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Original Article

Mean platelet volume and immature platelet fraction as predictors of early onset neonatal sepsis risk in neonates of 28-36 weeks gestational age

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Abstract

Background Early onset neonatal sepsis is a potential life-threatening problem for preterm infant. Diagnosing early onset neonatal sepsis is challenging. Difficulties in establishing diagnosis might cause delay definitive treatment.

Objective To analyze for potential associations between early onset neonatal sepsis (EONS) risk and mean platelet volume (MPV) as well as immature platelet fraction (IPF) in neonates of 28-36 weeks gestational age.

Methods A prospective cohort study was conducted at Dr. Hasan Sadikin General Hospital, Bandung, West Java. Mean platelet volume (MPV) and IPF were evaluated in the first ≤6 hours of life and during the 48-72 hours after the first examination. This examination was followed by observation for sepsis development. Double logistic regression analysis was used.

Results Of 115 subjects, 45 preterm infants (39.1%) developed early onset neonatal sepsis. The increase in both mean MPV and mean IPF were significantly different (P<0.05). Double logistic regression analysis revealed that an increase in mean MPV (ORadj=6.14; 95%CI 1.99 to 18.96; P=0.002) and mean IPF (ORadj=6.56; 95%CI 2.64 to 16.34; P<0.001) were significantly associated with increased risk of sepsis.

Conclusion The MPV and IPF increase are associated with greater incidence of EONS in preterm infants. **[Paediatr Indones. 2022;62:265-73 DOI: 10.14238/pi62.4.2022.265-73]**.

Keywords: *neonatal sepsis; preterm infant; mean platelet volume; immature platelet fraction*

In 2017, an estimated 2.5 million neonatal deaths occurred worldwide, and around 7000 neonates/day mostly died within first week of birth.[1] A reported 453 sepsis episodes affected 394 infants in Asia, with a 10.4% mortality rate.[2] *The Maternal Perinatal Audit* report at Dr. Hasan Sadikin General Hospital, Bandung, West Java, showed that sepsis contributed as the cause of death in 25 preterm infants among a total of 110 preterm infant deaths during January to May 2019.[3]

Diagnosing early onset neonatal sepsis itself is challenging since there are no specific clinical signs nor laboratory tests.[4] Establishing a diagnosis may be delayed by variations in clinical presentation. While positive blood culture is the gold standard of establishing a neonatal sepsis diagnosis,[5] cultures take time, leading to delayed definitive treatment. However, sepsis could still be diagnosed in neonates with negative culture results.[6]

Sepsis is closely associated with thrombocytopenia in neonates due to decreased megakaryopoiesis

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to regulate platelet consumption in blood clot formation. Increased platelet consumption activity in the endothelium and antimicrobial activity causes thrombocytopenia in sepsis. Overconsumption of platelets causing thrombocytopenia is called consumptive coagulopathy.[2] To fulfill this platelet need, bone marrow is stimulated to produce platelets, thus causing immature platelets to be found in the circulation; immature platelets are larger than mature platelets. Mean platelet volume (MPV) reveals the mean volume of platelets in the circulation. In thrombocytopenia, normal MPV value indicates no increase in platelet production. An increase of MPV during thrombocytopenia is a sign of increased destruction or increased platelet consumption. As an adaptation mechanism, the body compensates by forming new platelets. Large platelets are evidence that the bone marrow has been stimulated to produce more immature platelets in response to increased platelet consumption.[7] A study showed that MPV could be used as a simple, economical, and specific predictor for neonatal sepsis.[5] Moreover, another study found that umbilical cord and third day MPV could be examined as a substitute marker to predict early onset neonatal sepsis, and MPV was considered to be associated with mortality of preterm infants.[4]

The percentage of reticulated platelet (RP) is another useful indicator to determine the platelet production rate by bone marrow. A reticulated platelet is a newly-formed platelet characterized by higher ribonucleic acid (RNA) content compared to older platelets. This RP percentage is assessed as the immature platelet fraction (IPF).[7] Since the IPF directly detects immature platelets, it is a more accurate measure of platelet production than MPV. If the number of platelets is severely low, the laboratory machine analysis would not accurately measure the MPV value, but it would be able to measure the IPF.[8]

There are no known studies regarding the relationship between changes in MPV and IPF with the risk of early onset neonatal sepsis in neonates with gestational age from 28-36 weeks in Indonesia. However, there are still limited studies about association between immature platelet fraction with EONS, thus, a study regarding this issue, i.e., whether there is an association between increased MPV and IPF with EONS in infants with 28-36 weeks of gestational age, is needed. We aimed to assess for associations between increased MPV and IPF with EONS in serial examinations. These two parameters were selected as they can be measured in regular hematology exams, with MPV value obtained from the 22- and 35-parameter exams and IPF obtained from only the 35-parameter exam.[27]

Methods

This prospective cohort study was performed in neonates of 28-36 weeks gestational age and admitted to the Neonatal Ward, Dr. Hasan Sadikin General Hospital, Bandung, West Java, from October to December 2019. Subjects were evaluated for maternal risk factors, as well as physical and laboratory examinations. Subjects were selected through consecutive sampling based on order of admission to our research hospital until the minimum required sample size was fulfilled.

The minimum sample size was 100. The minimum sample size was determined by rule of thumb:

$$n = \frac{k.\nu}{p}$$

Notes:
k: constant set, which was 10
ν: number of independent variables used, which was 4
p: neonatal sepsis prevalence, which was 40% (0.4)

Infection risk factors included premature rupture of membranes (PROM) >18 hours, maternal urinary tract infection (UTI), preterm birth, 5-minute APGAR score <7, and low birth weight. Evaluated clinical signs were thermolability, skin lesions, hypotonia, lethargy, as well as gastrointestinal, cardiovascular, and respiratory problems.

Laboratory examinations included the 35-parameter hematology examination (including hemoglobin, hematocrit, leukocyte, platelet, differential count, I/T ratio, MPV, and IPF count), peripheral blood smear, CRP, random blood sugar, and blood culture. Blood specimens (3-3.5 mL) were obtained during the first ≤6 hours after birth and 48-72 hours after the first laboratory examination. since hemolytic anemia might alter accuracy of the MPV examination, peripheral blood smears were done to detect presence of hemolytic anemia. Patients with hemolytic anemia were excluded, as were patients with severe thrombocytopenia (<40,000/mm^3), since the *Sysmex*™ machine could not

approximate MPV value well in such patients.

Subjects were treated according to standard protocols at Dr. Hasan Sadikin General Hospital. Other subjects' characteristics were noted, including data from history-taking and maternal medical records, namely, name, age, address, and maternal risk factors related to infection. Physical examination included body length, birth weight, vital signs, skin color, respiration, abdomen, liver and muscle tone examination, APGAR score, and other routine examinations. Laboratory examinations were performed ≤6 hours after birth and the second laboratory examination was done 48 hours after the first laboratory examination. Subjects underwent sepsis evaluation according to the EMA criteria through history-taking, physical examination, and laboratory examination. A diagnosis of sepsis was established if the subject fulfilled two clinical criteria and two laboratory criteria, with or without positive culture results.[11] Incidence of EONS was recorded on an observation form. Subjects were observed for 72 hours or until sepsis resided.

Double logistic regression analysis was conducted in three phases: univariate, bivariate, and multivariate. The delta of MPV and IPF were further analyzed by receiver operating characteristic (ROC) curve to determine the cut-off values to be applied as EONS predictors. Results with P values <0.05 were considered to be statistically significant. An informed consental was obtained from parents of the newborns before participation in the study. This study was approved by the Health Ethics Commission of Dr. Hasan Sadikin Hospital, Bandung.

Results

Table 1 describes the characteristics of 115 subjects, of whom 45 (39.1%) developed early onset neonatal sepsis. Males (59; 51.3%) slightly outnumbered females. The majority of subjects had birth weight of 1,500-2,000 grams (43.5%), 5-minute APGAR scores of >7 (57.4%). They had similar gestational age composition of 28-32 weeks (49.65%) and 33-36 weeks (50.4%), as well as the following maternal risk factors: PROM (20%), UTI (12.2%).

Table 2 shows the analysis of subjects' characteristics and EONS status. Lower birth weight (P=0.034) and lower 5-minute APGAR score (P=0.024) had significant associations with EONS. EONS was noted in 54.8% of the 1,000 - <1,500 g birth weight group, 30% of the 1,500 - <2,000 g group, and 30.4% of the >2000 g group. With regards to 5-minute APGAR score, 51% of the <7 group had EONS, while 30.0% of the of >7 group had EONS.

Table 3 shows the analysis of MPV, IPF, and EONS at <6 hours of age and at 48-72 hours of age. At <6 hours of age, Mann-Whitney test revealed that MPV and IPF were not significantly different between the EONS and non-EONS groups (P>0.05). At 48-72 hours of age, MPV was not significantly different between the EONS groups (P=0.898), but IPF was (P<0.001). Nevertheless, the increase in both mean MPV and mean IPF were significantly different (P<0.05). The median MPV increase was 0 (range -6.3 - 2) fL in the EONS group, and 0.3 (range -7.0 - 1.8) fL in the non-EONS group. The median increase in IPF was 0.8 (range -10.34 - 17.10) % in the EONS group, and 0 (range -5.6 - 3.0) % in the non-EONS group.

The increases in MPV and IPF were further analyzed using ROC curve analysis (**Figure 1**). The cut-off value of change in MPV to be applied as a predictor of EONS was ≤0.5 fL, with 86.67% sensitivity and 34.29% specificity. For IPF increase, the cut-off value was >0.4%, with 65.91% sensitivity and 68.57% specificity. The cut-off points for MPV and IPF increase were analyzed by Chi-square test to determine a

Table 1. Subjects' characteristics

Characteristics	(N=115)
Infant gender, n (%)	
Male	59 (51.3)
Female	56 (48.7)
Birth weight, n (%)	
1,000 - <1,500 g	42 (36.5)
1,500 - 2,000 g	50 (43.5)
> 2,000 g	23 (20)
Median (range), g	1,590 (1,000-2,800)
Five-minute APGAR score, n (%)	
<7	49 (42.6)
>7	66 (57.4)
Median (range)	8 (1-10)
Maternal risk factors, n (%)	
PROM >18 hours	23 (20.0)
UTI	14 (12.2)
Gestational age	
28-32 weeks	57 (49.6)
33-36 weeks	58 (50.4)
EONS	45 (39.1)

Table 2. Analysis of subjects' characteristics and EONS

Characteristics	EONS		P value*
	Yes (n=45)	No (n=70)	
Infant gender, n (%)			0.238
Male	20 (33.9)	39 (66.1)	
Female	25 (44.6)	31 (55.4)	
Birth weight, n (%)			0.034
1,000 - <1,500 g	23 (54.8)	19 (45.2)	
1,500 - 2,000 g	15 (30)	35 (70)	
> 2,000 g	7 (30.4)	16 (59.6)	
Five-minute APGAR score, n (%)			0.024
<7	25 (51.0)	24 (49.0)	
>7	20 (30.3)	46 (59.7)	
Maternal risk factor, n (%)			0.339
PROM >18 hours			
Yes	11 (47.8)	12 (52.2)	
No	34 (37)	58 (63)	
UTI			
Yes	8 (57.1)	6 (42.9)	
No	37 (36.6)	64 (63.4)	
Gestational age			0.141
28-32 weeks	27 (47.4)	30 (52.6)	
33-36 weeks	18 (31.9)	40 (68.1)	

*Chi-square test

Table 3. Comparison of MPV and IPF between the EONS and non-EONS groups

Variables	EONS		P value*
	Yes (n=44)	No (n=70)	
Age < 6 hours			
MPV, fL			0.060
Mean (SD)	10.4 (0.88)	10.15 (1.15)	
Range	8.4-12.4	8.4-16.9	
IPF, %			0.059
Mean (SD)	4.57 (2.48)	3.73 (1.62)	
Range	1.7-13.1	1.7-9.8	
Age 48-72 hours			
MPV, fL			0.898
Mean (SD)	10.14 (1.14)	10.26 (0.73)	
Range	5.4-12.2	8.9-11.7	
IPF, %			<0.001
Mean (SD)	5.60 (2.99)	3.79 (1.22)	
Range	2.2-19.8	1.9-6.4	
Delta(Δ)			0.042
MPV, fL	-0.18 (1.18)	0.11 (1.14)	
Mean (SD)	-6.3 - 2.0	-7.0 - 1.8	
Range			<0.001
IPF, %			
Mean (SD)	1.34 (3.82)	0.06 (1.29)	
Range	-10.34 -17.10	-5.6 - 3.0	

*Mann-Whitney test

possible association between MPV and IPF increase with EONS.

Chi-square test revealed that infants with MPV increase of ≤0.5fL had a 2.26 times higher risk of EONS than increased MPV of >0.5fL. In addition, an increase of IPF >0.4% put preterm infants at

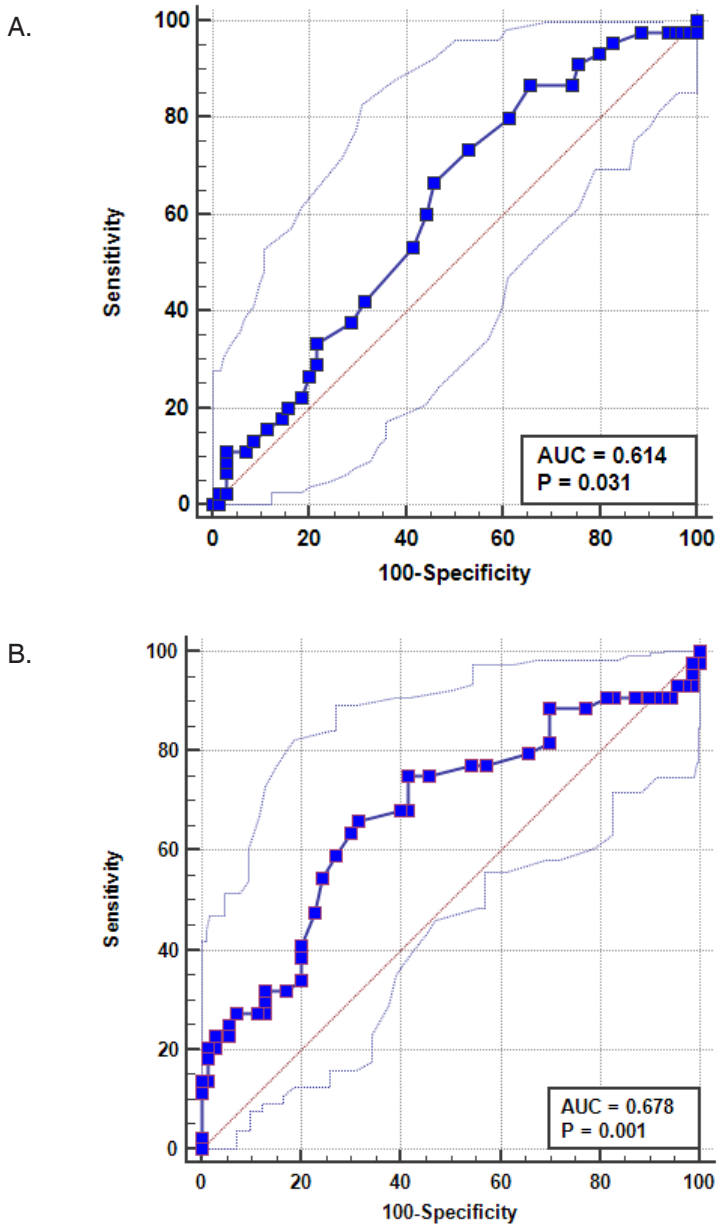

Figure 1. ROC curve analyses of change in MPV (A) and IPF (B) to determine cut-off points to predict EONS . Upper blue line shows the sensitivity analysis, lower blue line shows the specificity analysis, and the bold blue line with square shows the cut-off value.

2.39 times higher risk of EONS than increased IPF of <0.4% (**Table 4**).

To identify factors which were simultaneously associated with EONS, multivariate analysis with double logistic regression was conducted on variables that were significant by bivariate analysis (P<0.10). These variables, apart from increased MPV and IPF, were birth weight, gestational age, and 5-minute APGAR score. The three variables other than increase in MPV and IPF were not statistically significant (**Table 5**). The double logistic regression analysis revealed that IPF increase and MPV increase had significant associations with EONS in the final model. For IPF increase of >0.4%, the risk of preterm infant to contract EONS was 6.56 times higher compared to IPF increase of ≤0.4%. For MPV increase of ≤0.5 fL,

Table 4. Analysis of Delta MPV and IPF and EONS

Variables	EONS		RR (95% CI)	P value*
	Yes (n=44)	No (n=70)		
Delta MPV, n (%)			2.26 (1.06 to 4.80)	0.015
≤0.5 fL	38 (45.2)	46 (54.8)		
>0.5 fL	6 (20.0)	24 (80.0)		
Delta IPF, n (%)			2.39 (1.44 to 3.95)	<0.001
>0.4%	29 (56.9)	22 (43.1)		
<0.4%	15 (23.8)	48 (76.2)		

*Chi-square test; RR (95%CI): relative risk and 95% confidence interval

Table 5. Double logistic regression analysis of potential simultaneously-associated factors with EONS

Variables	Coeff (B)	SE (B)	ORadj (95% CI)	P value
Initial model				
Birth weight[a]				
1,000-<1,500 g	0.487	0.738	1.70 (0.40 to 7.19)	0.509
1,500 - <2,000 g	-0.190	0.646	0.80 (0.22 to 2.84)	0.769
Gestational age[b]				
28-32 weeks	0.155	0.520	1.18 (0.43 to 3.25)	0.825
IPF increase (>0.4%)	1.659	0.483	5.16 (2.03 to 13.08)	0.001
MPV increase (≤ 0.5fL)	1.846	0.583	6.18 (1.99 to 19.22)	0.002
5' APGAR score (≤ 7)	0.512	0.477	1.79 (0.71 to 4.51)	0.281
Final model				
IPF increase (>0.4%)	1.882	0.465	6.56 (2.64 to 16.34)	<0.001
MPV increase (≤ 0.5fL)	1.815	0.575	6.14 (1.99 to 18.96)	0.002

[a]Reference: ≥ 2,000 g; [b]Reference: 33-36 weeks; ORadj (95%CI): Adjusted odds ratio and 95% confidence interval.
Model accuracy=76.3%; R2 (Nagelkerke) = 26.9%

the risk of preterm infant to contract EONS was 6.14 times higher than MPV increase of >0.5 fL.

Discussion

In our study, 39.1% neonates born at 28-36 weeks gestational age had EONS. However, incidence rates of EONS in preterm infants have differed. About 50-60% of neonatal sepsis cases in India occurred in preterm and LBW infants,[9] while Cohen-Wolkowiez *et al.*[10] showed that only 0.6% of late preterm infants fulfilled the criteria of EONS with positive culture results. These differences may have been due to different diagnostic standards, some of which included a positive culture result, though a sepsis diagnosis could be established even without a positive culture result.[11]

The adaptive immune response takes about 5-7 days to develop. The infant immune response to infection varies according to the innate immune response, which consists of skin barrier, digestive and respiratory tract mucosa, sentinel immune cells (macrophages, endothelium, epithelium, and dendritic cells), antigen presenting cells (monocytes, macrophages, dendritic cells), as well as immune peptides and proteins (cytokines, chemokines, and acute phase reactants). The high incidence of EONS in preterm infants might be due to underdeveloped and under-functioning innate immune responses.[12]

Factors associated with higher EONS incidence were lower birth weight (P=0.034) and lower 5-minute APGAR score (P=0.024). Similarly, a study reported that birth weight had an association with EONS incidence in late preterm infants.[10] Another study showed that low birth weight increased the risk of EONS, especially in infants <1,000 g, 26% of whom had EONS.[13] Low birth weight affects infant immune systems. Preterm infants have less than optimal immune systems, both innate or adaptive, compared to normal birth weight infants. Neutrophil counts in LBW infants are generally lower than that of normal

birth weight infants, leading to infections that develop rapidly into severe sepsis and further neutropenia. The ability of neutrophils to migrate from the endothelium to the focus of infection was significantly reduced in LBW Infants. In addition, the complement system in LBW infants has 10% or less maternal complement content, such as C3 and C3b, which help to eliminate pathogenic organisms. In the adaptive immune system, severely reduced Th1 and Th2 lymphocytes cause delayed immune response, weakened cytotoxic and cytolytic ability, and diminished production of related cytokines. All these aspects make preterm LBW infants more susceptible to infection risk.[14]

The APGAR score was also associated with EONS incidence on neonates. Similarly, a study stated that lower APGAR score was associated with higher EONS risk.[15] Another study also showed that infants with APGAR score of <7 had a 14-fold higher risk of EONS.[16] In general, APGAR score is related to fetal stress during the intrapartum period. Hypoxic-ischemic condition during the perinatal period could be due to a number of issues, but infection is one of the causes of low APGAR score.[16]

The maternal risk factors of premature rupture of membranes (PROM) at >18 hours and UTIs were not significantly associated with EONS. Further study is recommended to determine if these findings were due to mothers receiving antibiotic treatment before labor. In contrast, a study showed that infants born to mothers with PROM history had a 7-fold higher risk of EONS.[17] A study also found an association between PROM of >18 hours and incidence of EONS in newborns.[18] Bacterial colonization of the vagina and urinary tract might result in asymptomatic transmission to the infant. One of the most frequent causes of infection was group beta-hemolytic *Streptococcu*s (GBS). Further infection could damage the chorioamnionic wall, increasing the infection risk in both mother and baby. Fetal exposure to pathogen colonization could increase the risk of EONS.[19] Another study reported that maternal UTI was a risk factor for EONS. Bacteria colonize around the vaginal tract, hence, during labor, the baby would have direct contact with bacteria.[19]

Russell *et al.*[13] found that infants of earlier gestational age had higher risk of EONS; preterm infants had a 3.36-fold higher risk of sepsis compared to full term infants. The higher risk of sepsis in preterm infants may have been due to their immature immune systems and organs. Hence, health care practitioners should take precautions to prevent infection, especially those related to health care practitioners, i.e., nosocomial infection during medical procedure.[20]

There was no significant difference in mean MPV results at <6 hours or at 48-72 hours of age between the EONS and non-EONS groups (P>0.05), similar to a previous study.[21] However, Shaaban *et al.*[4] noted a significant increase in MPV between the sepsis and non-sepsis groups on first and third days after birth. This finding could have been due to an inaccurate MPV value in neonates with severe thrombocytopenia. Since MPV refers to mean platelet size in circulation, it may have been small to undetectable.[22] An absence of MPV increase could also occur if MPV was not increased in localized infection or sepsis had been diagnosed with a negative culture result.[4]

There was no significant difference in IPF between the EONS and non-EONS groups at <6 hours of age, but there was at 48-72 hours of age. Cremer found that low platelet count on the first day of birth was not compensated well with an increase in platelet formation. They explained that infection in neonates might cause decreased platelet count, however, with normal IPF value; hence, the presence of thrombocytopenia would occur without an increase in IPF. Though thrombopoietin concentration had increased, it was still not enough to maintain normal platelet count. Hence, this stimulation process to increase thrombopoiesis should be monitored by evaluating IPF to guide decision-making about thrombocyte transfusions in infants with severe thrombocytopenia.[23]

There were significant differences between delta MPV (ΔMPV) and delta IPF (ΔIPF) at <6 hours and 48-72 hours of age in infants with EONS compared to those without EONS. Shaaban *et al.*[4] stated similar thing, i.e., there was a significant difference in MPV value between sepsis and non-sepsis group. This increase in MPV value is indicative of damage in the endothelium and its repair through platelet activation. During the acute phase of sepsis, platelet consumption would increase and MPV value would also rapidly increase along with the acute infection.[24] Increased MPV indicates invasive, systemic, and severe infection. Thus, MPV monitoring could be useful to determine the prognosis on patients with septic shock.[4]

We obtained MPV and IPF increase cut-offs by ROC curve to predict EONS. The cut-off value for

MPV increase was ≤0.5 fL, with 86.67% sensitivity and 34.29% specificity. Shalaby *et al*.[21] reported a cut-off of 0.629 fL, with 71% sensitivity and 63% specificity. In addition, a study also found that MPV value of >10.8 fL had sensitivity of 79.70% and specificity of 33.90% for detecting neonatal sepsis.[25] For IPF increase, the cut-off value was >0.4%, with 64.44% sensitivity and 70.0% specificity. To our knowledge, no other studies have utilized the IPF parameter for EONS either in infants in general, or preterm infants.

The MPV increase of ≤ 0.5 fL raised infant risk of EONS by 2.26 times compared to MPV increase of >0.5fL. IPF increase of >0.4% raised the EONS risk by 2.39 times compared to IPF increase of <0.4%. Double logistic regression analysis of the final model revealed that the significant variables associated with EONS were IPF and MPV increase. The IPF increase of >0.4% raised EONS risk by 6.56 times compared to IPF increase of ≤0.4%; and MPV increase of ≤ 0.5 fL raised infant risk of EONS by 6.24 times compared to MPV increase of >0.5fL.

Theoretically, the increase of MPV and IPF occurred alongside the course of sepsis. Sepsis leads to peripheral platelet utilization, thus, the body must stimulate platelet production. Increased immature platelets causes circulating platelets to have varied sizes, hence, the increase in MPV value.[26] Clinically, several studies have lacked agreement on MPV value as one of the simple, inexpensive, and quick diagnostic parameters for neonatal sepsis.[27]

Increased stimulus of platelets with immature thrombocytes of higher ribonucleic acid content leads to increased IPF value.[7] However, to date, no guidelines or studies have shown an association between the increase of IPF with increased EONS incidence in full term or preterm infants. The limitation of this study was that we did not assess all potentially contributing variables on EONS incidence.

In conclusion, the increase in MPV and increase in IPF have significant associations with EONS in neonates born at 28-36 weeks gestational age.[4] Further studies about whether platelet count affected MPV or IPF value should be conducted to determine the effect of MPV and IPF on late onset neonatal sepsis.

Conflicts of interest

None declared.

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