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The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early Onset Neonatal Sepsis

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ABSTRACT

Introduction: For neonates, early-onset sepsis is still a prevalent and deadly disease. In adult studies, the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been shown to have relevant relationships with inflammatory markers and the severity of various disorders.

Aim: The purpose of this study was to see how useful the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are as diagnostic adjunct tests for term infants with neonatal early-onset sepsis (EOS).

Methodology: A case-control study, comprised 150 newborns (100 newborns with neonatal sepsis who were admitted to NICU (Menoufia University Hospital, from December 2019 to February 2021) within the first three postnatal days as a case group and 50 healthy newborns as a control group). History taking, full clinical examination, complete blood picture, C-reactive protein and blood culture, neutrophil to lymphocyte ratio(NLR) and platelet to lymphocyte ratio (PLR) were done for all newborns.

Results: There were no-significant differences between patient and control groups as regard gestational age, gender, mode of delivery, gestational age and birth weight. Respiratory distress and tachycardia were the most common clinical sign so fearly-onset sepsis (EOS). As regard the vital data patient group had higher respiratory rate and heart rate of SPO2 neutrophil there was significant difference between patient and control groups as regard immature to total ratio. Patient group had higher neutrophil count, NLR and PLR ratios and CRP ratio than control group. As regard blood culture, Klebsiella, Pseudomonas and Staphaureus were the most common organism. Additionally, the sensitivity of NLR and PLR to diagnose sepsis were100%, 83.3%, respectively. Specificity was 100% and 100%, respectively, at cutoff value of ≥6.79 and >27.24, with accuracy of96%,85.6%, respectively.

Conclusion: As diagnostic indicators for early-onset newborn sepsis, the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), I/T ratio, and serum CRP levels demonstrated good sensitivity and specificity.

Key Words: Early Onset, Neonatal Sepsis, Neutrophil Lymphocyte Ratio, Pediatric intensive care, Platelet-lymphocyte ratio

INTRODUCTION

Neonatal Sepsis is a life-threatening condition with significantly high level of morbidity and mortality in both preterm and term infants. It is roughly characterized as a systemic inflammatory response that develops in the newborn era as a result of a verified or suspected infection.[1] Early detection and treatment of infections in newborns often insufficient in impoverished nations. Clinical findings of sepsis in neonates are difficult because many of the symptoms relating to sepsis are obscure and they can be revealed with noninfectious conditions.[1]

The main point in treatment is an early diagnosis and appropriate treatment with antibiotics much earlier before the blood culture results are obtained, and the importance of a suspicion index based on clinic and laboratory parameters should be emphasized.[2] Neonatal Sepsis is divided into early-onset sepsis(EOS)and late-onset sepsis.[3] Neonatal early-onset sepsis is defined as the onset of symptoms before 7 days of age, although some experts limit the definition to infections occurring within the first 72 hours of life.[4]

Neonatal early-onset sepsis defined as a positive blood or cerebrospinal fluid(CSF) bacterial culture at <72 hours of age, is 0.98 infections per 1000 live births, with rates

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inversely related to birth weight (BW), (0.57 per 1000 live births for > 2500g BW).[5] Numerous sepsis biomarkers have been evaluated for early detection of neonatal early-onset sepsis, but, to date, there is no single biomarker that fulfills all essential criteria.[6]

The neutrophil to lymphocyte ratio(NLR), because it combines neutrophils and lymphocytes in the calculation, is considered comparatively more stable than the absolute counts described above.[6] The neutrophil to lymphocyte ratio has been reported as a predictor of severity and clinical outcome in patients with community acquired pneumonia.[7]

Recently, two blood cell subtype ratios, the neutrophil to lymphocyte ratio and the platelet to lymphocyte ratio(PLR), have been reported as useful systemic inflammatory markers and prognostic indicators of adverse cardiovascular events and cancer.[8,9]

The aim of this study: To evaluate the value of NLR and PLR as diagnostic adjunct tests for early detecting of neonatal early-onset sepsis(EOS), workup among term of AGA neonates.

PATIENTS AND METHODS

A case-control study was conducted at Neonatal Intensive Care Units(NICUs) of the Pediatric Department at Menoufia University Hospital during the period from December 2019 to February 2021. The study was conducted on 150 term neonates, divided into **Group** I: The patient group composed of 100 term neonates who admitted to NICU within the first three postnatal days with clinical laboratory findings and clinical features suggesting EOS, and **Group II:** The control group composed of 50 term neonates, AGA, without any clinical, and laboratory signs of infection.

Ethical Consideration: All participants were volunteers. Written or informed consent was obtained from the parents of both patient and control groups after explaining the aim of study. Approval of the study protocol was obtained by Ethical Scientific Committee of Faculty of medicine, Menoufia University (ID: 8/2020PEDI5).

Inclusion criteria: included patients with term, AGA, neonates suffering suggested EOS.

Exclusion criteria: included patients with multiple pregnancies, prematurity(<37completed gestational weeks), post maturity (>42 completed gestational weeks), small for gestational age (SGA) or large for gestational age (LGA), negative value of CRP, maternal hypertension and pre-eclampsia, infant of diabetes mother(IDM), infant of mothers used , infant with congenital major anomalies, cyanoticcongenital heart disease and patients refused to participate in the study.

All selected patients included in this study were subjected to the following:

Full history taking including Personal, present, past and family history such as, name, age, sex, birthdate, BW, maternal age and mode of delivery. through Clinical examination: including weight, length, head circumference, neonatal reflexes and gestational age assessment. Local examination to detect clinical signs of sepsis including Respiratory dysfunction: respiratory distress, intercostal retraction, elevated oxygen demand and symptoms of respiratory distress. Circulatory dysfunction as impaired systemic breathing, hypotension, tachycardia, pain and excessive capillary refilling. Gastrointestinal dysfunction: gastrointestinal distension, bloody diarrhea, food intolerance, hepatomegaly and jaundice. Neurological dysfunction: irritability, hypotonic, lethargy.

Laboratory investigations were done: CBC, CRP, Immature to total neutrophil and blood culture. Then SPO2, NLR and PLR were calculated.

Statistical Analysis: Results were collected, tabulated, statistically analyzed by SPSSversion22. Two types of statistics were done. Descriptive statistics included Percentage (%), mean (x) and standard deviation (SD). Analytic statistics included chi-square test($\chi 2$), student t-test, Mann-Whitney test, Spearman's correlation(r), ROC curves and cutoff values which included sensitivity and specificity values. $P<0.05$ was considered statistically significant.

RESULTS

Table 1: Demographic data among the studied group.

Variables	Patients group N=100		Control group N=50		X^2	*p-value*
	No	%	No	%		
Mode of Delivery						
Vaginal	60	60	17	34	4.286	**0.038***
Caesarean section	40	40	33	66		
Maternal age/ year Mean ±SD	25.50±4.19		30.93±0.50		t= 1.27	0.480
Gender						
Male	43	43	17	34	0.635	0.426
Female	57	57	33	66		
Gestational age (weeks)	39.1±1.79		38.9±1.52		0.027	0.873
Birth Weight (Kg) Mean ±SD	2.78±0.82		3.40±0.67		t= 1.124	0.266
Length	35.4±6.12		32±8.5		1.180	0.675
Head Circumference	31.12±4.52		33.6±1.46		0.915	0.731

Table (1) showed that, there was statistically significant dif-

ference between patients' group and control group regarding mode of delivery, (p=0.038). On the other hand, there were no statistically, significant differences between patients' group and control group regarding maternal age, gender, gestational age, birth weight, length and HC(p>0.05).

Table 2: Clinical signs of early onset sepsis among the patients' groups.

Variables	Patients' groups N=100	
	No	%
Apnea		
No	63	63.0
Yes	37	37.0
Cyanosis		
No	60	60.0
Yes	40	40.0
Respiratory distress		
No	23	23.0
Yes	77	77.0
Poor feeding	10	10.0
No	90	90.0
Yes		
Tachycardia	50	50.0
No	50	50.0
Yes		
Bradycardia	61	61.0
No	39	39.0
Yes		
Jaundice		
No	82	82.0
Yes	18	18.0

Table (2) illustrated that, 37% of the studied patients had apnea and distention. While (40%) of them had cyanosis. Also, (77%, 90%, 50%, 39%, 18%) of the studied patients had Respiratory distress, Poor feeding, Tachycardia, and Jaundice, respectively.

Table 3: Vital signs among the studied groups.

Variables	Patients group N=100		Control group N=50		t	P value
	Mean±SD	Range	Mean±SD	Range		
Heart rate (beats/min)	142.42±2.54	140-145	128.48±7.95	120-140	41.982	**<0.001***
Respiratory rate(beats/min)	47.36±2.60	45-52	65.48±4.02	60-70	23.06	**<0.001***
Temperature(Cº)	37.14±0.15	37-37	37.19±0.27	37-37	0.689	0.29
Mean blood pressure (mmHg)					1.150	0.660
Systolic BP	115±4.8	100-120	118±2.0	110-120		
Diastolic BP	75±5.0	70-80	77±3.0	75-80		
Capillary refiring time (CRT)	3.8±0.8	3.7-3.8	3.7 ±1.0	3.7-3.8	2.918	**<0.001***
SPO2	92±2.23	90–100	96±2.23	92-100	1.16	0.710

Table (3) reported that, there was no significant difference between the studied groups regarding mean blood pressure. While, heart rate and capillary refiring time were significantly increased among patients' group(142.42±2.54, and 3.8±0.8) than control group(128.48±7.95, and 3.7±1.0). While, respiratory rate was significantly lower among patients' group(47.36±2.60), than control group(65.48±4.02). On the other hand, there was no significant difference between the studied groups regarding Mean blood pressure(mmHg),(p=0.66) and SPO2 (p=0.71).

Table 4:Laboratory investigations among the studied groups.

Lab investigations	Patient group N=100	Control group N=50	t	Pvalue
HGB(g/dl) Mean±SD	13.93±2.43	14.05±1.97	0.78	0.290
Platelets(×10 ³/UL) Mean±SD	147.53±99.37	311.83±42.81	3.255	**0.002***
WBCs(×10 ³/UL) Mean± SD	12.62±8.49	16.82±1.00	2.689	**0.009***
Neutrophils Mean±SD	13.88±0.47	3.30±0.47	U= 86.615	**<0.001****
Immature to total neutrophil Mean ±SD	0.30±0.20	0.15±0.07	4.052	**<0.001****
Lymphocyte Mean± SD	5.86±0.43	14.75±0.69	U= 59.748	**<0.001****
NLR Mean ± SD Range	2.38±0.21 2.08-2.48	0.22±0.03 0.16-0.25	56.699	**<0.001****
PLR Mean ± SD Range	5.35±1.07 4.66-6.47	6.40±0.86 5.24-7.21	4.195	**<0.001****
CRP Mean±SD	21.31±16.41	3.33±1.12	8.11	**<0.001****
CRP Negative Positive	50(50%) 50(50%)	50 (100%) 0 (0%)	X^2= 6.041	**<0.001****

WBC's: White Blood Corpuscles, HGB:Hemoglobin,CRP:C-reactive protein, SD: standard deviation
*t: independent t test U: Mann-Whitney test*significant*

Table (4) demonstrated that, WBCs, Platelets, Lymphocyte and PLR were significantly increased among control group(16.82±1.00,311.83±42.81,14.75±0.69,6.40±0.86)than patients' group (12.62±8.49, 247.53±99.37, 5.86±0.43, 5.35±1.07), respectively. While, CRP, Neutrophils, Immature to total neutrophil and NLR were significantly increased among patients' group(21.31±16.41,13.88±0.47,0.30±0.20,2.38±0.21) than control group (3.33±1.12,3.30±0.47,0.15±0.07,0.22±0.03), (p<0.05).

Table 5: Results of Blood culture among the studied groups.

Variables	Patients group N=100		X2	P value
	No	%		
Blood culture			60.00	<0.001*
No growth	**70**	**70.00**		
Positive	**30**	**30.00**		
Klebsiella	12	40.00		
Pseudomonas	6	20.00		
Staphaureus	4	13.33		
E-coli	6	20.00		
Candida	2	6.67		

Table (5) showed that, there was statistically highly significant difference between the studied patients regarding blood culture (p<0.001). Klebsiella, Pseudomonas and E-coli were the most common presented in patients' group by 40%, 20%and 20%, respectively.

Table 6: Correlation between NLR and PLR with laboratory investigation among sepsis patients.

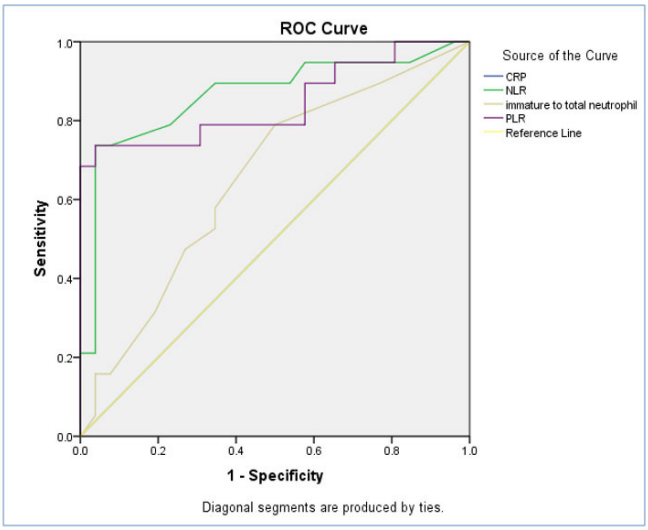
Variables	NLR		PLR	
	R	P value	r	P value
HGB(g/dl)	-0.133	0.485	-0.358	**0.005***
Platelets	0.344	0.063	-0.430	**0.001***
WBCs×10³/UL	0.261	**0.044***	0.462	**0.010***
I/Tratio	0.346	0.061	0.086	0.652
Abs. Neutrophils	-0.476	**<0.001****	0.299	0.108
Abs. lymphocyte	-0.229	0.078	0.090	0.635
CRPlevel	-0.091	0.550	0.362	**0.049***

Table (6) demonstrated that, there was significant correlation between PLR with WBCs and neutrophils (p<0.05). Also, there were significant correlations between PLR with HGB, platelet, WBCs and CRP level (p<0.05). On the other hand, Immature/ total ratio, Immature/mature ratio, absolute neutrophile and lymphocyte were no statistically.

Table 7: ROC curve results for NLR, PLR, I/Tand CRP.

Variable	Cutoff value	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
NLR	>2.52	97	100	100	97	98.2
PLR	>47.4	90	100	100	90	90.0
I/T	>0.14	76.7	96.7	95.8	90.7	97.2
CRP	>5	100	96.7	96.8	100	99.0

Table (7) presented that, the sensitivity of NLR to diagnose sepsis was 97%, specificity was 100% at cutoff value of>2.52,(100%) PPV,(97%) NPV with accuracy of 98.2%. The sensitivity of PLR to diagnose sepsis was 90%, specificity was 100% at cutoff value of >47.4, (100%) PPV, (90%) NPV with accuracy of 90%. The sensitivity of I/T to diagnose sepsis was 76.7%, specificity was 96.7% at cutoff value of >0.14, (95.8%)PPV,(90.7%) NPV with accuracy of 97.2%. The sensitivity of CRP to diagnose sepsis was100%, specificity was 96.7% at cutoff value of >5,(96.8%) PPV,(100%) NPV with accuracy of 99%, **(Figure 1).**



DISCUSSION

This cross-section case-control study was conducted at Neonatal Intensive Care Units (NICUs) of the Pediatric Department at Menoufia University Hospital from December 2019 to February 2021. The goal of this study was to see how useful the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are for early diagnosis of newborn early-onset sepsis in term AGA infants. This study was carried out on 150 terms AGA, neonates, they divided into two groups as patients' group included 100 septic terms, AGA, neonates with clinical and lab evidence of EOS, as well as control group included 50 healthy terms, AGA, neonates with no clinical, or laboratory evidence of sepsis. Full history taking, full clinical examination for all neonates included in this study and the laboratory investigations were done for all cases as complete blood count (CBC), Immature to a total neutrophil ratio (1/T ratio), neutrophil to lymphocyte ratio (NLR), Platelet to lymphocyte ratio (PLR), C-reactive protein (CRP) and Blood culture.

In our study, there was no significant difference between the patient and control group regarding gender, (table 1). This is in line with **Mira et al.**[10] who came at the same conclusion. In the sick group, however, the male gender predominated (43%). This male predominance is evident in almost all investigations of newborn animals, and it could be attributable to a gene on the X chromosome that is involved in thymus gland function or antibody manufacturing.[10]

Our findings revealed that spo2 was considerably decreased among patients compared to the control group (Table 3), which is consistent with **Can et al.**[11] findings.

Tachycardia (50%), jaundice (18%), lethargy and apnea (37%), and finally poor feeding (90%), bradycardia (39%), and cyanosis (40%) were the most common presenting signs of sepsis in our study (Table 2), which agrees with **Parajuli**

et al.[12] who found that the majority of patients had respiratory distress. **Can et al.**[11]**,** on the other hand, discovered that bradycardia and apnea were the most common indicators.

In this study, the patient group's mean platelet count was substantially lower than the control group's (P<0.001), (Table 4). **Karne et al.**[13] discovered a statistically significant difference between the patient and the control groups. This disparity is due to a combination of increased platelet breakdown and insufficient platelet synthesis during sepsis.[14]In contrast to our findings, **Can et al.**[11] discovered a nonsignificant difference in platelet count between patients and controls.

There was no significant change in WBCs between the patient and control groups (Table 4), which is consistent with **Can et al.**[11] **and Xiao et al.**[15]**.** Furthermore, **Jefferies et al.**[16] discovered that decreased WBCs were more likely to be linked to EOS than high TLC.

In our study, The I/T ratio in our study was substantially higher in the sick group than in the control group (Table 4). Our study did not correspond to **Can et al.**[11]Also, according to **Sahni et al.**[17] I/T ratio > 0.3 had a poor positive predictive value for diagnosis of EOS.

There was a highly statistically significant increase in neutrophil count between the patient and control groups in the current study (Table 4), which was consistent with **Can et al.**[11] who found that neutrophil count was significantly higher in the neonatal EOS group compared to the control group.

Table 4 shows that the lymphocyte count was considerably lower in the patient group compared to the control group, which is consistent with our findings. According to **Can et al.**[11]**,** the lymphocyte count in the patient group was considerably lower than in the control group. This difference in neutrophil and lymphocyte counts between the patient and control groups can be explained as follows: the physiological immune response of circulatory leukocytes to a variety of stressful events is characterized by increased neutrophil count and decreased lymphocyte count. An inflammatory reaction causes an increase in total leukocyte and neutrophil count, which is caused by a microorganism infection.[18]

In the current study, between the sick and control groups, there was a highly statistically significant change in NLR (Table 4). Our findings support those of **Can et al.**[11]**, Omran et al.**[19]**, and Wilar et al.**[20]**,** who found that NLR was considerably greater in the patient group compared to the control group.

In terms of PLR, our findings revealed a statistically significant rise in the patient group as compared to the control group (Table 4). This is in line with the findings of **Can et al.**[11]who discovered that PLR was considerably greater in the neonatal EOS group compared to the controls. **Omran et al.**[19]**,** on the other hand, discovered that there was no statistically significant difference between the patient and control groups.

In comparison to the control group, our findings revealed a very statistically significant increase in CRP levels in the patient group (Table 4). Our findings are consistent with those of **Can et al.**[11]**, and Omeran et al.**[19]

Only 30% of neonatal sepsis was culture positive in our study (Table 5). **Vaniya et al.**[21]found that culture-proven sepsis occurred in only 32% of cases with sepsis is low because it depends on the timing of the culture taken, blood volume, culture media, technique, temperature, organism density, and prepartum maternal antibiotics.

In the present study, Gram-negative bacilli, klebsiella reported (12%), gram-positive cocci (6%), staphylococcus (4%) of culture-proven sepsis, and Pseudomonas (6 %) were the most common organisms isolated (Table 5). This agrees with **Vaniya et al.**[21]**, Patel,**[22] **and Sharma,**[23] who discovered that gram-negative bacilli, primarily klebsiella, were the most common organisms. Other research, on the other hand, claimed that gram-positive bacteria, primarily staphylococci, were to blame **(Abdelhamid,**[24]**, Aku et al.**[25] **and Gowda et al.**[26] According to **Lee et al.**[27] gram-positive organisms were the most predooms organisms of EOS in Korea. This difference in isolated organisms fluctuates over time, and the antimicrobial combination should be adjusted based on the findings of the culture.

In our study, While **Omran et al.**[19] found a positive link between NLR and CRP, NLR showed a significantly negative correlation with platelet count and absolute lymphocyte count, i.e., NLR decreases when neutrophile or absolute lymphocyte count increases and vice versa (Table 6). PLR also had a strong positive connection with platelets in our investigation. i.e., PLR rises as platelets rise, and vice versa **(Table 6).**

At a cut-off point of >2.52, NLR had a sensitivity of 96 percent and a specificity of 100 percent in our investigation (Table 7). Otherwise, **Omran et al.**[19] found that the NLR cutoff point of 2.7 had a sensitivity of 80% and a specificity of 57%. This discrepancy is due to the fact that there is no correct NLR cutoff point in EOS, and all results were restricted in number of patients.

In our study, PLR had a sensitivity of 90% and a specificity of 100%, with a cut-off value of 47.4. (Table 7). While **Can et al.**[11] found that the NLR cutoff point of 6.76 had a sensitivity of 97 percent and a specificity of 100 percent in newborn early EOS, this discrepancy in results is attributable to the lack of a precise PLR cut-off point in EOS, as well as a lack of research on the subject.

In our study, the I/T ratio has a sensitivity and specificity of 96 percent in diagnosing EOS in a newborn in our in-

vestigation. In the diagnosis of EOS, however, **Saboohi et al.**[28] found that the I/T ratio had a sensitivity of 76% and a specificity of 83%.

In our study, In the diagnosis of newborn EOS, ERP level had a sensitivity of 100 percent and a specificity of 96 percent, whereas CRP level had a sensitivity of 76 percent and a specificity of 53 percent, according to **Hisamuddin et al.**[29] Furthermore, according to **Mehrotra,** [30] CRP level has a sensitivity of 90% and specificity of 42% in the diagnosis of neonatal EOS.

CONCLUSION

From our study, we concluded that: Blood culture sensitivity is decreased in people with EOS (23%). As a diagnostic marker for EOS, NLR, PLR, I/T ratio, and CRP demonstrated significant sensitivity and specificity.

RECOMMENDATION

Diagnostic adjunct tests for neonatal EOS work up in AGA neonates include NLR, PLK, I/T ratio, and serum CRP. With a high number of patients, multicenter studies are indicated, which cover all types of neonates, both term and preterm.

DISCLOSURE

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Conflicts of Interest: The authors declare no conflict of interest.

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