Research Article

Platelet to Lymphocyte ratio and Neutrophil to Lymphocyte ratio as new diagnostic markers for detection of Early-onset Neonatal Sepsis in Full-term newborns

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Abstract
Introduction: Neonatal sepsis is a significant cause of morbidity and mortality among newborn infants. It is divided into early-onset sepsis (EOS) and late-onset sepsis. Numerous sepsis biomarkers have been evaluated for early detection of neonatal EOS but 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 described above. **Aim of the work:** This is a prospective cross-sectional study aims to assess the Platelet to Lymphocyte ratio (PLR) and the Neutrophil to Lymphocyte ratio (NLR) in term neonates with early-onset sepsis (EOS) and compare it with healthy controls. **Subjects & methods:** The present study is a prospective cross-sectional study, was conducted on 80 neonates delivered in Obstetrics and Gynecology department, Minia University Children and Maternal hospital and admitted in our neonatal intensive care unit and the others during follow up in our NICU, during the period from July 2018 to January 2019. This study was performed with aim of assessment of the Neutrophil to Lymphocyte ratio (NLR) and the Platelet to Lymphocyte ratio (PLR) in term neonates with early-onset sepsis (EOS) ,and compare it with healthy matched controls. **Results:** NLR and PLR as predictors of early-onset neonatal sepsis, sensitivity of NLR was 67% and PLR was 70% and specificity of NLR was 99% and PLR was 73% and PPV of NLR was 98%, PLR was 72%. **Conclusion:** NLR, PLR are strong positive diagnostic markers in detecting early onset neonatal sepsis as PPV of NLR was 98%, PLR was 72%. Regarding to laboratory findings, Leucocytosis, thrombocytopenia, high CRP, high Procalcitonin and positive blood culture were associated with risk of neonatal sepsis.
Keywords: Early onset sepsis, neonates, neutrophils, lymphocytes.

Introduction
Neonatal sepsis is a significant cause of morbidity and mortality among newborn infants. It is divided into early-onset sepsis (EOS) and late-onset sepsis[(1)].Neonatal EOS is defined as the onset of symptoms before 7 days of age, although some experts limit the definition to infections occuring within the first 72 hours of life.[(2)]

Numerous sepsis biomarkers have been evaluated for early detection of neonatal EOS but 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 described above[(3)].

NLR has been reported as a predictor of severity and clinical outcome in patients with community acquired pneumonia or bacteremia[(4)]

Participants & study design:
A total of 80 neonates were enrolled in this study and were divided into 2 groups:

1. Group I:
Includes 40 newborns with postnatal age of 1 to 3 days and gestational age ≥37 weeks with confirmed diagnosis of early onset neonatal sepsis based on symptoms, signs and investigations e.g. blood culture and CRP.

2. Group II:
Fourty matched apparently normal healthy newborns were enrolled in the study as a control group.

Inclusion criteria for group I:

• Full-term neonates ≥37 weeks of gestation and <42 weeks of any mode of delivery, both gender.

• Symptoms and signs suggestive of neonatal sepsis based on standard risk factors of neonatal sepsis and confirmed diagnosis depending on investigations e.g. blood culture and CRP.

Inclusion criteria for group II:

• Full-term neonates ≥37 of gestation and <42 weeks who apparently healthy with no symptoms or signs of neonatal sepsis and their investigations were normal.

Exclusion criteria for group I:

• Prematurity (<37 gestational weeks), post-maturity (> 42 gestational weeks).

• Multiple pregnancies.

• Small for gestational age (SGA) or large for gestational age (LGA) neonates.

• Maternal Pre-eclampsia, gestational diabetes mellitus (GDM), chorioamnionitis.

• Congenital major anomalies.

• Cyanotic congenital heart disease.

• Birth asphyxia

Results:

Table (1): Comparison between cases and control groups regarding the demographic characteristics

	Cases N= 40	Control N= 40	P value
Age (days)			
Mean ± SD	2.25±0.9	1.8±0.8	0.02*
Median	3	1.5	
Interquartile range	1-3	1-3	
Weeks of gestation			
Mean ± SD	36.8±0.2	36.7±0.7	0.7
Median	37	37	
Interquartile range	36-37	36-37	
Birth weight			
Mean ± SD	2.9±0.2	3.08±0.2	0.006*
Median	2.9	3	
Interquartile range	2.7-3	2.9-3.4	
Maternal age			
Mean ± SD	25.8±4	25.7±4.1	0.9
Median	26.5	26	
Interquartile range	22.2-28	22-29	
Apgar score			
Mean ± SD	5.2±0.8	12.2±4.5	0.0001*
Median	5	9	
Interquartile range	5-6	9-18	
Sex			
Male	20 (50%)	26 (65%)	0.1
Female	20 (50%)	14 (35%)	
Delivery route			
Vaginal	8 (20%)	5 (12.5%)	0.3
CS	32 (80%)	35 (87.5%)	
Instrumental delivery(forceps)			
Yes	8 (20%)	5 (12.5%)	0.3
No	32 (80%)	35 (87.5%)	
Consanguinity			
positive	17 (42.5%)	7 (17.5%)	0.01*
negative	23 (57.5%)	33 (82.5%)	

P value calculated by Mann-Whitney test for all quantitative variables except for maternal age calculated by independent sample t-test and by chi-square test for qualitative variables(<0.05 is considered significant).

Table (2): Vital data of cases and control groups

	Cases N=40	Control N=40	P value
Temperature			
Mean ± SD	38.005±0.81	37.2±0.26	0.0001*
Median	38.2	37.2	
Interquartile range	38-38.5	37-37.5	
Mean BP			
Mean ± SD	40.6±2.3	61.2±5.7	0.0001*
Median	40	62.5	
Interquartile range	39-42	55-66	
Respiratory rate			
Mean ± SD	62.8±5	42.7±4.3	0.0001*
Median	62	44	
Interquartile range	60-66	40-46	
Heart rate			
Mean ± SD	173±6	142.4±8.4	
Median	172	144	0.0001*
Interquartile range	168-179	138-149.5	
Spo2 (%)			
Mean ± SD	81.5±4.6	95.4±2.7	0.0001*
Median	82	96	
Interquartile range	78-85	92-98	

P value calculated by Mann-Whitney test (<0.05 is considered significant)

Table (3): Maternal characteristics of cases and control groups

	cases (n=40)	Control (n=40)	P value
Maternal age			
Mean ± SD	25.8±4.05	25.7±4.1	0.9
Range			
Maternal illness			
No	18 (45%)	31 (77.5%)	
UTI	11 (27.5%)	0 (0%)	
Polyhydrominos	2 (5%)	0 (0%)	
Cardiac	2 (5%)	0 (0%)	0.003*
Abortion	4 (10%)	6 (15%)	
Abruptio	1 (2.5%)	0 (0%)	
HCV	2 (5%)	0 (0%)	
Oligohydrominos	0 (0%)	1 (2.5%)	
Morbid obesity	0 (0%)	1 (2.5%)	
Bleeding tendency	0 (0%)	1 (2.5%)	
PROM			
Yes	20 (50%)	2 (5%)	0.0001*
No	20 (50%)	38 (95%)	
Consanguinity			
Yes	17 (42.5%)	7 (17.5%)	0.01*
No	23 (57.5%)	33 (82.5%)	

P value calculated by independent sample t-test for maternal age, by fisher's exact test for PROM and by chi-square test for consanguinity and maternal illness (<0.05 is considered significant).

Table (4): Comparison between cases and control group regarding sepsis parameters

	Cases N=40	Control N=40	P value
WBCs			
Mean ± SD	17±9.3	11.9±4.7	0.004*
Median	15.5	11.7	
Interquartile range	10.2-22.4	8-15.8	
Platelets			
Mean ± SD	227.5±78.4	193±84	0.04*
Median	234	174.5	
Interquartile range	162.5-303.2	136-257.5	
Immature neutrophils			
Mean ± SD	13.6±19	2.8±12.3	0.0001*
Median	8	0	
Interquartile range	0-20.3	0-0	
I/T			
Mean ± SD	0.5-0.9	0.05-0.2	0.0001*
Median	0.1	0	
Interquartile range	0-0.5	0-0	
Lymphocytes			
Mean ± SD	23.2±15	37.9±15.5	0.0001*
Median	18.5	35.5	
Interquartile range	12.2-34.7	25-51.5	
CRP			
Mean ± SD	14-13.4	8.1±13.7	0.0001*
Median	7.7	2.8	
Interquartile range	4.9-17.9	1.3-8.6	
Procalcitonine			
Mean ± SD	94.4±77.9	55.9±30.5	0.08
Median	62	54.5	
Interquartile range	40.5-126.7	35.2-76	
NLR			
Mean ± SD	0.8±1.1	0.08±0.3	0.0001*
Median	0.4	0	
Interquartile range	0-1.1	0-0	
PLR			
Mean ± SD	15±12.4	5.9±3.5	0.0001*
Median	9.7	5.5	
Interquartile range	6.2-22	3.09-7.5	

P value calculated by Mann-Whitney test except for WBCs calculated by independent sample t-test (<0.05 is considered significant).
(WBCS=white blood cells , I/T=immature to total neutrophilic count, NLR= neutrophil to lymphocyte ratio, PLR= platelet to lymphocyte ratio)

Table (5): NLR and PLR as predictors of sepsis

	AUC	P Value	95% CI	Cutoff value	Sensitivity	Specificity	PPV	NPV	LR+	LR-
NLR	0.79	0.0001*	0.68-0.89	0.1	67%	99%	98%	75%	67	0.33
PLR	0.78	0.0001*	0.68-0.88	7	70%	73%	72%	71%	2.59	0.41

(NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio , PPV : positive predictive value , NPV : negative predictive value , LR+: positive likelihood ratio , LR-: negative likelihood ratio.)

Discussion

Neonatal sepsis is a significant global health problem associated with high mortality and poor long-term outcomes for survivors particularly in under-resourced settings. [5]
In Egypt, The total mortality rate for the proven neonatal sepsis was 51% and 42.9% for EOS and LOS, respectively.

Our results in table (1) indicated that there was no significant difference between the cases and control group regarding gestational age, maternal age, sex, delivery route, instrumental delivery(use of forceps).
Our results were in agreement with study done by [6] which was performed with a total of 405 infants developed EONS (<72 h of age)

Our results revealed that there is significant difference between case group and control group regarding birth weight ,age . These results agreed with[7] who studied a cohort of 7861 VLBW neonates (401 to 1500 gm) revealed that decreasing age was associated with increased rates of infection and early-onset sepsis was associated with a significantly prolonged hospital stay in VLBW.
In table (1) Our results revealed that there is significant difference between cases and control group regarding apgar score at 1st 5 mint

on the other hand control group had apgar score > 12 in 1st 5 min which is consistant with results of the study of [8] which was performed on One hundred one (64.7%) controls and 45 (57.7%) cases ,The proportion of neonates who had APGAR score < 7 at first minute was higher in the cases 31 (39.7%) than controls 12 (7.7%)

In table (2); our results revealed significance of vital data: temperature, blood pressure, respiratory rate, heart rate , spo2,These results compatible with criteria that have been adapted in the Integrated Management of Neonatal and Childhood Illness (IMNCI) clinical algorithm

In table (3) our results revealed that there is significant difference between cases and control group regarding maternal illness, these results agreed with[9] who stated that urinary tract infections might lead to congenital pneumonia or systemic infection and associated with an increased risk of sepsis, particularly group B Streptococcus (GBS) infection.[10]

In table (4) of our study, a P value of WBcs, Platelets in CBC was 0.004, 0.0001to indicate statistical significance of CBC in diagnosis of early –onset neonatal sepsis , these results agreed with[11] who stated that Complete blood cell count and peripheral smear are the mainstay of neonatal sepsis diagnosis. [11]

In table (4) shows statistical importance of certain laboratory parameters (CBC with differential, ESR, CRP, Procalcitonin, blood culture) that mentioned before in diagnosis of neonatal sepsis.

In table (5) shows also the statistical importance of Neutrophil to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) as significant hematological indices in diagnosis of EONS that agreed with [12]

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