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Original Article

Diagnostic value of platelet indices for neonatal bacterial sepsis

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Abstract

Background Neonatal bacterial sepsis is a major cause of neonatal morbidity and mortality worldwide. Blood culture as a gold standard, as well as C reactive protein (CRP), micro erythrocyte sedimentation rate (micro ESR), white blood count (WBC), and immature-to-total (I/T) ratio as a sepsis screens are currently used methods, but their utility may be limited due to delayed reporting. Platelet indices are one of the parameters which can be helpful in the diagnosis of neonatal bacterial sepsis.

Objective To evaluate the use of platelet indices, either alone or in combination, with other laboratory screening parameters to *diagnose neonatal bacterial sepsis*.

Methods Neonates admitted to the Neonatal Unit of RSUP Dr. Muhammad Hoesin Hospital, Palembang, South Sumatera, and showing symptoms of sepsis were included in this study. Subjects underwent testing for blood culture, sepsis screen (CRP, micro ESR, WBC, I/T ratio), and platelet indices [platelet count, mean platelet volume (MPV), and platelet distribution width (PDW)].

Results The 107 neonates who fulfilled the inclusion criteria consisted of 42 neonates with proven bacterial sepsis (positive blood culture), 10 neonates with probable bacterial sepsis (positive sepsis screen and negative blood culture), and 55 with clinical bacterial sepsis (negative in both blood culture and sepsis screen). There were no significant differences in platelet count among the proven bacterial sepsis, probable bacterial sepsis, and clinical bacterial sepsis groups. Platelet count < 150,000/μL, PDW ≥ 16.8 fL, MPV ≥ 10.8 fL and combinations of the three, were highly specific markers for proven sepsis, with specificities of 92.3%, 97%, 75.4%, and 80%, respectively. However, all of these parameters were poor predictive markers for positive cultures in neonatal clinical bacterial sepsis, with sensitivities of 19%, 7.1%, 35.7%, and 23.8%, respectively.

Conclusion Platelet indices have high specificity but low sensitivity for the prediction of proven neonatal bacterial sepsis. **[Paediatr Indones. 2020;60:253-8 ; DOI: 10.14238/pi60.5.2020.253-8]**.

Keywords: *platelet indices; bacterial sepsis; neonatal sepsis*

Neonatal sepsis is a major cause of neonatal morbidity and mortality worldwide, contributing to around 38% of all deaths in neonates. The situation is even more in low income underdeveloped countries.[1] However, neonatal sepsis is a diagnostic challenge, as there are overlapping signs and symptoms which preclude a specific diagnosis of sepsis.[2] Neonates are fragile and can deteriorate rapidly, thus, early diagnosis and prompt treatment is required.[1,2] Clinical symptoms and signs of neonatal sepsis include the following: core temperature greater than 38.5°c or less than 36°c and/or temperature instability; cardiovascular instability: bradycardia in the absence of external vagal stimulus, beta-blockers or congenital heart disease or tachycardia in the absence of external stimulus, chronic drugs and painful stimuli and/or rhythm instability, reduced urinary output (less than 1 mL/kg/h), hypotension, mottled skin, impaired peripheral perfusion; skin and subcutaneous lesions:

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petechial rash, sclerema; respiratory instability: apnoea or tachypnea episodes; gastrointestinal disturbances: feeding intolerance, poor sucking, abdominal distention; irritability, lethargy, and hypotonia.[3] Laboratory signs of neonatal sepsis including: white blood cell (WBC) count: <5,000 cells/mm^3 or > 34,000 cells/mm^3;[4] immature-to-total neutrophil ratio (I/T) ≥ 0.2;[3,4] C-reactive protein (CRP) > 9 mg/dL;[5] micro-ESR > 15 mm/hour.[4]

There is no ideal test or combination of tests that serve as benchmarks for diagnosis. Blood culture has always been the gold standard for the diagnosis of neonatal sepsis, but its usefulness is limited due to low positivity rates, delayed reporting, and high cost. To overcome these limitations, we usually rely on sepsis screening (CRP, micro ESR, WBC, and IT ratio), but its sensitivity and specificity vary.[1,2]

Hematological changes induced by culture proven and probable neonatal sepsis have been used to make an early diagnosis and detect complications. Besides other hematological findings, changes in platelet count and platelet indices induced by neonatal sepsis have been the focus of many studies.[6] Thrombocytopenia is a non-specific indicator of neonatal sepsis, with or without disseminated intravascular coagulation (DIC). It can be caused by bacterial, viral, fungal, and parasitic infections, as well as other non-infectious conditions.[7] Advantages of platelet indices are that the blood specimen for these can be drawn at the same time as for other investigations, require no special sampling techniques, and are easily available.[8]

A previous study reported that platelet indices may be helpful in the diagnosis of neonatal bacterial sepsis.1 To our knowledge, there are not many studies on this topic from our region. Hence, we aimed to to evaluate the use of platelet indices, either alone or in combination with existing sepsis screens, as a marker of neonatal bacterial sepsis.

Methods

This cross-sectional study was conducted over a period of 8 months from February to September 2019 in the Neonatal Division, Department of Child Health, Muhammad Hoesin Hospital, Palembang, South Sumatera, to evaluate for relationships between neonatal bacterial sepsis and platelet indices (platelet count, MPV, and PDW). While the primary objective was to evaluate platelet indices (platelet count, PDW, MPV) as a marker of neonatal bacterial sepsis, the secondary objective was to determine differences in platelet indices among proven bacterial sepsis, probable bacterial sepsis, and clinical bacterial sepsis groups. There were 107 subjects who met the inclusion criteria of neonates aged 0-28 days with clinical symptoms or signs suggestive of neonatal sepsis, gestational age 24-42 weeks, and never received antibiotic treatment. Neonates with congenital and acquired causes of thrombocytopenia other than sepsis, i.e., autoimmune disorders of platelets, allo-immune disorder of platelets, maternal anti-platelet medication use, intrauterine growth retardation (IUGR), and incomplete data were excluded. Thrombocytopenia is defined as a platelet count < 150,000/μL. The normal value of MPV was < 10.8 fL and PDW was < 16.8 fL.[1,8]

Soon after admission, 3 mL blood specimens were taken and processed for blood culture, total leukocyte count (TLC), micro-ESR, I/T neutrophil ratio, and CRP. Platelet indices (platelet count, MPV, PDW) were also determined with an automated hematology analyzer (SYMEX XN-1000R). Blood culture was observed for 5-7 days before labelling it sterile. The culture and sensitivity report was done by Bactec method.[9] All the above tests were done in the microbiology laboratory. Subjects were categorized into three groups:

1. Proven sepsis: characterized by positive blood culture with clinical and/or laboratory evidence of sepsis.
2. Probable sepsis: blood culture negative, but meeting the criteria of presence of at least two clinical symptoms and at least two laboratory signs (sepsis screen).
3. Clinical sepsis: presence of at least two clinical symptoms, but with neither laboratory signs nor positive blood culture.

Univariate and bivariate analysis was done using *SPSS version 21* statistical software. Categorical data were shown in numbers and percentages. Numerical data were shown in mean (standard deviation) or median (minimum-maximum) according to the

normality of data distribution. Independent T-test and Mann-Whitney U test were performed to compare laboratory parameters between proven, probable, and clinical bacterial sepsis. Variables with significant results were analyzed further to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. The value of $P<0.05$ were considered statistically significant with 95% confidence interval.

Results

Characteristics of the 107 subjects are shown in **Table 1**. There were no significant differences in age, sex, type of delivery, and frequency of pregnancy between the bacterial sepsis (probable and/or proven) and clinical sepsis groups. However, lower gestational age and birth weight were significantly more dominant in the bacterial sepsis (probable and/or proven) than in clinical sepsis group ($P<0.05$).

Table 2 shows the most common signs and symptoms found in subjects. Of our 107 subjects, 42 (39.3%) were cases of proven bacterial sepsis (positive blood culture), 10 (9.3%) were categorized as probable sepsis, and 55 (51.4%) were categorized as clinical sepsis. The types of microorganisms cultured from those with proven sepsis are shown in **Table 3**. Platelet indices were compared between the proven and clinical bacterial sepsis groups in **Table 4**. Mann Whitney U statistical analysis revealed no significant differences in the number of platelets, MPV, and PDW between the proven and clinical bacterial sepsis groups, while **Table 5** shows the Mann Whitney U statistical analysis revealed no significant differences in the number of platelets, MPV, and PDW between groups.

The calculated diagnostic values of platelet indices for diagnosis of bacterial sepsis are shown in **Table 6**. The diagnostic values of probable bacterial sepsis that are commonly used (<5,000 cells/mm^3 or > 34,000 cells/mm^3, I/T ratio $\mu \geq 0.2$, CRP > 9 mg/dL, and micro-ESR > 15 mm/hour) are shown in **Table 7**.

Probable bacterial sepsis with ≥ 2 positive parameters had a 42.9% sensitivity, 84.6% specificity, 64.3% positive predictive value, 69.6% negative predictive value, and 68.2% accuracy (**Table 7**).

Table 1. Subjects' characteristics

Characteristics	Sepsis (proven and probable) (n= 52)	Clinical sepsis (n = 55)	P value
Age, n (%)			0.102[a]
<72 hours	17 (32.7)	26 (47.3)	
3 - 7 days	19 (36.5)	21 (38.2)	
> 7 days	16 (30.8)	8 (14.5)	
Gender, n (%)			0.627[b]
Male	28 (53.8)	26 (47.3)	
Female	24 (46.2)	29 (52.7)	
Gestational age, n (%)			0.000[b]
<37 weeks	36 (69.2)	17 (30.9)	
37-42 weeks	16 (30.8)	38 (69.1)	
>42 weeks	0 (0)	0 (0.0)	
Birth weight, n (%)			0.005[b]
<2,500 gr	30 (57.7)	16 (29.1)	
2,500-4,000 gr	22 (42.3)	39 (70.9)	
> 4,000 gr	0 (0)	0 (0)	
Type of delivery, n (%)			0.136[a]
Normal	32 (61.5)	39 (70.9)	
Caesarean section	19 (36.5)	12 (21.8)	
Forceps	1 (1.9)	4 (7.3)	
Pregnancy, n (%)			0.071[b]
Primigravida	43 (82.7)	36 (65.5)	
Multigravida	9 (17.3)	19 (34.5)	

a=Pearson Chi-square, P=0.05 ; b=continous correction, P=0.05

Table 2. Subjects' common signs and symptoms (N=107)

Signs and/or symptoms	n (%)
Poor suckling	68 (63.5)
Diarrhea/bloating/vomiting	44 (41.1)
Fever	40 (37.4)
Hypoactive/ irritable	34 (31.8)
Tachypnea	26 (24.3)
Seizure	8 (7.5)
Umbilical infection	5 (4.7)

Note: (1 subject had μ ≥ 2 symptoms)

Table 3. Microorganisms cultured from 42 subjects

Microorganism	n(%)
Gram positive	16 (38.1)
Staphylococcus haemolyticus	9 (21.4)
Staphylococcus epidermidis	3 (7.1)
Staphylococcus aureus	2 (4.7)
Staphylococcus hominis Ssp hominis	1 (2.4)
Staphylococcus citreus	1 (2.4)
Streptococcus pyogenes	1 (2.4)
Streptococcus mitis/ oralis	
Gram negative	4 (9.5)
Klebsiella pneumoniae Ssp pneumoniae	2 (4.7)
Acinetobacter baumannii	2 (4.7)
Escherichia coli	1 (2.4)
Burkholderia cepacea	
Total	42 (100)

Table 4. Mean platelet indices in the proven and clinical bacterial sepsis groups

Parameters	Proven sepsis (n=42)	Clinical sepsis (n=55)	P value
Mean platelet count (SD), $10^3/\mu L$	305.5 (177.1)	310.6(132.3)	0.570
Mean MPV (SD), fL	10.63 (1.035)	10.27 (0.824)	0.057
Mean PDW (SD), fL	12.36 (3.342)	11.48 (2.138)	0.303

Table 5. Mean platelet indices in the probable and clinical bacterial sepsis groups

Parameters	Probable sepsis (n=10)	Clinical sepsis (n=55)	P value
Mean platelet count (SD), $10^3/\mu L$	299.4 (116.5)	310.6 (132.3)	0.985
Mean MPV (SD), fL	10.51 (1.124)	10.27 (0.824)	0.422
Mean PDW (SD), fL	12.35 (2.241	11.48 (2.138)	0.153

Discussion

In our study, we grouped probable and proven bacterial sepsis patients together (52/107; 48.5%); subjects with proven bacterial sepsis were 42/107 (39.2%). Hence, the sepsis group consisted of probable bacterial sepsis (10/52 subjects) and proven bacterial sepsis (42/52 subjects). The most common clinical signs and symptoms in our subjects were poor suckling, gastrointestinal disorders, temperature instability, hypoactivity, and respiratory disorders. A previous study noted that common clinical signs of studied groups were poor suckling (42%), lethargy (30%), poor Moro reflex (14%), and respiratory distress (8%).[10]

Blood cultures were positive in 42 subjects. The most commonly cultured microorganisms were Gram-positive bacteria in 33/42 (78.5%) subjects consisting of *Staphylococcus haemolyticus* (38%), *Staphylococcus epidermidis* (21.4%), *Staphylococcus aureus* (7.1%), *Staphylococcus hominis* (4.7%), and *Staphylococcus citreus*, *Streptococcus pyogenes*, and *Streptococcus mitis/ Streptococcus oralis* (2.3%). Gram negative bacteria were cultured from 9/42 (21.5%) subjects and consisted of *Klebsiella pneumoniae Ssp pneumoniae* (9.5%), *Acinetobacter baumannii* (4.7%), *E. coli* (4.7%), *Burkholderia cepacea* (2.3%). A previous study reported that of 469 patients, 136 (29%) were cases of culture proven sepsis, and 333 (71%) were categorized as probable sepsis. Among culture proven sepsis cases, 84 (61.8%) had Gram positive pathogens and 52 (38.2%) had Gram negative sepsis.[6] In contrast, another study reported that most cultured microorganisms were Gram negative (67.5%).[7]

In our study, the probable sepsis group had the lowest platelet count, while the proven sepsis group had the highest MPV and PDW. These findings indicate that patients with low platelet levels, high MPV, or high PDW become septic. In contrast, a previous study showed a significant difference in platelet indices of their sepsis group compared to the control group (healthy neonates).11 Our study showed that platelet count < 150,000/μL, PDW ≥16.8 fL, and MPV ≥10.8 fL individually and in combination were highly specific markers for predicting proven bacterial sepsis, with specificities of 92.3%, 97%, 75.4%, and 80%, respectively. However, these parameters were poor predictive

Table 6. Performance variables of platelet indices for diagnosis of bacterial sepsis compared to blood culture as the gold standard in proven sepsis group (n=42)

Diagnostic value	Platelet <150x10^3/µL	MPV ≥ 0.8 fL	PDW ≥ 16.8 fL	Combination ≥ 2 parameter
Sensitivity, %	19	35.7	7.1	23.8
Specificity, %	92.3	75.4	97	80
NPV, %	63.8	64.5	64.5	62
PPV, %	61.5	48.4	60	43.5
Accuracy, %	63.5	55.1	61.7	57.9

Note: combination ≥ 2 paramaters consisted of Plt + MPV or Plt + PDW, or MPV + PDW

Table 7. Performance variables of sepsis screen for diagnosis of probable bacterial sepsis compared to blood culture results

Parameters biomarker sepsis screen		Blood culture		Total
		Positive	Negative	
WBC > 34x10^3/mm^3 or < 5x10^3/mm^3	≥ 2 positive parameters	18	10	28
I/T ratio ≥ 0.2 ESR > 15 mm/hour CRP > 9 mg/dL	< 2 positive parameters	24	55	79
Total		42	65	107

markers for culture positivity in clinical bacterial sepsis, with sensitivities of 19%, 7.1%, 35.7%, and 23.8%, respectively. We noted that ≥ 2 positive sepsis screen parameters had higher accuracy (68.2%) and higher Youden index score than platelet indices. The accuracy of 68.2% indicates that the degree of measurement conformity (reliability) was good.

A previous study found that platelet count was the most sensitive marker for sepsis, with 83.70% sensitivity, followed by 75.20% for MPV and 66.70% for PDW. Their specificity of platelet count was also highest at 65%, followed by 64.30% for MPV and 57.80% for PDW. When any two of the platelet indices were combined, the specificity increased to a maximum of 67.0% (platelet count and MPV combined). The maximum sensitivity was 85.80% (platelet count and MPV combined) as a marker for sepsis. However, when all three parameters were taken together, the sensitivity was 84.10% and specificity was 65.50%.1 Likewise, another study in Egypt reported MPV sensitivity and specificity values of 100% each, in their study of 140 subjects with healthy individuals as a control group.[10]

In conclusion, platelet indices have high specificity but low sensitivity for the prediction of proven neonatal bacterial sepsis.

Conflict of Interest

None declared.

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