sepsis. These findings are consistent with Hornik et al. (2012), which identified abnormal WBC counts as a common feature in neonates with sepsis. Regarding the diagnostic accuracy of AEC, the median count for the sepsis group was 110, significantly lower than the 300 median in the non-sepsis group. The area under the curve (AUC) for AEC was 0.898, suggesting strong diagnostic potential [24]. With a cutoff of 140, AEC demonstrated high sensitivity (96.6%) and moderate specificity (65%), making it a useful marker for detecting EONS. This finding is consistent with previous studies that reported significantly lower AEC in septic infants. The

Neutrophil-to-Lymphocyte Ratio (NLR) was also evaluated as a diagnostic tool [25].

The median NLR was significantly higher in the sepsis group (2.471) compared to the non-sepsis group (1.550). The AUC for NLR was 0.662, showing moderate diagnostic accuracy. With a cutoff value of 1.57, NLR demonstrated a sensitivity of 80.1% and specificity of 52.3%, indicating its potential utility in diagnosing EONS, though with lower specificity compared to AEC[26]. Blood culture results revealed 30% of the EONS group had positive cultures. This finding is consistent with previous research, which suggests that blood culture sensitivity in detecting neonatal sepsis can vary based on factors such as antibiotic use, culture techniques, and organism load [27]. In conclusion, this study provides valuable insights into the risk factors and diagnostic markers for EONS, particularly the role of AEC and NLR. The findings reinforce the importance of early diagnosis and intervention in neonates, especially in premature, LBW, and clinically at-risk infants, to reduce the mortality and morbidity associated with neonatal sepsis [28].

This study included 80 neonates with risk factors or clinical features of sepsis, 51 of whom were diagnosed with sepsis, 70% of them clinically. Blood cultures identified 15 cases (30%) of culture-positive sepsis, with *Klebsiella pneumoniae* being the most common pathogen. EONS incidence increased with decreasing gestational age. Leucopenia was observed in 18 cases, all of which had sepsis, while leucocytosis was seen in 17 cases, with 58.8% testing positive for sepsis. The mean absolute neutrophil count (ANC) and eosinophil count (AEC) were significantly lower, while neutrophil-to-lymphocyte ratio (NLR) was higher in sepsis cases. AEC cut-off value was 140, with 96.6% sensitivity and 65% specificity. NLR cut-off was 1.57, with sensitivity of 80.1% and specificity of 52.3%.

Conclusion

Eosinopenia and elevated NLR are valuable diagnostic markers for early onset neonatal sepsis (EONS). AEC exhibited higher sensitivity and specificity than NLR. When combined with clinical signs and traditional markers like CRP, these parameters can improve early EONS diagnosis. The study highlights the higher prevalence of EONS in premature and low birth weight infants, emphasizing the importance of vigilant monitoring in these high-risk groups to ensure timely detection and intervention. These findings suggest that incorporating AEC and NLR into routine assessments can enhance neonatal sepsis management and potentially reduce associated morbidity and mortality.

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