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Original article

Neutrophil and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis

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ABSTRACT

Background: Neonatal sepsis [NS] is associated with severe morbidity and mortality. Clinical manifestations range from subclinical infection to severe local or systemic infection. The diagnosis of NS remains a challenge as it has subtle and distinct signs and symptoms. Although blood culture is the gold standard in the diagnosis of NS, the search for high-sensitivity NS markers continues to overcome the drawbacks of blood cultures.

The aim of the work: This study aimed to investigate the effectiveness of the neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting early onset sepsis in neonates.

Patients and Methods: A case control study, comprised 120 newborns [60 newborns with neonatal sepsis as a case group and 60 healthy newborns as a control group], based on patient records at neonatal intensive care unit [NICU] of Al-Azhar University Hospital [Damietta], from January 2018 to January 2019. All were subjected to adequate history taking, full clinical examination, complete blood picture, C-reactive protein and blood culture. After that, neutrophil to lymphocyte ratio [NLR] and platelet to lymphocyte ratio [PLR] were calculated.

Results: NLR was significantly higher in neonates with sepsis. However, there were no association between PLR and early onset sepsis [EOS]. Although, the diagnostic cutoff value for NLR was 1.0 with 72% sensitivity, 100% specificity, there was no association between PLR and EOS.

Conclusion: NLR increases significantly in neonatal sepsis, and can be used as a marker for detection of early onset neonatal sepsis.

Keywords: Neonate; Early Onset Sepsis; Neutrophil Lymphocyte Ratio; Platelet lymphocyte ratio;

* Main subject and any subcategories have been classified according to the research topic.

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INTRODUCTION

Neonatal sepsis is defined as the neonatal systemic condition arises from bacterial, viral or fungal etiology [1]. It is classified as early-onset, late-onset and very late-onset according to the time of onset of the clinical manifestations. The early-onset neonatal sepsis [EOS] describes clinical manifestations at the first three days of life [<72 hours]. Late-onset neonatal sepsis describes cases diagnosed on the fourth to the 30th days [2]

Clinical manifestations of sepsis may be subtle and non-specific, such as tachycardia, bradycardia, apnea, and the infant's departure from its ordinary feeding or activity pattern [3]. Early diagnosis of EOS remains difficult due to its nonspecific manifestations. However, early diagnosis and prompt treatment reduces the mortality rate [4].

Physiological leucocyte immune responses to multiple stressful events are characterized by an increase in the neutrophil and a reduction of lymphocyte counts. The neutrophil lymphocyte ratio [NLR] become a useful marker of inflammation than neutrophilia or lymphocytopenia alone to assess bacterial infection [4].

Epidemiological studies related to neonatal sepsis since the early 1980s have shown a reduction in EOS, especially with Group B Streptococcus [GBS]. This is due to improvement of obstetric care and the use of intra-partum antibiotic prophylaxis. On the other side, there was an increase in the late-onset neonatal sepsis associated with increased survival rates and long hospitalization times of premature babies [5,6].

Neonatal EOS occurs in the uterus as a result of either trans-placental transmission or, more commonly, ascending infection reaching the uterus from the vaginal environment after membrane rupture [6].

Early diagnosis is crucial for a better outcome. Here, the current study seems to share in the literature by assessment of new biomarkers for early diagnosis.

AIM OF THE WORK

This study was designed to assess the effectiveness of the NLR and PLR in the diagnosis of the neonatal early onset sepsis.

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PATIENTS AND METHODS

Study design:

A Case Control study design was assumed to carry out this study.

Study setting:

The study was conducted at NICU of Al-Azhar University Hospital [Damietta], from January 2018 to January 2019.

Ethical considerations:

It was approved by the Ethics and Research Committee of Damietta Faculty of Medicine, Al-Azhar University. In addition, it had been completed in line the ethical codes of the Helsinki declaration. Parents were advised about the study, and an informed consent had been obtained. Confidentiality and anonymity of neonates were assured by using codes instead of names

Study subjects:

Sixty neonates of both sexes diagnosed with neonatal sepsis based on clinical and laboratory data as the study group [Group I]. On the other hand, another 60 apparently healthy neonates with no clinical signs or laboratory evidence of sepsis, were selected as a control group [Group II].

Inclusion criteria

Term and preterm babies of both genders with suspected neonatal sepsis, which depends on sepsis related clinical signs [temperature instability, apneic spells, tachycardia, bradycardia, tachypnea, feeding intolerance, abdominal distention, necrotizing enterocolitis, or convulsions].

The criteria employed for defining the sepsis score

High probable sepsis [HPS]	At least 3 sepsis-related clinical signs* CRP>5mg/ml At least 2 other altered serum parameters ⨎ Blood culture: positive or negative
Probable sepsis [PRS]	Less than 3 sepsis-related clinical signs* CRP>5mg/ml At least 2 other altered serum parameters ⨎ Blood culture: negative
Possible sepsis [POS]	Less than 3 sepsis-related clinical signs* CRP < 5mg/ml At least 2 other altered serum parameters ⨎ Blood culture: negative
No sepsis [NS]	No sepsis-related clinical signs* CRP < 5mg/ml No altered serum parameters ⨎ Blood culture: negative

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Study tools:

Data was collected using the following study tools

- **Tool I,** for complete history taking [name, age, sex, birth date, place of labor, and mode of labor].
- **Tool II,** for pre-natal history, to detect maternal risk factors for neonatal infection as premature rupture of membrane [PROM] ≥18h, maternal fever >38°C, vaginal bleeding, chorioamnionitis, maternal antibiotics administration and maternal urinary infection.
- **Tool III,** for natal history [diagnosis of neonatal risk factors for sepsis, mode of birth, Apgar score and gestational age].
- **Tool IV,** for post-natal history, to detect the most common symptoms of sepsis.
- **Tool V,** for General examination [e.g., Apgar ratings 1 and 5 minutes, weight, length and head circumference, neonatal reflexes [Moro's, grasping and suckling, etc.], and gestational age assessment].
- **Tool VI:** Local examination to detect clinical signs of sepsis:

    Respiratory dysfunction: apnea, intercostal retraction, elevated oxygen demand and symptoms of respiratory distress.

    Circulatory dysfunction: 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.

Investigations: complete blood count [CBC], C-reactive protein [CRP] and blood culture. Then, NLR and PLR were calculated.

Administrative process

Official letters from Damietta Faculty of Medicine, Al-Azhar University were obtained and directed to inform responsible persons about the study and to seek their permission to conduct the study.

Meetings were held with the directors of the selected units to explain the aim of the study, set the date and time of data collection, and to gain their approval and cooperation.

Data collection

The data was collected at a suitable time using study tools after a brief discussion about the aim and the nature of the study with the parents.

Specimen collection: Three samples were taken each time: one sample was for complete blood count in a clean glass Pipe of ethylene diamine tetra acetic acid [EDTA] by using Mythic 18 cell counter. The other sample was put into a clean plain tube, left to clot and centrifugated at 3000 rpm for 10 minutes then clear serum obtained was taken for CRP and the third sample for blood culture. Samples from controls were collected at the time of examination.

Laboratory techniques:

CBC: Peripheral blood was collected in the EDTA vacutainer tube to do a CBC. It was carried out by an automated blood cell counter [Cell-Dyn 3700, Abbott Laboratories, IL, USA]. The ratio of neutrophils to lymphocytes and platelets to lymphocytes was calculated. They were obtained from the same CBC results. Samples were analyzed for accurate mean platelet volume [MPV] calculation, 60 minutes after the sample collection to prevent platelet swelling and false results.

CRP: Was tested by slide latex agglutination test [Rapitex CRP kit], and it was positive if the titer was > 6 mg/L.

Blood culture: The blood sample was taken at the time of diagnosis of the sepsis. Aerobic and anaerobic cultures were formed on 10 percent CO_2 blood agar plates and on MacConkey agar plates. Insulated colonies were further recognized by the inspection of their morphology, reaction to gram-stain, and bio-chemical reactions. True bacteremia was deemed when the blood culture was stable in 72 hours. If no growth was observed, the sample was incubated on solid media for up to 10 days with additional subcultures every other day. If there was no development after 10 days of incubation, the blood culture was considered negative.

Statistical analysis:

The data were coded and fed to an excel sheet, and then transferred to the statistical package of social science [SPSS] version 20 [IBM®SPSS® Inc., USA] for

analysis. Data were presented in, minimum, maximum, mean±SD [Standard deviation] or frequency and percentage according to the type of data. The level of significance was p ≤ 0.05.

Chi square test was used for testing the relationship between qualitative data. Monte Carlo P-value [MCP] to test the significance was used whenever more than 20% of cells had expected count less than five [invalid Chi square test]. Otherwise, student "t" test was used for comparison between two means and Pearson's correlation coefficient for correlation between variables. The receiver operative characteristics curve was built to test sensitivity and specificity.

RESULTS

Table [1] illustrates the comparison between the patients and the controls regarding demographic data. There was no statistically significant difference regarding sex distribution [p=.804], and mean age [4.28±1.55 vs 4.60±1.69 days, respectively] [p=.41].

Table [2] showed the distinction between the two groups tested by weeks of gestation, the mean gestational age in the study group was 35.73±1.99 compared to 36.1±1.62 weeks for the control group. Results revealed that, there was a significant increase in weight and height in control group than the study group. On the other side, the head circumference showed insignificant difference between groups.

This study showed that 77% of the study group had feeding intolerance, 70% developed lethargy, 83% developed tachycardia, 50% had poor perfusion, 47% had temperature instability, 37% had convulsion, and 84% developed apnea.

In the current work, there were highly significant reduction in hemoglobin, and platelets count in the study than the control group. Additionally, there were highly significant increase in white blood cell [WBC] count, red cell distribution width [RDW] and neutrophil to lymphocyte ration in the study than the control group but PLR was not statistically significant.

Table [3] presented the Spearman correlation test; and there was a statistically significant positive correlation between NLR and sepsis score among study group [Spearman rho=0.23, p=0.02].

Table [4] portrays the significant difference in the proportion of sepsis level within WBC category. The high probable neonatal sepsis increased in neonates with WBCs > 25000 cells/cc, followed by those with count <5000cell/cc and finally those with values between 5000 to 25000 cells/cc. The probable sepsis was higher among WBCs < 5000 cells, while possible sepsis was more common among group (5000- 25000 cells) followed by those (>25000). There was significant association between WBCs category and sepsis category.

In the present work, 67% of case group had either neutrophilia or neutropenia, while 100% of control group had normal neutrophilic count.

In the current work, in the patients group it was found that 26.0% had a positive blood culture and 80.0% of the patients show a positive C-reactive protein test.

Figure [1]: showed the ROC curve NLR that indicated that, the diagnostic accuracy of NLR to diagnose sepsis was a statistically significant [AUC=82.3%, p<.001], the best cutoff point was 1 that has Sensitivity 72%, and specificity 100 %.

Table [1]: Comparison between the patients' group and control group according to demographic data

		patients [Group I] [n = 60]		Controls [Group II] [n = 60]		Total [n = 120]		Test	P
		No.	%	No.	%	No.	%		
Sex	Male	38	63.3	31	51.7	69	57.5		
	Female	22	36.7	29	48.3	51	42.5	X^2 =0.061	0.804
Age Mean± SD		4.28±1.55		4.60±1.69		4.33±1.57		t=.82	0.41

Table [2]: Comparison between the two studied groups according to week of gestation and according anthropometric measures.

	Group I Patients [n = 60]	Group II Control [n = 60]	t-test	p
Week of gestation [weeks] Range	31-40	32-40	1.33	0.136
Mean±S.D.	35.73±1.99	36.1±1.62		
Anthropometric measures				
Weight [kg] Range	1.3-4.0	1.3-3.4	3.25	0.011*
Mean ±S.D.	2.27±0.58	2.9175±0.45		
Length [cm] Range	39-53	45-50	2.366	0.0398*
Mean ±S.D.	44.31±5.78	47.40±1.53		
Head circumference [cm] Range	28-39	31-43	0.898	0.4469
Mean ±S.D.	33.01±1.66	32.95±2.54		

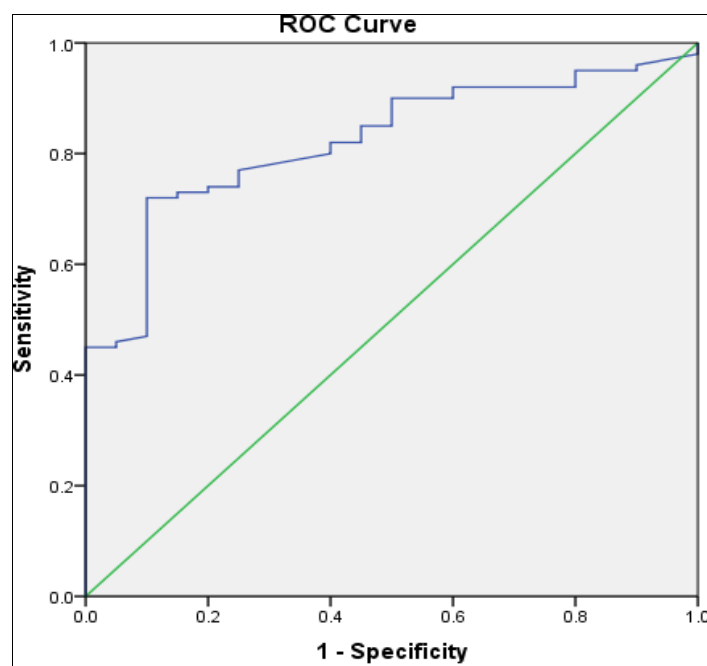t-test = student t-test,   * Statistically significant at p ≤ 0.05

Table [3]: Correlations between sepsis score and NLR and PLR in group I

	Sepsis score	
	Correlation Coefficient	Sig. [2-tailed]
NLR	0.444	<0.001*
PLR	0.166	0.099

Table [4]: Relation between white blood cell count and sepsis score.

		Total		No sepsis		sepsis score					
						Possible		Probable		High probable	
		n.	%	n.	%	n.	%	n.	%	n.	%
WBCs	<5000	4	100.0%	0	0.0%	0	0.0%	2	50.0%	2	50.0%
	5000-25000	43	100.0%	0	0.0%	24	41.9%	11	25.6%	8	18.6%
	>25000	53	100.0%	0	0.0%	6	9.4%	16	30.2%	31	58.5%
Total		100	100.0%	0	0.0%	30	30.0%	29	29.0%	41	41.0%

Percent calculated in relation to WBC category   P value <.001

Figure [2]: ROC Curve NLR

DISCUSSION

Neonatal period is a very critical period in the life span. It is associated with major developmental changes of the neonates regarding the physical and cognitive levels. The neonatal sepsis diagnosis is usually difficult and challenging. The etiology of this difficulty arises from the hard to differentiation of its clinical symptoms from other neonatal conditions. Cultures of blood or cerebrospinal fluid are the gold standards for diagnosis of neonatal sepsis, particularly, that of bacterial origin. However, it is a time consuming, which could postpone the intervention and lead to wide distribution of pathogenic organisms [7]. About four million of neonatal deaths were reported worldwide annually. One third of these deaths is due to sepsis. Bacterial meningitis and sepsis are the main causes of neonatal mortality, particularly of very low birth weight neonates [8]. Prompt identification and management of neonatal sepsis is necessary to prevent serious and life-threatening consequences. The diagnosis of suspected neonatal sepsis is challenging compared to clear and valuable therapeutic options. In preterm infants, the diagnosis of sepsis is more difficult due to non-specific clinical presentation and lack of reliable diagnostic tests [9].

In the current work, there was no significant difference according to gestational age [GA]. This comes in agree with Can *et al*. [10], mean GA for case group was 39.1 and for control group was 39.4, while Altunhan *et al*. [11], reported that, GA was 33.8 and 34.8 for the patients and the controls, respectively. According to this report, there was no significant gender disparity between the two groups surveyed, because 58% and 55% of the patients and the controls were males. This is in line with Omran *et al*. [12] who reported that, 62% of the patients were males and 48% of the control groups were males. But, Gebremedhin *et al*. [13] recorded a 56 [71.8 %] higher proportion of male neonates in the patients than the controls 86 [55.1 %].

In the current study, lower birth weight was found to be significantly associated with increased incidence of sepsis. The mean weight was 2.264 kg and 2.917 kg for the patients and the controls, respectively. In several other studies, comparable results were reported by Turhan *et al*. [14], De Benedetti *et al*. [15], Gomella *et al*. [16], and Gerdes [17]. Since newborns with low birth weight have inadequate immunological response, these have low levels of various complement systems as well as weak mucosal defenses. However, Can *et al*., [10] illustrated that there was no difference between studied groups according to birth weight.

Clinical examination of neonates with sepsis in the present study showed that the most common clinical symptom as and signs were feeding aversion [77%], lethargy [70%], low perfusion [50%], temperature instability [45%]. This comes in agreement with Mustafa *et al*. [18] who described them as the major clinical presentations of sepsis.

According to Can *et al*. [10], the most frequent clinical signs in the neonatal EOS were tachycardia, bradycardia, and apnea.

Thirty seven percent [37%] of case group had convulsions but according to Abdollahi *et al*. [19] it was 5.3%.

This research showed a significant decrease in hemoglobin levels, RBC counts and platelet counts and a significant increase in WBC counts, and RDW in patients than controls. These results correlated with those of Annam *et al*. [20] and Narasimha *et al*. [21].

In the current study, CRP was significantly higher among patients than in controls [80% of the patients group had positive CRP, and 100% of the control group had negative CRP]. This comes in line with the results of Ganesan *et al*. [22], Hisamuddin *et al*. [23], Park *et al*.[24], and Hofer *et al*. [25]. They reported that, CRP is one of the acute phase reactants which are synthesized in the liver in response to trauma or invasion of microorganisms.

In the present study, twenty-six patients had positive results in culture [26%] and seventy-four patients had negative results in culture [74%]. Similar results were found in the Hisamuddin *et al*. [23] study, which found that culture proven sepsis occurred in 30% of sepsis group. Furthermore, Edmond & Zaidi [26] reported that there are difficulties in recognizing pathogenic organisms in neonates with sepsis syndrome. Bacterial load can be weak because of prepartum or intrapartum antibiotics in mothers and because only small amounts of blood can often be obtained from newborns. Contamination levels can also be very high in small babies because of the technical difficulties of sterile venipuncture. The role of coagulase-negative staphylo-cocci [e.g., *S. epidermidis*] may also be misinterpreted, since these organisms are both normal skin flora and pathogenic organisms in preterm and infants with catheters in the blood vessels.

In this study, there was significant difference of PLR

between patients and control groups. This results not correlated with those of Can *et al.* [10], in which mean PLR was 52 in case group and 12.44 in control group, with a statistically significant difference.

To sum up, all efforts must be done by governmental organizations, hospitals in order to make early detection of neonatal sepsis as NLR can be used as a marker for diagnosing early onset neonatal sepsis at cutoff value of 1.0 with 72% sensitivity and 100% specificity.

Conclusion: Success in diagnosing NS depends on understanding early symptoms, results of the laboratory investigations. The findings of this study showed that, NLR increases significantly in neonatal sepsis, and can be used to as a marker for prediction of early onset of neonatal sepsis as a marker.

The present study has some limitations including small number of patients and to study the prognostic role of NLR in EO. PLR has not significant in detecting early onset neonatal sepsis. Blood culture is not always positive in the patients with EOS, as only 20 % of the patients had positive blood culture. Thus, this study recommended that, NLR should be further tested and studied systematically in the early diagnosis of neonatal sepsis. Admission NLR can be utilized as a cheap, readily available diagnostic tool for early onset neonatal sepsis.

Financial and Non-financial Relationships and Activities of Interest

None

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