Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.59, No.6(2019). p. 289-93; doi: http://dx.doi.org/10.14238/pi59.6.2019.289-93

Original Article

Diagnostic value of mean platelet volume in neonatal sepsis

Kristopher May Pamudji, I Made Kardana

Abstract

Background Neonatal sepsis is a severe disease with potentially serious impacts if not treated early. However, the symptoms and clinical signs are not specific. Several studies have been conducted to find early infection markers for detection of neonatal sepsis, but without satisfactory results. Mean platelet volume (MPV) is a new marker of infection that has good potential for diagnosing neonatal sepsis.

Objective To assess the diagnostic value of MPV in early detection of neonatal sepsis.

Methods This retrospective study with diagnostic testing was done with data collected from medical records of neonates with neonatal sepsis who were admitted to the Neonatology Department in Sanglah Hospital, Denpasar from December 2018 to March 2019. Mean platelet volume cut-off point was determined using a receiver-operating characteristic (ROC) curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MPV in neonatal sepsis were determined using a 2x2 table.

Results Of 82 subjects, 55 subjects were male (67%). Positive blood culture results were found in 25 subjects (30%). Mean platelet volume with a cut-off point of 7.44 fL had 80% sensitivity, 84.2% specificity, 69% PPV, and 90.6% NPV.

Conclusion Mean platelet volume with a cut-off point of 7.44 fL can be used to diagnose neonatal sepsis with a sensitivity of 80% and specificity of 84.2%. **[Paediatr Indones. 2019;59:289-93; doi: http://dx.doi.org/10.14238/pi59.6.2019.289-93]**.

Keywords: *mean platelet volume; neonatal sepsis; sensitivity; specificity*

Neonatal sepsis is a severe disease with serious impacts if not treated in a timely manner. Neonatal sepsis remains a cause of high perinatal morbidity and mortality, especially in developing countries. The development of medical science in terms of neonatal care has increased the life expectancy of neonates. However, neonatal sepsis still continues to make a significant contribution to neonatal morbidity and mortality.[1]

Neonatal sepsis is a clinical syndrome of systemic disease accompanied by bacteremia that occurs in the first 28 days of life.[2] The incidence of neonatal sepsis varies from 7.1 to 38 per 1,000 live births in Asia, 6.5 to 23 per 1,000 live births in Africa, and 3.5 to 8.9 per 1,000 live births in South America.[3] The national incidence of neonatal sepsis in Indonesia is unknown. However, the incidence of neonatal sepsis in Cipto Mangunkusumo Hospital, Jakarta was 13.7% with a mortality rate of 14%.[4] Sanglah Hospital, Denpasar had a 5% incidence of neonatal sepsis with a mortality rate of 30.4%.[5]

From the Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital, Denpasar, Bali, Indonesia.

Corresponding author: Kristopher May Pamudji. Jalan Diponegoro, Dauh Puri Klod, Denpasar Barat, Bali 80113, Indonesia. Email: maypamudji@gmail.com.

Submitted June 25, 2018. Accepted November 8, 2019.

Neonatal sepsis is a severe systemic disease, but the symptoms and clinical signs are not specific and include temperature instability, tachycardia or bradycardia, hypotension, poor tissue perfusion, metabolic acidosis, apnea, respiratory distress, grunting, cyanosis, lethargy, seizures, feeding intolerance, abdominal distension, jaundice, petechiae, purpura, and bleeding.[6] The gold standard in diagnosing neonatal sepsis is blood culture, however, it requires a long examination time and is not always effective for identifying microorganisms. Hence, a negative blood culture result does not always indicate an absence of microorganisms in the patient. Such a false negative situation can be caused by a small volume blood specimen or administration of antibiotics to the mother before delivery. Some examinations such as white blood cell count, absolute neutrophil count, immature-to-total neutrophil ratio (IT ratio), platelet count, C-reactive protein (CRP), and procalcitonin (PCT) have been used as markers of early infection to help diagnose neonatal sepsis. Yet, they have not been able to provide significant benefits as such.[7]

Several studies have been conducted to find early infection markers of neonatal sepsis with good sensitivity and specificity as well as low cost, so that any health care facility can use it. Complete blood examination is inexpensive and routine in almost all health care facilities. Mean platelet volume (MPV) is an indicator of platelet function that reflects platelet production. Some studies found that MPV was associated with course of the disease, such as in neonatal sepsis, acute pyelonephritis, and gastric cancer.8 As such, MPV may be a new marker of infection with good potential to diagnose neonatal sepsis.8 Hence, we aimed to assess the diagnostic value of MPV in early detection of neonatal sepsis.

Methods

This retrospective study with diagnostic testing design was conducted in the Neonatology Ward at Sanglah Hospital, Denpasar. Data were taken from medical records of patients admitted from December 2018 to March 2019. The inclusion criteria were neonates with suspected neonatal sepsis. The exclusion criteria were patients with incomplete medical record data, immunodeficiency diseases, autoimmune diseases, malignancies, hematological disorders, and major congenital anomalies.

Consecutive sampling was used to collect subjects who met the inclusion criteria until reaching the desired sample size. The minimum required sample size was calculated to be 76 subjects using a diagnostic test formula with sensitivity output, error rate set at 5% with $Z\alpha=1.96$, sensitivity set of 0.75, research precision of 17.5%, and disease prevalence of 0.347.9 This study was approved by the Research Ethics Commission of the Universitas Udayana Medical School/Sanglah Hospital, Denpasar. Operational definitions of variables in this study were as follows: neonatal sepsis was a clinical syndrome of systemic diseases accompanied by bacteremia that occurs in the first month of life, with positive blood culture; mean platelet volume (MPV) was the average platelet size value obtained from complete blood count examination at the time of neonatal sepsis diagnosis. Gestational age was clasified into preterm (<37 weeks) and term (37-42 weeks). Birth weight was divided into low (<2500 grams) and normal (2500-4000 grams). Premature rupture of membranes was rupture of the membranes (amniotic sac) before labor occurs (≥12 hours before delivery). Chorioamnionitis was defined as an infection that occurs in the amniotic membrane (chorion), amniotic fluid (amnion), and placenta. Multiple pregnancy was a pregnancy with two or more fetuses. Asphyxia was a condition where the baby is not immediately crying after birth with an APGAR score in the first minute less than 7.

Data collected in this study were gender, gestational age, birth weight, delivery mode, premature rupture of membranes, chorioamnionitis, multiple pregnancies, asphyxia, blood culture result, and MPV count. Data analysis was carried out using *SPSS software*. Mean platelet volume cut-off point was analyzed by ROC curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MPV in neonatal sepsis were determined by a 2x2 table.

Results

There were 89 neonatal sepsis patients during the study period. Five neonates were excluded because of major congenital anomalies and 2 others were

excluded because of incomplete medical records. Thus, the total sample size was 82 subjects, 55 (67%) of whom were male. Blood culture results were positive in 25 subjects (30%). The characteristics of subjects are shown in **Table 1**.

Table 1. Characteristics of subjects

Characteristics	Blood culture results	
	Positive (n = 25)	Negative (n = 57)
Sex, n		
Male	16	39
Female	9	18
Gestational age, n		
Preterm	16	35
Term	9	22
Birth weight, n		
Low	16	34
Normal	9	23
Delivery mode, n		
Vaginal	12	24
Caesarean section	13	33
Premature rupture of membranes, n	3	9
Yes	22	48
No		
Chorioamnionitis, n		
Yes	0	1
No	25	56
Multiple pregnancy, n		
Yes	2	7
No	23	50
Asphyxia, n		
Yes	2	26
No	23	31
Median MPV (range), fL	10.66 (5.66-16.76)	6.13 (4.22-9.96)

The ROC curve analysis revealed an MPV cut-off point of 7.44 fL for neonatal sepsis, with area under curve (AUC) 0.89 (95%CI 0.81 to 0.98) (**Figure 1**). The MPV cut-off point 7.44 fL had 80% sensitivity, 84.2% specificity, 69% PPV, and 90.6% NPV (**Table 2**).

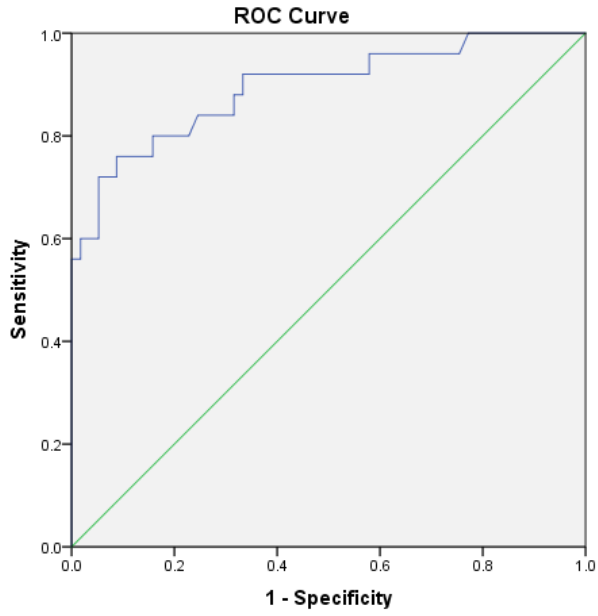

Figure 1. ROC curve of MPV

Discussion

Blood culture is the gold standard for diagnosing neonatal sepsis, but it is insensitive. Maternal antimicrobial treatment and inadequate volumes of blood specimens provided for culture may lead to false negative culture results in infants. Such results can miss up to 75% of cases among those who meet sepsis terminology guidelines.[7] A previous study reported obtaining positive blood culture results in only 40.7% of 344 infants with neonatal sepsis.[10] Similarly, another study obtained positive blood culture results in only 34.7% of 150 infants with neonatal sepsis,[9] and a study obtained positive blood culture results in 41.2% of 102 infants with neonatal sepsis.[11] In our study, blood culture results were positive in only 30% of 82 infants with suspected neonatal sepsis, in accordance with previous studies.

Mean platelet volume is the arithmetic mean volume of the platelets derived from platelet histogram

Table 2. Diagnostic value of MPV in neonatal sepsis

MPV, fL	Blood culture		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Positive	Negative				
≥7.44	20	9	80	84.2	69	90.6
<7.44	5	48				

on an automated Coulter counter. The platelet volume is regulated by cytokine-dependent megakaryocyte ploidy and platelet number.[12] The role of platelets in the inflammatory response is associated with the release of cytokines and chemokines that attract leukocytes and facilitate adhesion to endothelium at the site of damage. Platelets may interact with leukocytes during the inflammatory process by forming platelet-leukocyte aggregates. These bindings are possible through adhesion proteins expressed on the platelets cell surface during activation. Platelets also support leukocytes to eliminate bacterial infections via direct contact, encapsulation of bacteria, and release of reactive oxygen species and platelet microbicidal proteins (PMP).[13]

The mechanism of changing platelet function in sepsis is still unclear. Platelet shape changes from discoid to spherical with pseudopodia during activation. Mean platelet volume reflects the average size of platelets. Young platelets are larger than old platelets. An increased number of young platelets indicates increased platelet production due to overconsumption induced by inflammation. Larger platelets are functionally, metabolically, and enzymatically more active than smaller ones. They contain more intracellular thromboxane A2 and increased expression of procoagulant surface proteins such as P-selectin and glycoprotein IIIa, causing greater prothrombotic potential. Moreover, platelet-neutrophil interactions and platelet-endothelial interactions facilitate a variety of immune activation instances.[14]

Elevated MPV may indicate endothelial damage as well as platelet activation, and is an easily accessible hematological parameter. In a clinical study, thrombocyte consumption and MPV values escalated in acute infections.[15] The studies conducted on neonatal sepsis patients reported that MPV values were high and the increase in the MPV values was significant in terms of prognosis and mortality.[15]

The median MPV in this study was higher in the positive blood culture group compared to the negative blood culture group (10.66 and 6.13 fL, respectively). A study reported that MPV with cut-off point of 9.7 fL was significant and considered to be clinically useful, with 75% sensitivity and 69.4% specificity (accuracy 72.3%) in predicting mortality.[16] Another study found that an MPV cut-off point of 8.5 fL had sensitivity 48.7% and specificity 75.8%.[17] In our study, MPV also showed good accuracy in diagnosing neonatal sepsis with AUC 0.894 (95%CI 0.812 to 0.976). The MPV cut-off point of 7.44 fL was used based on ROC curve analysis. There were 29 subjects (35%) who had MPV ≥7.44 fL.

The MPV cut-off point of 7.44 fL had 80% sensitivity, suggesting that MPV may be a marker of neonatal sepsis. The 84.2% specificity of MPV in our study was also good, and indicated that this MPV cut-off was able to determine that 84.2% of subjects did not have neonatal sepsis. The PPV in our study was 69%, indicating that a positive diagnostic outcome (MPV value ≥7.44 fL) was actually neonatal sepsis 69% of the time. Further examination (such as blood culture test) would be needed to confirm the diagnosis. The NPV in our study was 90.6%, indicating that 90.6% of subjects did not suffer from neonatal sepsis if their MPV value was <7.44 fL, however, we must consider the prevalence of neonatal sepsis in the region because PPV and NPV were influence by prevalence of the disease.

A limitation of this study was its retrospective design. The other weakness was that the media used to grow blood culture microorganisms was only useful for bacteria and fungi. Other causes of neonatal sepsis such as viruses could not be detected. Future studies using a prospective design and blood culture media that can grow bacteria, fungi, or viruses need to be done to further assess the MPV diagnostic value for neonatal sepsis. Our results of the diagnostic test indicate that MPV examination can be used to diagnose neonatal sepsis with 80% sensitivity and 84.2% specificity. The cut-off value of MPV <7.44 fL may be used to exclude a diagnosis of neonatal sepsis (NPV 90.6%).

Conflict of interest

None declared.

Acknowledgements

We thank our colleagues from the Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital who provided insight and expertise that greatly assisted us in this study.

Funding acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014;5:170-8.
2. Coetzee M, Mbowane NT, de Witt TW. Neonatal sepsis: highlighting the principles of diagnosis and management. S Afr J Child Health. 2017;11:99-103.
3. Shaha CK, Dey SK, Shabuj KH, Chisti J, Mannan MA, Jashimuddin, *et al*. Neonatal sepsis- A review. Bangladesh J Child Health. 2012;36:82-9.
4. Aminullah A. Sepsis pada bayi baru lahir. In: Kosim MS, Yunanto A, Dewi R, Sarosa GI, Usman A, editors. Buku ajar neonatologi. 1st ed. Jakarta: Badan Penerbit IDAI; 2010. p. 170-87.
5. Putra PJ. Insiden dan faktor-faktor yang berhubungan dengan sepsis neonatus di RSUP Sanglah Denpasar. Sari Pediatri. 2012;14:205-10.
6. Shane AL, Sanchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770-80.
7. Iroh Tam PY, Bendel CM. Diagnostics for neonatal sepsis: current approaches and future directions. Pediatr Res. 2017;82:574-83.
8. Senturk M, Azgin I, Ovet G, Alatas N, Agirgol B, Yilmaz E. The role of the mean platelet volume and neutrophil-to-lymphocyte ratio in peritonsillar abscesses. Braz J Otorhinolaryngol. 2016;82:662-7.
9. Khoshdel A, Mahmoudzadeh M, Kheiri S, Imani R, Shahabi G, Saedi E, *et al.* Sensitivity and specificity of procalcitonin in diagnosis of neonatal sepsis. Iran J Pathol. 2008;3:203-7.
10. El-Din EM, El-Sokkary MM, Bassiouny MR, Hassan R. Epidemiology of neonatal sepsis and implicated pathogens: a study from Egypt. Biomed Res Int. 2015;2015:1-11.
11. Juniatiningsih A, Aminullah A, Firmansyah A. Profil mikroorganisme penyebab sepsis neonatorum di Departemen Ilmu Kesehatan Anak Rumah Sakit Cipto Mangunkusumo Jakarta. Sari Pediatri. 2008;10:60-5.
12. Bhat YR. Platelet indices in neonatal sepsis: a review. World J Clin Infect Dis. 2017;7:6-10.
13. Korniluk A, Koper-Lenkiewicz OM, Kaminska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm. 2019;2019:9213074.
14. Tajarernmuang P, Phrommintikul A, Limsukon A, Pothirat C, Chittawatanarat K. The role of mean platelet volume as a predictor of mortality in critically ill patients: a systematic review and meta-analysis. Crit Care Res Pract. 2016;2016:4370834.
15. Orak M, Karakoc Y, Ustundag M, Yildirim Y, Celen MK, Guloglu C. An investigation of the effects of the mean platelet volume, platelet distribution width, platelet/lymphocyte ratio, and platelet counts on mortality in patients with sepsis who applied to the emergency department. Niger J Clin Pract. 2018;21:667-71.
16. El Rahman HM, Mahmoud SF, Ezzat AW, Roshdy AE. Mean platelet volume versus total leukocyte count and C-reactive protein as an indicator for mortality in sepsis. Egypt J Hosp Med. 2018;71:2373-9.
17. Dursun A, Ozsoylu S, Akyildiz BN. Neutrophil-to-lymphocyte ratio and mean platelet volume can be useful markers to predict sepsis in children. Pak J Med Sci. 2018;34:918-22.