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Original Article

The Role of Mean Platelet Volume in the Diagnosis of Neonatal Sepsis

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Abstract

Background: Neonatal sepsis is still one of the main issues with unspecific signs and symptoms with high mortality and morbidity rates to assess Mean Platelet Volume (MPV) as a laboratory value for predicting neonatal sepsis.

Methods: In this cross-sectional study, we recruited 72 term and late preterm newborns diagnosed with sepsis who were admitted into the neonatal ward of the children's medical center of Tehran University of Medical Sciences (TUMS) from March 2016 to May 2017 case group. The control group consisted of 50 healthy term infants (mean age: 5.46±3.59 days). The blood test was performed at the time of admission. Hematologic markers including MPV, White Blood Cell (WBC), and C-Reactive Protein (CRP) were compared between two groups.

Results: There were statistically significant differences between WBC (p=0.019), CRP (Mean Difference: 9.38, 95% CI: 4.19 to 14.58, p=0.001) and MPV (Mean Difference: 0.56, 95% CI: 0.25 to 0.86, p<0.001) in case group in comparison with the control group. The area under the curve was 68.71 for MPV. Diagnostic cut-off levels with sensitivity (80.56%) and specificity (52%) were found to be MPV> 9.2 *fL*. There was no significant association between MPV and disease status (case group: 9.80 ±0.88 *vs.* control group: 9.24 ±0.75).

Conclusion: Despite higher MPV during neonatal sepsis, the MPV values' sensitivity and specificity were inadequate to be used as diagnostic tests. CRP is still a better marker for early suspicion of neonatal sepsis. MPV may be used in combination with CRP for identifying neonatal sepsis.

Keywords: C-reactive protein, Mean platelet volume, Neonatal sepsis

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Introduction

Despite the rapid advances in equipment and neonatal care management in NICU and prenatal care, policies for decreasing neonatal mortality and morbidity incidence rates are still among the essential concerns for public health, especially in developing countries. Neonatal sepsis is still one of the main issues with unspecific signs and symptoms with high mortality and morbidity rates (1,2). Although blood culture is still the gold standard diagnostic test for defining the pathogens, the needs including minimum of 24 hours for microbial growth in bactec, differentiation of the actual infection from a potential contaminant pathogen, false negative blood culture, and presence of fungal and viral infections are the main issues in these situations (3,6). Due to the high prevalence rate of clinical sepsis during neonatal periods (4), early suspicion of infants with sepsis through laboratory tests and clinical status is crucial.

Clinical evidence suggests that platelets play a crucial role in inflammatory responses. Endothelial damage and aggregation of platelet lead to thrombocytopenia during bacterial infection (7). On the other hand, pro-inflammatory cytokines stimulate megakaryocytes to increase platelets' numbers in response to inflammation. This results in a high Mean Platelet Volume (MPV) (8). MPV, as a predictor of mortality in critically ill adult patients, has already been studied (9).

The possible correlation between MPV and neonatal sepsis in preterm infants and MPV's role as a predictor of the severity of sepsis in preterm infants has already been evaluated in a few studies (10,13).

This study aims to assess the feasibility of MPV during the time of admission to identify term and late preterm infants prone to neonatal sepsis and determine whether it can serve as an available marker for predicting neonatal sepsis and comparing its effectiveness with C-Reactive Protein (CRP). As the previous study focusing on NICU admitted preterm infants, this is the first study designed for the term and stable preterm infants with sepsis, to the best of our knowledge.

Materials and Methods

In this cross-sectional study, all term newborns with Gestational Age (GA) of ≥ 37 weeks and preterm newborns with GA of ≥ 35 weeks with a diagnosis of sepsis who were admitted into the neonatal ward of the children's medical center of Tehran University of Medical Sciences (TUMS) from March 2016 to May 2017 were included in this study and considered as the case group. This hospital is one of the governmental children's referral hospitals in iran. Written consent was obtained from parents before enrollment. This study was approved as a student thesis by the research and medical ethics committee of TUMS under the Helsinki declaration. Sepsis was defined based on the international pediatric sepsis consensus criteria (14), and clinical trials defined by the EMA (15). Exclusion criteria: 1. Infants born to a mother with chorioamnionitis or preeclampsia or any drug history could negatively affect platelet counts; 2. History of antibiotics before admission in the newborn; 3. Congenital thrombocytopenia (platelet < 150,000 ×109/*L*); 4. Major congenital abnormalities at birth 5. Any immune thrombocytopenia.

Healthy, full-term newborns that were admitted for treatment of non-hemolytic jaundice were considered as a controlled study. The case group was divided into two subgroups Ia: newborns with clinical and laboratory manifestations of sepsis with positive blood culture, subgroup Ib: with clinical and laboratory manifestations of sepsis with negative blood culture. Newborns in the case group were further subdivided into two groups based on the time of development of sepsis; if recognition of sepsis occurred within the first 72 hours of life, it would be considered as Early-Onset Sepsis (EOS), whereas presentation of sepsis after the third days of life was regarded as Late-Onset Sepsis (LOS).

In the case of groups, blood samples were performed at the time of admission and contained CBC, CRP, and blood culture. The culture of Cerebrospinal Fluid (CSF) and urine were also sent, in case they were obtained. Blood cultures were analyzed using a fully automated BACTEC method by BACTEC 9240 (Becton Dickinson, Heidelberg, Germany). Serum concentrations of CRP were measured by a Tinaquant CRP (Latex) high sensitive immune turbidimetric assay on a Roche Modular P analyzer (Rochekit, Roche Diagnostics, Mannheim, Germany). Platelet counts and MPV were evaluated *via* a coulter LH analyzer. And all these types of equipment were calibrated.

Blood samples were repeated within 3-5 days of admission for assessment of laboratory responses to treatments based on their indications. Leukocytosis was considered as leukocyte count ≥ 20000/μL, leukopenia was identified as leukocyte count ≤ 5000/μL, and immature/total neutrophil ratio > 0.2 was deemed to be significant (16). Thrombocytopenia was defined as platelet count < 150000/μL (8). Demographic data including sex, gestational age, birth weight, age of admission, and laboratory data, were recorded. In control groups, CRP, also of Icter workup tests, were performed.

Statistical analysis

Categorical and continuous variables were expressed as number (percentage) and mean ± (standard deviation). A student's t-test was used to compare the continuous variables. Comparisons of proportions were performed with a chi-squared test or Fisher's exact test. A Receiver Operating Characteristic (ROC) curve analysis was utilized to select the best cut-off value for MPV in neonatal sepsis prediction. Then the thresholds that provided the maximum sensitivity and specificity for MPV to predict neonatal sepsis were identified using the maximal Youden Index. Areas Under the Curve (AUC) and their standard error were calculated.

A logistic regression analysis was performed to determine the relationship between CRP, MPV, and the occurrence of neonatal sepsis after adjusting for baseline variables, including the age of neonate, the weight of neonate, WBC, and platelet count. p values <0.05 were considered statistically significant. Statistical analysis was performed using Stata version 13.0 statistical software (Stata, College Station, TX).

Results

Our hospital received a total of 435 term and late preterm babies. Seventy-two of them (mean age 9.61 ± (8.15) days) met the criteria for sepsis diagnosis. All 72 newborns participating in this trial were followed up without any missing data. 4(5.6%) of the participants had proven sepsis (Group Ia), and 68(94.4%) had clinical sepsis (Group Ib). The control group consisted of 50 term infants [mean age 5.46 ± (3.59) days]. The demographic and clinical variables of the two groups are described in table 1.

There was no significant difference between gestational age and gender in the case group (61.1% male) and the control group (58% male). However, there were statistically significant differences between WBC (p=0.019), CRP (Mean Difference: 9.38, 95% CI: 4.19 to 14.58, p=0.001) and MPV (Mean Difference: 0.56, 95% CI: 0.25 to 0.86, p<0.001) in case group in comparison with the control group.

Overall, Gram-positive bacteria were isolated in four patients with proven sepsis. They contained non-hemolytic streptococcus (viridian's group) in 2

Table 1. Demographic and clinical characteristics of newborns according to the presence or absence of sepsis

	Sepsis		
Characteristics	Present(n=72)	Absent(n=50)	p-value
Age (days)	9.61 ± (8.15)	5.46 ± (3.59)	<0.001
Birth weight (*g*)	2992.78 ± (630.29)	2976.70 ± (556.50)	0.88
Gestational age (weeks)	38.17 ± (1.92)	37.64 ± (1.75)	0.12
WBC(/mm^3)	11.59 ± (5.57)	9.84 ± (2.29)	0.01
Plt	318.39 ± (135.36)	299.10 ± (86.00)	0.33
MPV(*fL*)	9.80 ± (0.88)	9.24 ± (0.75)	<0.001
CRP	10.53 ± (21.42)	1.14 ± (3.46)	0.001
Gender			
Boy	44(61.1)	29(58)	0.85
Girl	28(38.9)	21(42)	
Values are given as mean ± SD (standard deviation), or number (percentage) unless otherwise indicated			

White blood cells (WBC), platelet (Plt), mean platelet volume (MPV), C-reactive protein (CRP)

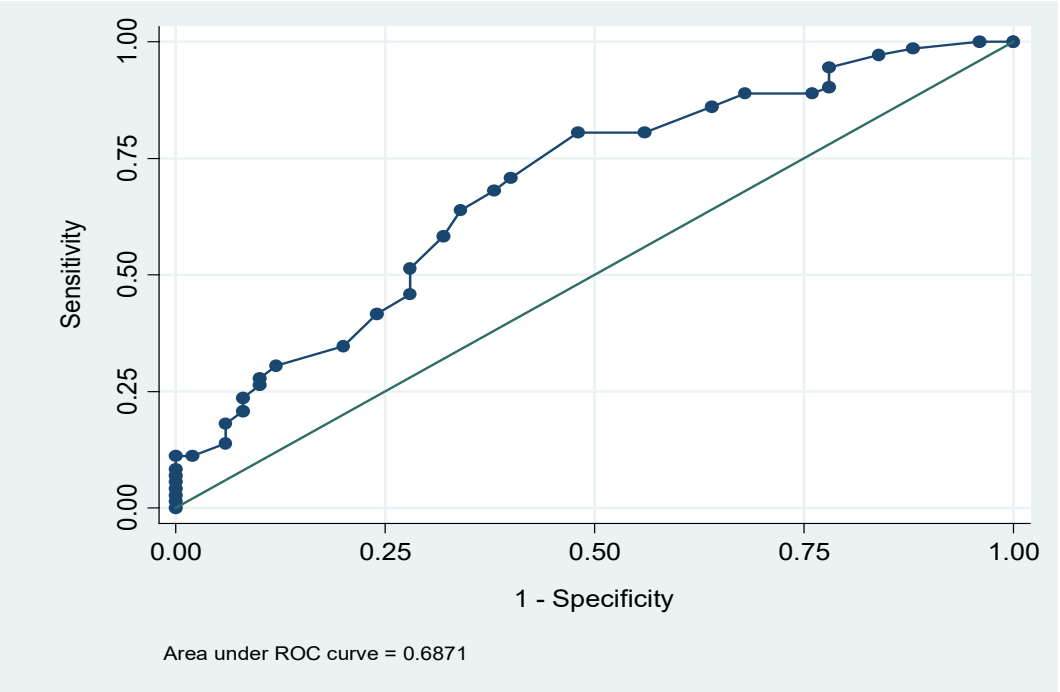

Figure 1. ROC curve representing AUC (area under the curve) for term neonates with sepsis. The area under the curve was 68.71(95% CI: 59.83 to 76.92) for MP.

cases, staphylococcus coagulase-negative in 1 point, and *staphylococcus aurous* in the last one. Figure 1 shows the ROC curve illustrating the sensitivity and specificity of MPV for the diagnosis of neonatal sepsis. The ROC curve area was 68.71 for MPV [95% Confidence Interval (CI), 59.83 to 76.92].

Diagnostic cut-off levels with the optimum sensitivity (80.56%) and specificity (52%) derived from the ROC curve were found to be MPV > 9.2 *fL*.

In a multiple regression model in which CRP served as continuous variables, each one *mg/L* increase in CRP was associated with a 20% increase in sepsis (OR: 1.20; 95% CI: 1.01–1.45, p=0.04). There was no significant association between MPV and disease status (OR: 1.56; 95% CI: 0.88–2.77, p=0.12). Table 2 presents the results of multivariate logistic regression.

Discussion

Neonatal sepsis is still one of the main concerns for public health, with high mortality rate13-15% (13,17). Increasing pro-inflammatory cytokines due to infection leads to rising CRP and stimulates megakaryocytes to increase platelets' number in response to inflammation. In this study, we assessed the feasibility of MPV during the time of admission to identify term and late preterm infants prone to neonatal sepsis. Infants with a mean gestational age of 38.17±1.92 were included in our study. Mean MPV at the time of admission was 9.808 ± 0.88 in comparison with 9.248 ± 0.75 in the control group. Although previous studies have evaluated the correlation between neonatal sepsis and MPV, another mean MPV is suggested by different studies. Catals study's mean of MPV in survival preterm infants was 10.34±0.2 compared to the non-survival group (10.6±1.2) (11). In the survey designed by Zhao *et al*, mean of MPV in preterm infants with invasive fungal diseases were (12.8 ± 1.1) in comparison with preterm infants with bacterial sepsis (12.7 ± 1.9) and with the control group (12.1 ± 1) (12). As the studies were designed for preterm infants, the mean MPV was higher than our study. In Tiwari's research, the mean of MPV in the septic group was 11.66 ± 1.36 on day one and 11.81 ± 1.30 on day 3 (18). In their study, gestational ages of neonates and percent of positive blood group have not been determined, and despite their treatment, a minor increase in MPV was visible. In the current study, mean age at the onset of sepsis was (7.81 ± 7.62). There were no significant changes in the PLT count between the sepsis group and the control group. All of the infants except two were presented with late-onset sepsis. Despite higher MPV

Table 2. The adjusted odds ratio for the relationship between neonatal sepsis and its predictors

Variables	Adjusted OR	Std. Err	95% CI	p-value
Weight(*g*)	0.99	0.0004	0.98-1.01	0.91
WBC(*/mm*^{3})	1.05	0.07	0.91-1.22	0.43
Plt	0.99	0.0004	0.98-1.01	0.91
CRP	1.20	0.11	1.01-1.45	0.04
MPV	1.56	0.45	0.88-2.77	0.12

White blood cells (WBC), platelet (Plt), mean platelet volume (MPV), C-reactive protein (CRP)

in our case group, unfortunately, the small number of early-onset sepsis cases in this study and few positive blood cultures preclude a meaningful comparison between these subgroups.

Moreover, in three different studies, Wang *et al* (2), Shaaban *et al* (19), Shalaby *et al* (20), it was demonstrated that MVP was higher in neonatal sepsis than in the control group. They suggested MVP as a marker for diagnosing early sepsis. Similarly, Pamudji *et al* claimed that MVP with a cut-off of 7.44 *fl* might have a diagnostic value for neonate sepsis with 80% sensitivity and 84.2% specificity (21).

However, despite the decent number of infants in each subgroup in Catal's study compared with this study, there were no significant changes in either platelet counts or MPV of infants between two subgroups and different infectious pathogens (bacterial and fungal infections) (11). These were inconsistent with Zhao's study that lower platelet counts with higher MPV were associated with invasive fungal disease (12). Previous studies focus on the role of MPV as a predictor marker of mortality and severity of sepsis (11, 12).

Catal study's role of MPV in diagnosing and following-up of sepsis in preterm infants has been studied. They considered an MPV value of 10.35 *fL* as the cut-off value in patients with a diagnosis of sepsis with a sensitivity of 97.8% and specificity of 78.7% (AUC = 0.949; p<0.001) and MPV value of 10.75 *fL* as the cut-off value in patients possibly resulting in death with a sensitivity of 95.2% and specificity of 84.9 % (AUC = 0.944; p<0.001) (11). Zhao *et al* found that platelet count (PC) and platelet crit (PCT) showed better accuracy than Platelet Distribution Width (PDW), an MPV for the diagnosis of invasive fungal disease in preterm infants (12). These are quite unlike Cekmez's study, which found no correlation between MPV and neonatal sepsis (22). As NICU admitted, infants were not enrolled in our study, thus mortality and morbidity due to sepsis were not detected since mortality was absent in our study groups.

In this study, the area under the ROC curve was 68.71 for MPV (95% CI), 59.83 to 76.92) and diagnostic cut-off levels with the optimum sensitivity (80.56%) and specificity (52%) derived from the ROC curve were found to be MPV > 9.2 *fL*. Regarding the multivariate regression model, there was no significant association between MPV and neonatal sepsis (OR: 1.56; 95% CI: 0.88–2.77, p=0.12). Simultaneously, each one *mg/L* increase in CRP was associated with a 20% increase in sepsis (OR: 1.20; 95% CI: 1.01–1.45, p=0.04).

It seems that the prematurity complications, such as respiratory distress syndrome, intraventricular hemorrhage, bronco pulmonary dysplasia, and necrotizing enterocolitis, may trigger inflammatory and oxidative processes that may lead to high MPV. The severity of these situations and neonatal sepsis may explain how MPV can be a predictor of mortality of preterm infants. Unlike the previous studies which have been conducted in preterm infants, Tajarernmuang *et al* conducted a systematic review and meta-analysis study to evaluate the association between MPV and mortality in critically ill adult patients. They concluded that regarding high heterogeneity between studies, MPV might be a valuable predictor of prognosis only in early sepsis. The coagulation system and the platelets are activated but not during late or severe sepsis. They also concluded that high MPV might not be used as a prognostic marker of mortality in critically ill adult patients (9). This is in concordance with the results of the present study that despite significant higher MPV levels in the septic group in comparison with the control group, the sensitivity and specificity of the MPV values were not at a required standard to

be used as a predictor tool for sepsis, therefore CRP is still a better marker between the other acute phase reactants and MPV may be utilized in combination with CRP but not separately.

There were some limitations to this study. First, the levels of IL-6 and other markers of inflammation were not analyzed. They involved the diagnosis and pathogenesis of sepsis and their correlations with MPV. Secondly, the efficacy of serial MPV measurements in follow-up sepsis was not considered due to a short course of antibiotic therapy in clinical septic infants and few positive blood cultures with non-invasive pathogens. Finally, further research is required to determine the association between MPV and the severity of sepsis with invasive pathogens and their mortality in term and late preterm infants.

Conclusion

Despite higher MPV during neonatal sepsis, the MPV values' sensitivity and specificity were inadequate to be used as diagnostic tests. CRP is still a better marker than the other acute phase reactants for early suspicion of neonatal sepsis. However, MPV may be used in combination with the other laboratory tests for identifying neonates with sepsis.

Acknowledgements

None

Conflict of Interest

The authors have no conflicts of interest relevant to this study.

References

1. Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, Haque K, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med 2011 Sep 29;365(13):1201–11.

2. Wang J, Wang Z, Zhang M, Lou Z, Deng J, Li Q. Diagnostic value of mean platelet volume for neonatal sepsis: A systematic review and meta-analysis. Medicine (Baltimore) 2020 Aug 7;99(32):e21649.

3. Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med 2013 Sep;14(7):686–93.

4. Lukacs SL, Schrag SJ. Clinical sepsis in neonates and young infants, United States, 1988-2006. J Pediatr 2012 Jun;160(6):960–5.

5. Civardi E, Tzialla C, Baldanti F, Strocchio L, Manzoni P, Stronati M. Viral outbreaks in neonatal intensive care units: what we do not know. Am J Infect Control 2013 Oct;41(10):854–6.

6. Smit PM, Pronk SM, Kaandorp JC, Weijer O, Lauw FN, Smits PHM, et al. RT-PCR detection of respiratory pathogens in newborn children admitted to a neonatal medium care unit. Pediatr Res 2013 Mar;73(3):355–61.

7. Storm W. Use of thrombocytopenia for the early identification of sepsis in critically ill newborns. Acta Paediatr Acad Sci Hung 1982;23(3):349–55.

8. Yazici S, Yazici M, Erer B, Erer B, Calik Y, Ozhan H, et al. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. Platelets 2010;21(2):122–5.

9. 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.

10. O'Connor TA, Ringer KM, Gaddis ML. Mean platelet volume during coagulase-negative staphylococcal sepsis in neonates. Am J Clin Pathol 1993 Jan;99(1):69–71.

11. Tayman C, Tonbul A, Akca H, Bilici M. Mean platelet volume (MPV) may simply predict the severity of sepsis in preterm infants. Clin Lab 2014;1.

12. Zhao D, Qiu G, Luo Z, Zhang Y. Platelet parameters and (1, 3)-β-D-glucan as a diagnostic and prognostic marker of invasive fungal disease in preterm infants. PLoS One 2015;10(4):e0123907.

13. Oncel MY, Ozdemir R, Yurttutan S, Canpolat FE, Erdeve O, Oguz SS, et al. Mean platelet volume in neonatal sepsis. J Clin Lab Anal 2012;26(6):493–6.

14. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit care Med 2005 Jan;6(1):2–8.

15. Rossi P, Botgros R, Tibby S. Report on the expert meeting on neonatal and paediatric sepsis. Eur Med Agency [en línea][consultado el 04/07/2018] Dispon en http//www. ema. eur eu/docs/en_GB/document_library/Report/2010/12/WC500100199 pdf. 2010.

16. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr 1979 Jul;95(1):89–98.

17. Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and late infections in newborns: where do we stand? A review. Pediatr Neonatol 2016 Aug;57(4):265–73.

18. Tiwari R, Mahtabuddin AQR, Sharma RC. Study of mean platelet volume as predictive index of neonatal sepsis. Int J Biomed Res 2017;8(04):220–3.

19. Shaaban HA, Safwat N. Mean platelet volume in preterm: a predictor of early onset neonatal sepsis. J Matern Neonatal Med 2020 Jan;33(2):206–11.

20. Shalaby MM, Sobeih AA, Abdulghany WE, Behiry EG, Ismail YM, Abd-El-Aziz MA. Mean platelet volume and serum uric acid in neonatal sepsis: A case-control study. Ann Med Surg 2017 Jun 8;20:97–102.

21. Pamudji KM, Kardana IM. Diagnostic value of mean platelet volume in neonatal sepsis. Paediatr Indones 2019 Nov 8;59(6):289–93.

22. Cekmez F, Tanju IA, Canpolat FE, Aydinoz S, Aydemir G, Karademir F, et al. Mean platelet volume in very preterm infants: a predictor of morbidities. Eur Rev Med Pharmacol Sci 2013;17(1):134–7.