THE VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO AND PROCALCITONIN LEVEL FOR DETECTING EARLY-ONSET NEONATAL SEPSIS

By

Nasser MM, Afia AA, EL-Khatib GZ and Ibrahim MI

Department of Pediatrics, Faculty of Medicine, Al-Azhar University, Cairo

ABSTRACT

Background: *Early-onset sepsis remains a common and serious problem for neonates. The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are easily accessible biomarkers that have been reported to have meaningful correlations with inflammatory markers and some diseases severity in adult trials.*

Objectives: *We aimed to evaluate the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and procalcitonin as a diagnostic adjunct tests for early detection of neonatal early-onset sepsis (EOS).*

Patients and Methods: *This study was carried out on 60 term infants at the Neonatal Intensive Care Unit (NICU) of Al-Hussien University Hospital. They were divided into two groups: Group A (patients group) which included thirty term AGA neonates, suffering from EOS and group B (controls group) which included thirty healthy term AGA neonates. Neonates with prematurity, postmaturity, small for gestational age (SGA), large for gestational age (LGA), multiple pregnancies, major congenital anomalies, cyanotic congenital heart disease, negative values of together C-reactive protein (CRP), and procalcitonin, and neonates who had mothers with hypertension or preeclampsia, diabetes mellitus (pre-existing or gestational)and tobacco use during pregnancy were excluded. History-taking, complete clinical examination, chest x-ray, blood culture, complete blood count (CBC), C-reactive protein (CRP), procalcitonine level, immature to total neutrophil ratio (I/T ratio), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were done.*

Results: *There were no significant differences between the study groups regarding age, gender, mode of delivery, GA, BW, length and HC. As regard vital data, patients group had higher RR, HR and SPO2. Respiratory distress and tachycardia were the most common clinical signs of EOS. There was a significant difference between patients and controls as regard platelet count and I/T ratio. Patients group had significantly higher absolute neutrophil counts, NLR, PLR, C-reactive protein, and procalcitonin levels compared with the controls group. As regard blood culture, Klebsiella was the most common organism followed by Staphylococcus aureus. An NLR of 2.52 was determined as the predictive cutoff value of neonatal EOS (sensitivity*

96.7%; specificity 100%; P=0.001). A PLR of 47.4 was determined as the predictive cutoff value of neonatal EOS (sensitivity 90.0%; specificity 100%; P=0.001). Procalcitonin (PCT) showed a sensitivity of 96.7 % and specificity 100% at a cut-off point of 1.04 ng/mL. I/T ratio, at a cut-off value at (0.12), had sensitivity of 76.7% and specificity of 96.7%. CRP, at a cut-off value at (5), had sensitivity of 100% and specificity of 96.7%.

Conclusion: Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), I/T ratio, serum CRP and procalcitonin levels had high sensitivity and specificity as diagnostic markers for early-onset neonatal sepsis.

Keywords: Early-onset sepsis, procalcitonin, lymphocyte, neutrophil.

INTRODUCTION

The term neonatal sepsis is used to designate a systemic condition of bacterial, viral, fungal, or parasitic origin that is associated with hemodynamic changes and other clinical manifestations and results in substantial morbidity and mortality **(Shane et al., 2017)**.

Neonatal sepsis is a significant cause of morbidity and mortality among newborn infants. It is divided into neonatal early-onset sepsis (EOS) and neonatal late-onset sepsis **(Chauhan et al., 2017)**.

Neonatal EOS 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 **(can et al., 2018)**.

Numerous sepsis biomarkers have been evaluated for early detection of neonatal EOS, but to date, there is no single biomarker that fulfills all essential criteria. The neutrophil to lymphocyte ratio (NLR), because it combines neutrophils and lymphocytes in the calculation, is considered comparatively more stable than the absolute counts **(Dirican et al., 2015)**.

The NLR has been reported as a predictor of severity and clinical outcome in patients with community acquired pneumonia or bacteremia **(de Jager et al., 2012**; **Loonen et al., 2014)**.

Recently, two blood cell subtype ratios, the NLR and the platelet to lymphocyte ratio (PLR), have been reported as useful systemic inflammatory markers and prognostic indicators of adverse cardiovascular events and cancer **(Lian et al., 2015**; **Yodying et al., 2015**; **Acet et al., 2016**; **Yin et al., 2016)**.

Procalcitonin (PCT) is the peptide precursor of calcitonin. It is released by parenchymal cells in response to bacterial toxins,

leading to elevated serum levels in patients with bacterial infections. Several observational studies have suggested that PCT may be a useful marker to identify neonates who are infected **(Hedegaard et al., 2015)**.

AIM OF THE STUDY

The aim of this study was to evaluate the value of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and procalcitonin level as diagnostic adjunct tests for early detection of neonatal early-onset sepsis (EOS) workup among term, AGA, neonates.

Ethical Consideration

1. Approval of ethical committee, Faculty of Medicine, Al-Azhar University.

2. Written consents from the parents of the patients.

3. The patients have the right to withdraw from the study at any time.

4. All the obtained data are confidential and the patients have the right to keep them.

5. The authors declare that there is no any financial conflict regarding the research and publication.

6. No conflict of interest regarding the study and publication.

PATIENT AND METHODS

This cross-sectional case control study was conducted at the Neonatal Intensive Care Unit (NICU) of Al-Hussien university Hospital during the period from (1/8/2018) to (31/1/2019).

Study Groups:

This study was carried out on 60 terms, AGA neonates. They were divided into two groups:

Patients Group:

It included 30 septic terms, AGA neonates with clinical and lab evidence of EOS.

Controls Group:

It included 30 healthy term, AGA neonates with no clinical and laboratory evidence of sepsis.

Inclusion Criteria:

• Term neonates,

• Appropriate for gestational age (AGA), and

• Neonates suffering from EOS.

Exclusion Criteria:

• Prematurity (<37 completed gestational weeks) and postmaturity (≥42 completed gestational weeks).

- Small for gestational age (SGA) and large for gestational age (LGA).

- Multiple pregnancies.

- Maternal Hypertension and Preeclampsia.

- Maternal Diabetes mellitus (pre-existing and gestational).

- The mother used tobacco during pregnancy.

- Infant with major congenital anomalies.

- Cyanotic congenital heart disease.

- Negative values of together C-reactive protein (CRP) and procalcitonin.

Methodology:

All patients were subjected to the following:

A. Complete history taking.

B. Thorough clinical examination.

C. The following investigations were done:

  - Blood culture using (BACTEC 9050, BECTON DICKINSON, Japan).

  - Complete blood count (CBC) using (Sysmex KX-21N, Automated Hematology, Japan).

  - Immature to total neutrophil ratio (I/T ratio).

- Neutrophil/lymphocyte ratio (NLR).

- Platelet/lymphocyte ratio (PLR).

- C-reactive protein (CRP) (POC CRP analyzer, Japan).

- Procalcitonine level using (point of care testing, Australia).

Statistical Analysis:

The data were collected, tabulated, and analyzed by SPSS (Statistical Package for Social Science) computer software program version 20.0.

Two types of statistics were done:

- Descriptive statistics {e.g. percentage (%), mean (x) and standard deviation (SD)},

- Analytical statistics: which include the following tests:

  - **Student (t) test:** was used to study statistical significance between two quantitative variables.

  - **Chi-square test (x2):** was used to study statistical significance between two qualitative variables.

  - P-value of < 0.05 was considered statistically significant.

RESULTS

Table (1): Demographic Data of the Study Groups

	Patients (n-30)	Controls (n-30)	Tests	
			X^2/ t	P-value
Mode of delivery				
CS	25(83.3%)	26(86.7%)	0.131	0.718
VD	5(16.7%)	4(13.3%)		
Age (day)				
Range	2-4	1-4	1.364	0.178
Mean±SD	2.24±0.53	2.07±0.43		
Gender				
Female	11(36.7%)	16(53.3%)	1.684	0.194
Male	19(63.3%)	14(46.7%)		
GA (wk)				
Range	37-39	37-39	0.916	0.364
Mean±SD	37.67±0.71	37.83±0.70		
Birth weight (kg)				
Range	2.64-3.43	2.71-3.61	1.887	0.064
Mean±SD	2.97±0.26	3.10±0.29		
Length (cm)				
Range	45-51	45-50	0.234	0.816
Mean±SD	46.63±1.81	46.53±1.48		
HC (cm)				
Range	35-37	35-37	0.000	1.000
Mean±SD	35.50±0.68	35.50±0.68		

CS: caesarean section, VD: vaginal delivery, GA: gestational age, HC: head   circumference.

There was no statistically significant difference between patients and controls as regard mode of delivery, age, gender, GA, BW, length and HC.

Table (2): Vital Signs Distribution among the Study Groups

	Patients (n-30)		Controls (n-30)		t-test	
	Mean± SD	Range	Mean± SD	Range	t	P-value
HR (BPM)	148.37± 11.47	137-179	135.33± 7.10	124-150	5.291	<0.001**
RR (BPM)	66.77± 7.67	51-78	44.37± 3.36	39-50	14.649	<0.001**
Temperature (°C)	37.33± 0.34	36.7-37.9	37.33± 0.22	36.9-37.8	0.091	0.928
Capillary refilling time (sec)	2.5± 0.5	2.1-3.2	2.25± 0.5	2.15-3	1.936	0.062
SPO2 (%)	92.4± 2.37	90-94	94.22± 2.16	93-100	3.109	0.003*
MBP (mmHg)	38.6± 4.57	36-40	39.2± 3.4	37-43	0.577	0.566

HR: heart rate, RR: respiratory rate, SPO2: blood oxygen saturation, MBP: mean blood pressure.

There were statistically significant differences between patients and controls as regard HR, RR and SPO2 while non-significant differences as regard temperature, CRT and MBP.

Table (3): Clinical Signs of Early-Onset Neonatal Sepsis among Patients Group

Clinical signs	Frequancy	
	n	%
Respiratory distress	18	60.0
Tachycardia	3	10.0
Bradycardia	1	3.3
Cyanosis	1	3.3
Jaundice	2	6.7
Lethargy	2	6.7
Apnea	2	6.7
Poor feeding	1	3.3
Total	30	100.0

Respiratory distress was the most frequent clinical sign of EOS represented 60%, followed by tachycardia 10.0% then jaundice, lethargy and apnea by 6.7% and lastly poor feeding,

bradycardia and cyanosis by   3.3%.

Table (4): Lab Parameters Distribution among Studied Groups

	Patients		Controls		t-test	
	Mean± SD	Range	Mean± SD	Range	T	P-value
Hct (%)	44.24± 17.59	30.9-131	46.78± 7.64	30.8-60.4	0.726	0.471
Plt (10³/ µL)	204.57± 29.69	193-353	253.70± 39.21	158-281	5.472	<0.001**
W.B.Cs (10³/ µL)	19.56± 2.88	15-24.5	19.07± 2.09	9.1-15.8	0.754	0.453

Hct: hematocrit, Plt: platelet, W.B.Cs: weight blood cells.

There was a statistically significant decrease in platelet count (Plt)   between patients and controls while there were non- significant differences as regarding hematocrit value (Hct) and weight blood cells count (W.B.Cs).

Table (5): Immature to Total Neutrophil Ratio Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
I/T ratio	Range	0.1-0.3	0.0-0.1	10.106	<0.001**
	Mean±SD	0.17±0.05	0.06±0.03		

There was statistically significant increase between patient and control as regarding I/T ratio.

Table (6): Absolute Neutrophil Count Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
Absolute Neutrophil count(10³/ µL)	Range (cells/µL)	12-17	4-9	24.887	<0.001**
	Mean±SD	14.32±1.5	5.27±1.31		

There was a statistically significant increase of absolute neutrophil count among patients compared to that among controls.

Table (7): Absolute Lymphocyte count Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
Absolute Lymphocytes (10^3/ μL)	Range (cells/μL)	4.0-6.0	9-17.5	24.124	<0.001**
	Mean±SD	4.64±0.58	15.58±2.18		

There was a statistically significant decrease of absolute lymphocyte count among patients than that among controls.

Table (8): Neutrophil to Lymphocyte Ratio Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
NLR	Range	2.5-4.25	0.26-0.95	28.659	<0.001**
	Mean±SD	3.13±0.49	0.38±0.18		

There was a statistically significant increase of NLR among patients more than that among controls.

Table (9): Platelet to Lymphocyte ratio Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
PLR	Range	47.0-58.0	11.2-16.0	60.880	<0.001**
	Mean±SD	51.97±3.21	13.33±1.33		

There was a statistically significant increase of PLR among patients more than that among controls.

Table (10): C - reactive protein Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
CRP(mg/L)	Range	8.6-96	1.3-5	6.166	<0.001**
	Mean±SD	29.19±24.04	2.1±1.09		

There was a statistically significant increase of CRP among patients more than that among controls.

Table (11): Procalcitonin level Distribution among the Study Groups

		Patients	Controls	t-test	
				t	P-value
Procalcitonin (ng/mL)	Range	1.0-8.1	0.0-0.5	10.210	<0.001**
	Mean±SD	4.00±2.11	0.07±0.02		

There was a statistically significant increase of Procalcitonin among patients more than that among controls.

Table (12): Results of Blood Culture among Patients Group

Patients	Blood culture	
	n	%
No growth	23	76.7
Klebsiella	5	16.7
Staphylococcus aureus	2	6.6
Total	30	100.0

Blood culture was negative among the majority of patients (76.7%) only (23.3%) of patients showed positive blood culture; 5 (16.7%) revealed klebsiella and 2 (6.6%) revealed Staphylococcus aureus.

Table (13): Correlation Coefficient "r" between NLR and Other Lab Parameters among Patients Group

Lap parameters	NLR	
	R	**P-value**
Hct	0.161	0.396
Plt count	-0.570	<0.001**
W.B.C count	-0.143	0.452
I/T ratio	-0.026	0.891
Absolute neutrophil count	-0.118	0.536
Absolute lymphocyte count	-0.672	<0.001**
CRP	-0.017	0.927
PCT	0.151	0.425

There was a negative Correlation between NLR showed significant negative correlations with platelets count and absolute lymphocytes, but no significant correlation with the other lab parameters.

Table (14): Correlation Coefficient "r" between PLR and Other Lab Parameters among Patients Group

Lap parameters	PLR	
	r	**P-value**
Hct	0.320	0.084
Plt count	0.476	0.008*
W.B.C count	0.294	0.115
I/T ratio	-0.048	0.802
Absolute neutrophil count	0.090	0.637
Absolute lymphocyte count	0.047	0.803
CRP	-0.258	0.168
PCT	-0.133	0.485

PLR showed a significant positive correlation with platelets count, but no significant correlation with the other lab parameters.

Table (15): ROC Curve Results for NLR

ROC curve results for NLR					
Cut off	Sens.	Spec.	PPV	NPV	Accuracy
> 2.52	96.7%	100.0%	100.0%	96.8%	98.2%

Sens: sensitivity, Spec: specificity, PPV: Positive Predictive value, NPV: Negative Predictive value.

NLR, at a cut-off value of 2.5, had a sensitivity of 96.7%, specificity of 100% and accuracy of 98.2%

Table (16): ROC Curve Results for PLR

ROC curve results for PLR					
Cut off	Sens.	Spec.	PPV	NPV	Accuracy
> 47.4	90.0%	100.0%	100.0%	90.9%	96.0%

PLR, at a cut-off value of 47.4%, had a sensitivity of 90.0%, specificity of 100% and accuracy of 96.0%.

Table (17): ROC Curve Results for PCT

ROC curve results for PCT					
Cut off	Sens.	Spec.	PPV	NPV	Accuracy
> 1.04	96.7	100.0	100.0	96.8	98.2

PCT, at a cut-off value of 1.04, had sensitivity of 96.7%, specificity of 100% and accuracy of 98.2%.

Table (18): ROC Curve Results for I/T ratio

ROC curve results for I/T ratio					
Cut off	Sens.	Spec.	PPV	NPV	Accuracy
> 0.12	76.7%	96.7%	95.8%	80.6%	87.3%

I/T ratio, at a cut-off value of 0.12, had sensitivity of 76.7%, specificity of 96.7% and accuracy of 87.3%.

Table (19): ROC Curve Results for CRP

ROC curve results for CRP					
Cut off	Sens.	Spec.	PPV	NPV	Accuracy
> 5	100%	96.7%	96.8%	100%	99%

CRP, at a cut-off value of 5, had sensitivity of 100%, specificity of 96.7% and accuracy of 99%.

DISCUSSION

This cross-sectional case control study was conducted at the Neonatal Intensive Care Unit (NICU) of Al-Hussien university Hospital during the period from (1/8/2018) to (31/1/2019). The aim of this study was to evaluate the value of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and procalcitonin level as diagnostic adjunct tests for early detection of neonatal early-onset sepsis (EOS) workup among term, AGA, neonates. This study was carried out on 60 terms, AGA neonates. They were divided into two groups:

Patients Group: It included 30 septic terms, AGA neonates with clinical and lab evidence of EOS.

Controls Group: It included 30 healthy terms, AGA neonates with no clinical and laboratory evidence of sepsis.

Full history taking, full clinical examination for all neonates included in this study and the following investigations were done to all cases:

• Blood culture.

• Complete blood count (CBC).

• Immature to total neutrophil ratio (I/T ratio).

• Neutrophil/lymphocyte ratio (NLR).

• Platelet/lymphocyte ratio (PLR).

• C-reactive protein (CRP).

• Procalcitonine level.

In our study, there was no significant difference between patients and controls groups regarding gender. This comes in agreement with **Parajuli et al., (2017)** and **Xiao et al., (2017)** who found the same result.. However, male gender predominated in the patients group (63.3%). This male predominance is apparent in almost all studies of neonatal sepsis such as the study done by **Bohanon et al., (2017)** who found that male gender was predominate in their studies. This may be due to gene located on the X chromosome which is involved with the function of the Thymus gland or with synthesis of immunoglobulins **(Bianchi et al., 2012)**.

The results of our study showed that, SPO2 was significantly lower among patients compared to controls group, which comes in agreement with **Can et**

al., (2017) who found the same result.

As regard, HR and RR were significantly higher in patients compared to controls group, which comes in agree with **Xiao et al., (2017)**. This result disagreed with **Can et al., (2017)** who found that there was a non-significant difference between patients and controls group regarding HR and RR.

In our study, the main presenting signs of sepsis were tachypnea observed among (60%) of patients followed by tachycardia (10.0%) then jaundice, lethargy and apnea (6.7%) and lastly poor feeding, bradycardia and cyanosis (3.3%). This agrees with **Maharaja et al., (2017)** who found that the majority of patients had respiratory distress. On the other hand, **Can et al., (2017)** found the main presenting sings were Apnea and bradycardia.

In this study the mean platelet count in patients group was significantly lower than that of controls group (p<0.001). **Karne et al., (2017)** and **Ree et al., (2017)** also found a statically significant difference between patients and controls. This difference due to combination of increased destruction and inadequate production of platelets

during sepsis **(Bhat, 2017)**. In contrast to our results, **Can et al., (2017)** found that there was a non-significant difference between patients and controls regarding platelet count.

Regarding WBCs, there was non-significant difference between patients and controls group, which comes in agree with **Can et al., (2017)** and **Xiao et al., (2017)**. Moreover, **Jefferies (2017)** found that a low WBCs was more likely to be associated with EOS than high TLC.

In our study, I/T ratio was significantly higher in patients group compared to controls group. This was also proven by **Cekmez et al., (2017)**. Findings from our study, did not correspond to **Can et al., (2017)** who found that there was no statistically significant differences between the neonatal EOS group's I/T ratio and the control group.

In the present study, there was a highly statistical significant increase in the neutrophil count between patients group and controls group. This was in agreement with, **Can et al., (2017)** who observed that neutrophil count was significantly higher in the neonatal EOS group compared to the controls group.

Our results showed that, the lymphocytes count was significantly decrease in patients group compared to controls group. In concordance with our results, **Can et al., (2018)** found that the lymphocyte count was significantly lower in patients group than controls group. This variation between patients and controls groups in neutrophil and lymphocyte count can be explained as follow, the physiological immune responses of circulating leukocytes to numerous stressful events are characterized by raised neutrophil count and minimized lymphocyte count. Inflammatory reaction gives rise to elevated total leukocytes and neutrophil counts caused by a microorganism infection **Wyllie et al., (2004)** and **Yoon et al., (2013)**.

In the current study, there was a highly statistical significant increase in NLR between patients group and controls group. Our result comes in agreement with, **Can et al., (2017)**, **Omran et al., (2018)** and **Wilar et al., (2018)** who observed that NLR was significantly higher in the patients group compared to the controls group.

Regarding PLR, our results showed a highly statistical significant increase among patients group compared to controls group. This is in agreement with, **Can et al., (2017)** who found that PLR was significantly higher among the neonatal EOS group compared to the controls group. On the other hand, **Omran et al., (2018)** found that there was no statistically significant difference between the neonatal EOS group's PLR and the controls group.

Our results showed a highly statistical significant increase in CRP levels between patients and controls group. Our results come in agreement with, **Can et al., (2017)**, **Omran et al., (2018)** and **Xiao et al., (2017)**.

We found that neonates in the sepsis group had significantly higher procalcitonin levels compared with that in the controls group. This agrees with the study done by **Joram et al., (2012)**, **Leena et al., (2017)** and **Steinberger et al., (2014)** who found that the procalcitonin level was significantly higher in the sepsis group compared to the non-septic group. Furthermore, in a recent study done by **Can et al., (2017)** and **Rashwan et al., (2019)** who found that the procalcitonin level was significantly higher in patients group than controls group.

The results of blood cultures in our study showed that only 7

(23.3%) of neonates with sepsis were culture-positive. **Vaniya et al., (2016)** found that culture-proven sepsis occurred in only 51% of cases with sepsis, while **Maore (2015)** found that culture-proven sepsis occurred in only 32% of cases with sepsis. The sensitivity of blood cultures in neonatal sepsis is low and depends on the number and timing of cultures taken, blood volume, culture medium, technique, and temperature and organism density. Furthermore, the implementation of peripartum maternal antibiotic treatment makes the diagnostic value of neonatal blood cultures uncertain **(Osman et al., 2015)**.

In the present study the frequency of organisms isolated was gram negative bacilli, Klebsiella, represented 16.7% and gram-positive cocci, Staphylococcus aureus, which represented 6.6% of culture-proven sepsis. This comes in agreement with **(Patel, 2014, Sharma, 2016 and Vaniya et al., 2016)** who were found that Gram negative bacilli were the most common organisms, mainly Klebsiella. However other studies stated that gram-positive bacteria, mainly staphylococci accounts for the majority of the culture growth **(Abdelhamid, 2017, Aku et al., 2018 and Gowda et al., 2017)**.

Lee et al., (2015) also reported that Gram-positive organisms were the most predominant organisms of EOS in Korea. This difference in isolated organisms shows that every neonatal unit has its own pattern of microorganisms, which change from time to time, and antimicrobial combinations should be altered according to culture results.

In our study, NLR showed a significantly negative correlation with platelets and absolute lymphocyte count, i.e. NLR decreases when platelets or absolute lymphocyte count increase and vice versa, while **Omran et al., (2018)** reported a positive correlation between NLR and salivary CRP. Also, in our study PLR showed a significant positive correlation with platelets i.e. PLR increase when platelet increase and vice versa.

In our study, NLR showed a sensitivity of 96.7 % and a specificity of 100% at a cut-off point of 2.5, while **Can et al., (2017)** reported that NLR of 6.76 was determined as the predictive cutoff value of neonatal EOS showed a sensitivity of 97.4% and a specificity of 100%.Otherwise, **Omran et al., (2018)** observed that NLR at a cut-off point of 2.7, presented 80% sensitivity and 57.1% specificity. Moreover,

Wilar et al., (2018) found that NLR at cut off point of 1.42 showed 83.3% sensitivity and 93.3% specificity. These variations because there is no accurate cut off point for NLR in EOS, all researches were limited in number.

In our study, PLR showed a sensitivity of 90.0 % and a specificity of 100% at a cut-off point of 47.4, while **Can et al., (2017)** reported that PLR of 94.05 was determined as the predictive cutoff value of neonatal EOS showed a sensitivity of 97.4% and a specificity of 100%. This difference between results is due to absence of accurate cut off point for PLR in EOS and there is no enough researches in this issue.

In our study, procalcitonin (PCT) showed a sensitivity of 96.7 % and a specificity of 100% at a cut-off point of 1.04ng/mL, while **Pontrelli et al., (2017)** reported that PCT showed a sensitivity of 85 % and a specificity of 54% at a cut-off point 2.0ng/mL.

A systematic review and meta-analysis study done by **Chiesa et al., (2015)** in neonates. They studied the PCT accuracy in neonates from 1998-2014 using the standards for reporting of diagnostic accuracy (STARD) initiative and they found that PCT sensitivity ranged from 47.4% to 100% and specificity from 35.3% to 100%.

In our study, I/T ratio showed a sensitivity of 76.7% and a specificity of 96.7% in diagnosis of neonatal EOS. However, **Saboohi et al., (2019)** reported that I/T ratio showed a sensitivity of 76.47% and a specificity of 83.82% in diagnosis of neonatal EOS.

In the current study, CRP level showed a sensitivity of 100% and a specificity of 96.7% in diagnosis of neonatal EOS. While **Hisamuddin et al., (2015)** reported that CRP level showed a sensitivity of 76.9% and a specificity of 53.49% in diagnosis of neonatal EOS. Moreover, **Mehrotra, (2017)** reported that CRP level showed a sensitivity of 90.32% and a specificity of 42.10% in diagnosis of neonatal EOS.

CONCLUSION

From our study we concluded that:

- The sensitivity of blood cultures in patients with EOS is low (23.3%).

- Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), I/T ratio, serum CRP and procalcitonin levels had high sensitivity and specificity as diagnostic

markers for early onset neonatal sepsis.

RECOMMENDATION

From our study we recommend that:

• NLR, PLR, I/T ratio, serum CRP and procalcitonin levels can be used as diagnostic adjunct tests for neonatal EOS workup among term, AGA, neonates.

• Multicenter studies are needed with large number of patients and include all categories of neonates.

REFERENCES

1. **Abdel hamid S M. (2017):** Time to positivity and antibiotic sensitivity of neonatal blood cultures. Journal of global infectious diseases, 9 (3), 102.

2. **Acet, H., Ertaş, F., Akıl, M. A., et al., (2016):** Relationship between hematologic indices and global registry of acute coronary events risk score in patients with ST-segment elevation myocardial infarction. Thrombosis/Hemostasis, 22(1), 60-68.

3. **Aku F Y., Akweongo P., Nyarko K, et al., (2018):** Bacteriological profile and antibiotic susceptibility pattern of common isolates of neonatal sepsis, Ho Municipality, Ghana-2016. Maternal Health, Neonatology and Perinatology, 4(1), 2.

4. **Bhat, R. (2017):** Platelet indices in neonatal sepsis: A review. World Journal of Clinical Infectious Diseases, 7(1), 6-10.

5. **Bianchi I., Lleo A., Gershwin M E., and Invernizzi P. (2012):** The X chromosome and immune associated genes. Journal of autoimmunity, 38(2-3), J187-J192.

6. **Bohanon F J., Lopez O N., Adhikari D., et al., (2017):** Race, Income, and Insurance Status Affect Neonatal Sepsis Mortality and Healthcare Resource Utilization. The Pediatric infectious disease journal.

7. **Can, E., Hamilcikan, Ş., & Can, C. (2017):** The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. Journal of pediatric hematology/oncology, 40(4), e229-e232.

8. **Cekmez Y, Güleçoğlu M, Özcan C, Karadeniz L, Kıran G (2017):** The utility of maternal mean platelet volume levels for early onset neonatal sepsis prediction of term infants. Ginekologia Polska; 88, 6: 312–314.

9. **Chauhan, N., Tiwari, S., & Jain, U. (2017):** Potential biomarkers for effective screening of neonatal sepsis infections: an overview. Microbial pathogenesis, 107, 234-242.

10. **Chiesa, C., Pacifico, L., Osborn, J. F., et al., (2015):** Early-onset neonatal sepsis: still room for improvement in procalcitonin diagnostic accuracy studies. Medicine, 94(30).

11. **De Jager, C. P., Wever, P. C., Gemen, E. F., et al., (2012):** The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PloS one, 7(10), e46561.

12. **Dirican, A., Kucukzeybek, B. B., Alacacioglu, A., et al., (2015):** Do the derived neutrophil to lymphocyte ratio and the neutrophil to lymphocyte ratio predict prognosis in breast cancer?. International journal of clinical oncology, 20(1), 70-81.

13. **Gowda H., Norton R., White A. and Kandasamy Y. (2017):** Late-onset Neonatal Sepsis—A 10-year Review From North Queensland, Australia. The Pediatric infectious disease journal, 36(9), 883-888.

14. **Hedegaard S S., Wisborg K. andHvas A M. (2015):** Diagnostic utility of biomarkers for neonatal sepsis–a systematic review. Infectious Diseases, 47(3), 117-124.

15. **Hisamuddin, E., Hisam, A., Wahid, S., & Raza, G. (2015):** Validity of C-reactive protein (CRP) for diagnosis of neonatal sepsis. Pakistan journal of medical sciences, 31(3), 527.

16. **Jefferies, A. L. (2017):** Management of term infants at increased risk for early-onset bacterial sepsis. Paediatrics & child health, 22(4), 223-228.

17. **Joram N, J.-B. Muller, S. Denizot, J.-L.et al., (2012):** Umbilical Cord Blood Procalcitonin Level in Early 1 Neonatal Infections: A 4- 2 year University Hospital Cohort Study Springer Verlag, 2011, 30 (8), pp.1005-1013. <10.1007/s10096-011-1187-0>. <hal-00669195>.

18. **Karne T K., Joshi D D., Zile U. and Patil S. (2017):** Study of Platelet Count and Platelet Indices in Neonatal Sepsis in Tertiary Care Institute. MVP Journal of Medical Science, 4(1), 55-60.

19. **Leena B. Mithal1, Hannah L. Palac, Ram Yogev, et al., (2017):** Cord Blood Acute Phase Reactants Predict Early Onset Neonatal sepsis in preterm infants. Plos One DOI:10.1371/journal.pone.0168677 January 3, 2017.

20. **Lian, L., Xia, Y. Y., Zhou, C., Shen, X. M.,et al., (2015):** Application of platelet/lymphocyte and neutrophil/lymphocyte ratios in early diagnosis and prognostic prediction in patients with resectable gastric cancer. Cancer biomarkers, 15(6), 899-907.

21. **Loonen, A. J., de Jager, C. P., Tosserams, J., et al., (2014):** Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PloS one, 9(1), e87315.

22. **Maharaja P. and Mangayakarasi V. (2017):** Clinical Profile And Risk Factors In Neonatal Septicaemia.Int J Pharm Bio; 8(3): (B) 489-495.

23. **Maore D N K. (2015):** Antimicrobial Sensitivity And Treatment Outcomes Of Neonatal Sepsis At Pumwani Maternity Hospital (Doctoral dissertation, University of Nairobi).

24. **Mehar V., Agarwal S., Singh R., et al., (2016):** Relationship between gestational age and mode of delivery with neonatal septicemia. International Journal of Contemporary Pediatrics, 3(3), 891-

895.

25. **Mehrotra, G. (2017):** Study of C-reactive protein in neonatal sepsis. Int J Contemp Pediatr, 4, 890-5.

26. **Omran, A., Maaroof, A., Saleh, M. H., & Abdelwahab, A. (2018):** Salivary C-reactive protein, mean platelet volume and neutrophil lymphocyte ratio as diagnostic markers for neonatal sepsis. Jornal de Pediatria (Versão em Português), 94(1), 82-87.

27. **Osman A S., Awadallah M G., Tabl H A M., et al., (2015):** Presepsin as a Novel Diagnostic Marker in Neonatal Septicemia. The Egyptian Journal of Medical Microbiology (EJMM), 24(3).

28. **Pontrelli, G., De Crescenzo, F., Buzzetti, R., et al., (2017):** Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC infectious diseases, 17(1), 302.

29. **Parajuli R., Pant N D., Bhandari R., et al., (2017):** Bacteriological Profile of Neonatal Sepsis and Antibiogram of the Isolates. Journal of Nepal Paediatric Society, 37(1), 5-9.

30. **Patel D., Nimbalkar A., Sethi A., et al., (2014):** Blood culture isolates in neonatal sepsis and their sensitivity in Anand district of India. The Indian Journal of Pediatrics, 81(8), 785-790.

31. **Rashwan, N. I., Hassan, M. H., El-Deen, Z. M. M., & Ahmed, A. E. A. (2019):** Validity of biomarkers in screening for neonatal sepsis–A single center–hospital based study. Pediatrics & Neonatology, 60(2), 149-155.

32. **Ree I M., Fustolo-Gunnink S F., Bekker V., et al., (2017):** Thrombocytopenia in neonatal sepsis: Incidence, severity and risk factors. PloS one, 12(10), e0185581.

33. **Saboohi, E., Saeed, F., Khan, R. N., & Khan, M. A. (2019):** Immature to total neutrophil ratio as an early indicator of early neonatal sepsis. Pakistan journal of medical sciences, 35(1), 241.

34. **Shane A L., Sánchez P J. and Stoll B J. (2017):** Neonatal sepsis. The Lancet.

35. **Sharma R S., Tiwari M. and Bansal R P. (2016):** Neonatal septicemia: isolates and their sensitivity pattern with emergence of Citrobacter septicemia. International Journal of Research in Medical Sciences, 4(4), 1128-1131.

36. **Steinberger E, Hofer N, Resch B (2014):** Cord blood procalcitonin and interleukin-6 is highly sensitive and specific in the prediction of early-onset sepsis in preterm infants. Scand J Clin Lab Invest. 2014; 74:432Ð436.

37. **Vaniya H V., Patel N M., Agrawal J M., et al. (2016):** Antimicrobial culture sensitivity pattern in neonatal sepsis in a tertiary-care hospital. International Journal of Medical Science and Public Health, 5(4), 661-666.

38. **Wilar, R. (2018):** Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio on early onset

neonatal sepsis. Korean journal of pediatrics, 62(6), 217.

39. **Wyllie, D. H., Bowler, I. C. J. W., & Peto, T. E. A. (2004):** Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. Journal of clinical pathology, 57(9), 950-955.

40. **Xiao T., Chen L P., Liu H., et al., (2017):** The Analysis of Etiology and Risk Factors for 192 Cases of Neonatal Sepsis. BioMed research international, 2017.

41. **Yin, X., Xiao, Y., Li, F., Qi, S., Yin, Z., & Gao, J. (2016):** Prognostic role of neutrophil-to-lymphocyte ratio in prostate cancer: a systematic review and meta-analysis. Medicine, 95(3).

42. **Yodying, H., Matsuda, A., Miyashita, M.,Matsumoto, S., et al., (2016):**Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. Annals of surgical oncology, 23(2), 646-654.

43. **Yoon, N. B., Son, C., & Um, S. J. (2013):** Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Annals of laboratory medicine, 33(2), 105-110

قيمة نسبة خلايا النيتروفيل الي الخلايا الليمفاوية ونسبة الصفائح الدموية الى الخلايا الليمفاوية ومستوى البروكالسيتونين في كشف إنتان الدم الوليدى المبكر

أ. د./مُسلم محمد السيد ناصر, أستاذ طب الأطفال ـ كلية الطب ـ جامعة الأزهر

أ. د./ على عبداللطيف عافية, أستاذ طب الأطفال ـ كلية الطبـ جامعة الازهر

د./ جمال زكريا المرسى الخطيب ,مدرس الباثولوجيا الاكلينيكيةـ كلية الطب ـ جامعة الازهر

محمد ابراهيم عبد العزيز ابراهيم, بكالوريوس الطب والجراحة ـ جامعة الأزهر

الهـدف : نهـدف الـى تقيـيم نسبة خلايـا النيتروفيـل إلـى نسبة الخلايـا الليمفاويـة (NLR) ، ونسـبة الصـفائح الدمويـة إلـى نسبة الخلايـا اللمفاويـة (PLR) ومسـتوى البروكالسـيتونين كاختبـارات تشخيصية مساعدة في كشف إنتان الدم الوليدى المبكر.

المنهجيـة: أجريـت هـذه الدراسـة علـى ٦٠ طفـلا مبتسـرا وتـم تقسيمهم الى مجموعتين:

المجموعـه الاولـي : مجموعـة المرضـي وهـم ٣٠ طفـل مبتسر يعانون من تسمم دموي مبكر.

المجموعـة الثانيه : المجموعـة المقارنـه وهـم ٣٠ طفـل مبتسر لايعانون من تسمم دموي.

تــم اخــذ التــاريخ المرضــي الكامــل والفحــص الشــامل لجميع المواليد واجريت الفحوصات الاتيه لهم:

- تعداد الدم الكامل .

- نسبة الصفائح الدموية / الخلايا اللمفاوية الخلايا اللمفاوية.

- بروتين سي التفاعلي.

- مزرعة الدم.

- نســبة خلايــا النيتروفيــل الغيــر ناضــجة إلــى إجمــالي خلايــا النيتروفيل.

- مستوي البروكالسيتونين.   .

- اشعة سينية على الصدر.

- نسبة خلايا النيتروفيل / الخلايا اللمفاوية.

النتائج:

أظهــرت النتــائج عــدم وجــود فــرق بــين المجمــوعتين فيمــا يتعلــق بجــنس الطفــل وطريقــة الــولادة والــوزن عنــد الــولاده والعمــر الرحمي والطول ومحيط الراس.

يوجــد فــرق ذو دلالــة إحصــائية بــين المجمــوعتين فيمــا يتعلق بنسبة خلايا النيتروفيل الي الخلايا اللمفاوية (NLR).

كمــا يوجــد فــرق بــين المجمــوعتين فيمــا يتعلــق نســبة الصفائح الدموية الي الخلايا اللمفاوية الخلايا اللمفاوية(PLR).

وايضــا يوجــد فــرق ذو دلالــة إحصــائية بــين المجمــوعتين فيما يتعلق بمستوي البروكالسيتونين.

الاستنتاجات:

يمكــن اسـتخدام كــلا مــن نسـبةخلايا النيتروفيـل إلــى الخلايــا الليمفاويـة (NLR) ، ونسـبة الصـفائح الدمويـة إلــى الخلايــا الليمفاويـة (PLR) ومعـدل البروكالسـيتونين كعلامــات تشخيصـية لإنتــان الــدم الوليــدي المبكــر نظــرا لمــا لهــا حساسـية وخصوصـية عالية.

التوصيات:

يمكــن اسـتخدام كــلا مــن نسـبةخلايا النيتروفيـل إلــى الخلايــا الليمفاويــة (NLR) و ونسـبة الصـفائح الدمويــة إلــى الخلايــا الليمفاويـة (PLR) كاختبــارات تشخيصـية لإنتــان الــدم الوليـدي المبكــر ، غيــر ان هنــاك حاجــة إلــى مزيـد مــن الدراسـات الواسـعة التـي تجـري علـي عـدد كبيـر مــن الحـالات وتشـمل جميـع فئـات الأطفال حديثي الولادة.

● يمكــن اسـتخدام مسـتوى البروكالسـيتونين كاختبــار تشخيصـي جيـد لإنتــان الــدم الوليـدي المبكــر , فإننــا نوصـي باسـتخدام مسـتوى البروكالسـيتونين فـي جميـع حـالات انتــان الــدم الوليدي المبكر.