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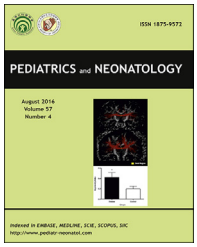

Original Article

# Platelet parameters and the association with morbidity and mortality in Preterm Infants

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**Abstract** *Background:* There is growing recognition of the role of platelets in inflammation and immune responses, and platelets have been associated with various cardiovascular diseases. It is also known that neonatal morbidities are related to overall platelet activity, and platelet parameters may have the potential to predict morbidities and mortality in preterm infants. This study aimed to assess the initial platelet parameters and the association with major morbidities and mortality in preterm neonates.
*Methods:* We retrospectively reviewed data from very preterm neonates with a gestational age (GA) <32 weeks who were admitted between June 2020 and May 2021 for platelet parameters (counts, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (platelet counts x MPV/10000(%)) at birth. Major morbidities included early- onset sepsis (EOS) ≤3 days after birth, severe intraventricular hemorrhage (IVH) grade ≥3, and early or overall mortality.
*Results:* A total of 197 very preterm neonates were studied. Their mean (±SD) GA was 28.0 ± 2.4 weeks, birth weight was 990 ± 293 g, platelet counts were 245 ± 81 x1000/μL, MPV was 10.0 ± 0.7 fl, PDW was 11.0 ± 1.6 fl, and plateletcrit was 0.24 ± 0.08%. MPV had a weak negative correlation with both GA ($r = -0.234$, $p = 0.001$) and BW ($r = -0.343$, $p < 0.001$). A lower plateletcrit was associated with EOS (0.14 (0.04–0.22) % vs. 0.23 (0.19–0.30) %, $p = 0.027$), severe IVH ≤7 days after birth (0.18 (0.14–0.27) % vs. 0.23 (0.20–0.30) %, $p = 0.022$), and early and overall mortality (0.15 (0.20–0.30) % vs. 0.23 (0.20–0.30) %, $p = 0.049$; 0.20 ± 0.09 % vs. 0.25 ± 0.07 %, $p = 0.008$).
*Conclusion:* A lower plateletcrit within 24 hours of birth was associated with EOS, severe IVH ≤7 days after birth, and first-week and overall mortality in very preterm neonates.

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## 1. Introduction

Apart from the critical function of platelets in hemostasis and thrombosis, there is growing recognition of their roles in inflammation and immune responses.[1] Under conditions of increased platelet consumption, numerous enlarged platelets are released from megakaryocytes in response to acute platelet needs.[2] The activation of platelets releases a wide array of cytokines with both pro-inflammatory and anti-inflammatory effects.[3,4] Platelet count and function are both essential for hemostasis and inflammation control.

Platelet count, mean platelet volume (MPV), and platelet distribution width (PDW) are common platelet parameters provided by commercial hematological analyzers. Plateletcrit, also known as the platelet mass index, is an index that indicates the percentage of platelet volume in whole blood and is positively correlated with the platelet count and size. As the number of younger and larger platelets increases in response to inflammation and oxidative stress, a higher MPV and plateletcrit indicate more platelets that are active and could serve as markers for platelet function.

Platelet parameters have been widely investigated in adulthood cardiovascular diseases such as sepsis,[5] ischemic and hemorrhagic stroke,[6] chronic obstructive pulmonary disease,[7] and acute myocardial infarction.[8] Several expanding studies have also investigated the role of platelet parameters in the diagnosis of pediatric diseases.[9–11] Given that platelet function is related to maturity and neonatal morbidities usually involve platelet function, a few studies have discussed the correlation between platelet parameters and morbidities in preterm neonates. Studies on respiratory distress syndrome (RDS),[12,13] intraventricular hemorrhage (IVH),[13–15] patent ductus arteriosus (PDA),[16,17] necrotizing enterocolitis (NEC),[13,14] retinopathy of prematurity (ROP),[14,18] sepsis,[19,20] and mortality[13] have yielded conflicting results. Therefore, we hypothesized that platelet parameters within the first day of life may reflect a neonate's inflammatory and thrombotic conditions at birth. We aimed to assess the initial platelet parameters of neonates with different gestational ages (GA) and birth weights (BW), and to explore the associations between platelet parameters and major morbidities in very preterm neonates.

## 2. Methods

### 2.1. Study design

This retrospective cohort study was conducted at the Chang Gung Memorial Hospital Linkou Branch, and was approved by the institutional review board (No. 202200122B0). We included preterm neonates with GA <32 weeks who were admitted to our neonatal unit between June 2020 and May 2021. Neonates without complete platelet parameters (described below) on the first day of life were excluded.

### 2.2. Data collection

Blood samples were obtained from arterial punctures or central venous catheters within the first day of life (mostly <2 h postnatal age). Platelet parameters, including platelet count, MPV, and PDW, were measured using Sysmex XN-L Series automated hematology analyzers (Sysmex, Kobe, Japan). Plateletcrit was calculated using the following formula: *platelet count* × *MPV/10000 (%)*. Thrombocytosis and thrombocytopenia were defined as platelet counts of >450,000/μL and <150,000/μL, respectively. General data, including GA, BW, sex, mode of delivery, Apgar scores, and small for gestational age SGA (BW < 10th percentile), were recorded. Moreover, maternal histories, including preeclampsia, gestational diabetes mellitus, rupture of membrane >18 h, chorioamnionitis, antenatal magnesium sulfate, and steroid use, were collected. To obtain a clear definition, the cohort was screened only for severe forms of the respective morbidities.

The complications within the first week of life are early morbidities, which included RDS requiring artificial surfactant use, IVH of any grade or severe IVH (grade ≥3), and early mortality. Early onset sepsis (EOS) was defined as culture-proven bacteremia at <72 h.[21] Several morbidities later in life included PDA requiring pharmacological or surgical treatment, NEC requiring surgical intervention, IVH developed after the first week of life, oxygen need at 28 days after birth, postmenstrual age (PMA) of 36 weeks, severe ROP stage ≥3, and overall mortality before discharge.

### 2.3. Statistics

Statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, New York, USA). Correlations between demographics and platelet parameters were examined using Pearson's correlation test. For subgroup analyses by varied morbidities, continuous data were compared using Student's t-test, while categorical data were tested using Chi-square or Fisher's exact tests. Univariate and multivariate logistic regression analyses with backward elimination procedures were performed to determine the independent risk factors. Receiver operating characteristic (ROC) curve analysis was performed to determine the platelet parameter cutoffs for different morbidities. The statistical significance was set at $p < 0.05$.

## 3. Results

Among 200 preterm neonates with a GA <32 weeks who were admitted to our neonatal unit, three were excluded

for incomplete platelet parameters, and the rest 197 neonates were analyzed. The enrollment flowchart is shown in Fig. 1. Their mean (±SD) GA was 28.0 ± 2.4 weeks, BW was 990 ± 293 g and 64 (33%) neonates were SGA. The platelet parameters were as follows: platelet counts: 245 ± 81 × $10^3/\mu L$; MPV: 10.0 ± 0.7 fL; PDW: 11.0 ± 1.6 fL; and plateletcrit: 0.24 ± 0.08%. The demographic characteristics, maternal history, and morbidities are shown in Table 1.

The correlations between GA or BW and platelet parameters are shown in Fig. 2. For our very preterm neonates, MPV had a weak negative correlation with both GA ($r = -0.234$, $p = 0.001$) and BW ($r = -0.343$, $p < 0.001$). The correlation remained significant when SGA neonates were excluded. PDW also had a weak negative correlation with BW ($r = -0.217$, $p = 0.002$). However, platelet counts were not correlated with either GA or BW.

Neonates with RDS requiring surfactant had significantly lower platelet count and plateletcrit and a higher MPV; however, these parameters were not significant in multivariate regression after adjustment for GA and perinatal factors. Neonates with EOS had significantly lower platelet counts and plateletcrit (median (IRQ) 148 (39–216) vs. 237 (193–302) x $10^3/\mu L$, $p = 0.026$; 0.14 (0.04–0.22) % vs. 0.23 (0.19–0.30) %, $p = 0.027$, respectively). Plateletcrit remained significant in differentiating the EOS group (OR 0.787, 95% CI 0.659–0.941, $p = 0.009$) after adjustment with platelet counts and perinatal factors (Supplementary Table 1). No difference in platelet parameters was seen in neonates with IVH, but neonates who developed severe IVH ≤7 days after birth had lower platelet counts and plateletcrit (174 (136–272) vs. 237 (199–302) x $10^3/\mu L$, $p = 0.025$; 0.18 (0.14–0.27) % vs. 0.23 (0.20–0.30) %, $p = 0.022$, respectively) (Supplementary Table 2). In multivariate regression, lower GA (OR 0.369, 95% CI 0.190–0.716, $p = 0.003$), the lack of antenatal steroids (OR 0.165, 95% CI 0.031–0.893, $p = 0.036$) and lower plateletcrit (OR 0.870, 95% CI 0.778–0.972, $p = 0.014$) were independent risk factors for severe IVH. Moreover, we found that eight neonates with early mortality had significantly lower platelet counts and plateletcrit (164 (109–256) vs. 237 (194–302) x $10^3/\mu L$, = 0.035; 0.15 (0.20–0.30) % vs. 0.23 (0.20–0.30) %, = 0.049, respectively) (Supplementary Table 3). Plateletcrit (OR 0.876, 95% CI 0.784–0.980, $p = 0.020$) remained independent risk factors for early mortality after adjusting for RDS, EOS, IVH, and perinatal factors. A summary of the association between platelet parameters and major morbidities is presented in Table 2.

Initial platelet counts and plateletcrit were higher in neonates with NEC requiring surgical intervention (331 × $10^3/\mu L$ vs. 235 × $10^3/\mu L$, $p = 0.001$; 0.33% vs. 0.23%, $p = 0.001$), but the ratio of thrombocytosis was similar. In univariate analysis, lower GA, BW, Apgar score, platelet counts, and plateletcrit were associated with overall mortality (). In multivariate analysis, lower GA (OR 0.557, 95% CI 0.424–0.730, $p < 0.001$) and lower plateletcrit (OR 0.895, 95% CI 0.831–0.964, 0.003) were independent risk

**Table 1** The demographics and characteristics of studied preterm neonates.

| Demographics | N = 197 |
|---|---|
| GA (weeks) | 28.0 ± 2.4 |
| BW (g) | 990 ± 293 |
| Male | 96 (49%) |
| Cesarean section | 141 (72%) |
| SGA | 64 (33%) |
| Apgar Score (1 min) | 6 (5–8) |
| Apgar Score (5 min) | 8 (7–9) |
| Apgar Score <7 at 5 min | 30 (15%) |
| **Maternal history** | |
| Maternal preeclampsia | 34 (17%) |
| Gestational diabetes mellitus | 23 (12%) |
| Rupture of membrane >18 h | 64 (33%) |
| Chorioamnionitis | 18 (9%) |
| Antenatal magnesium sulfate | 173 (88%) |
| Antenatal steroid | 183 (93%) |
| **Platelet parameters** | |
| Platelet counts (x$10^3/\mu L$) | 245 ± 81 |
| MPV (fL) | 10.0 ± 0.7 |
| PDW (fL) | 11.0 ± 1.6 |
| Plateletcrit (%) | 0.24 ± 0.08 |
| **Major complications** | |
| RDS requiring surfactant | 92 (47%) |
| EOS ≤3 days | 4 (2%) |
| IVH ≤7 days | 25 (13%) |
| Severe IVH ≤7 days | 14 (7%) |
| Mortality ≤7 days | 8 (4%) |
| PDA requiring treatment | 84 (44%) |
| Surgical NEC | 9 (5%) |
| Oxygen demand on postnatal day 28 | 106 (60%) |
| Oxygen demand on PMA 36 weeks | 86 (50%) |
| Severe ROP | 33 (18%) |
| Overall mortality | 24 (12%) |

GA, gestational age; BW, birth weight; SGA, small for gestational age; MPV, mean platelet volume; PDW, platelet distribution width; RDS, respiratory distress syndrome; EOS, early-onset sepsis; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity.
Numbers are mean ± SD, n (%) or median (interquartile range).

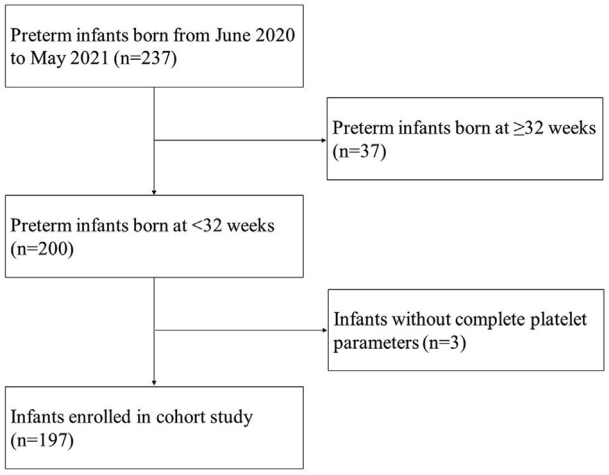


**Figure 1** Flow chart of study enrollment.

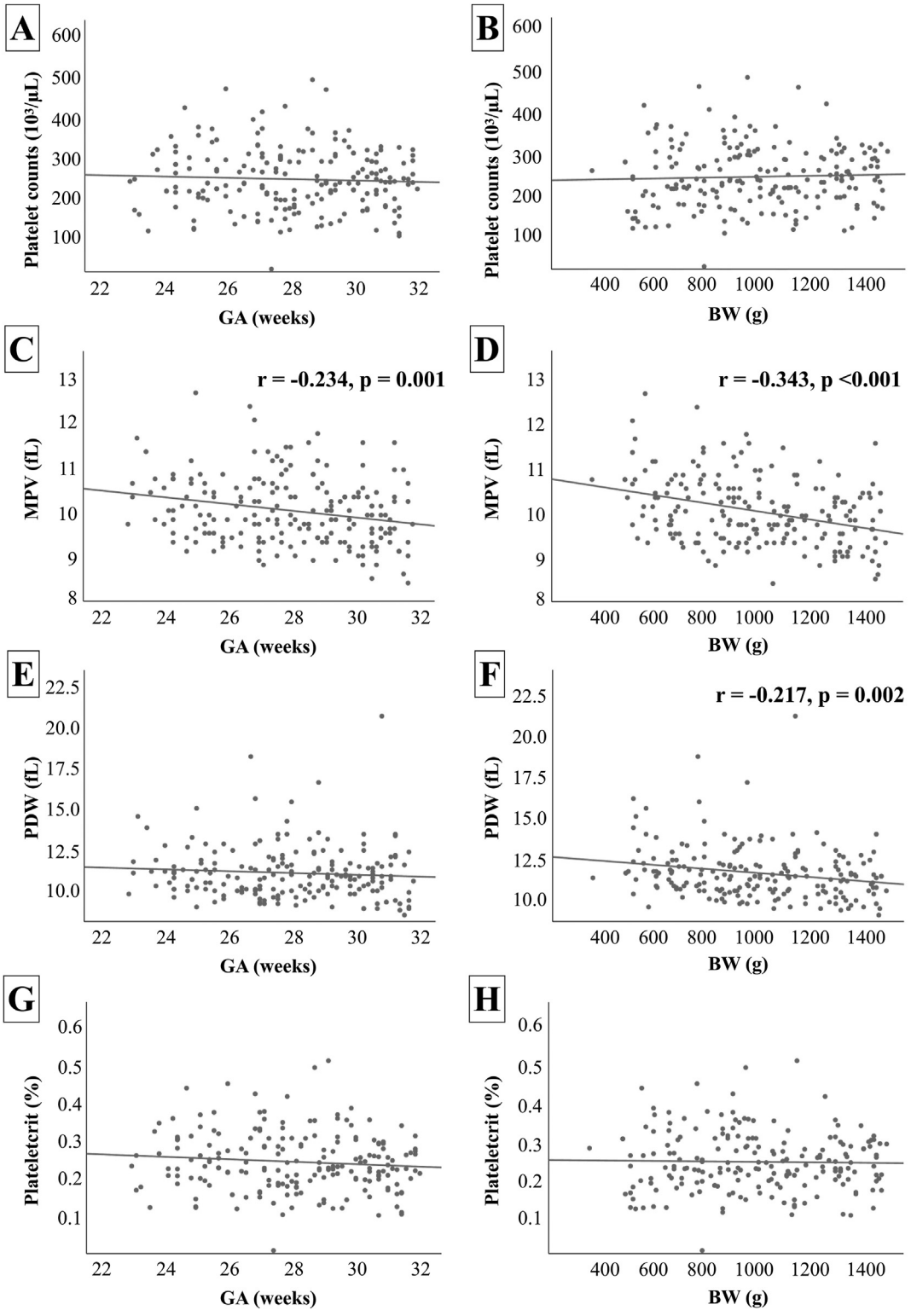


**Figure 2** Correlations between respective platelet parameters and GA or BW. Weak negative correlations were seen between MPV and GA ($r = -0.234$, $p = 0.001$) or BW ($r = -0.343$, $p < 0.001$), and between PDW and BW ($r = -0.217$, $p = 0.002$). GA, gestational age; BW, birth weight; MPV, mean platelet volume; PDW, platelet distribution width.

factors for overall mortality (Table 2). No significant differences in platelet parameters were observed in terms of PDA requiring treatment, oxygen demand on postnatal day 28, PMA of 36 weeks, and severe ROP.

Using ROC curves to determine the cutoff value of plateletcrit in predicting EOS, severe IVH $\leq$7 days after birth, and early and overall mortality, the cutoff values were 0.157%, 0.186%, 0.177%, and 0.186%, respectively (Fig. 3).

**Table 2** Summary of the associations between platelet parameters and major morbidities in very preterm neonates.

| Major morbidities | Platelet counts ($\times 10^3/\mu L$) | | MPV (fL) | | PDW (fL) | | Plateletcrit (%) | |
|---|---|---|---|---|---|---|---|---|
| | UA | MVA | UA | MVA | UA | MVA | UA | MVA |
| RDS requiring surfactant | ○ | – | ○ | – | – | – | ○ | – |
| EOS ≤3 days | ○ | – | – | – | – | – | ○ | ● |
| IVH ≤7 days | ○ | – | – | – | – | – | ○ | – |
| Severe IVH ≤7 days | ○ | – | – | – | – | – | ○ | ● |
| Mortality ≤7 days | ○ | – | – | – | – | – | ○ | ● |
| PDA requiring treatment | – | – | – | – | – | – | – | – |
| Surgical NEC | ○ | ● | – | – | – | – | ○ | – |
| Oxygen demand on postnatal day 28 | – | – | ○ | – | – | – | – | – |
| Oxygen demand on PMA 36 weeks | – | – | ○ | – | – | – | – | – |
| Severe ROP (stage ≥3) | – | – | – | – | – | – | – | – |
| Overall mortality | ○ | – | ○ | – | – | – | ○ | ● |

MPV, mean platelet volume; PDW, platelet distribution width; RDS, respiratory distress syndrome; EOS, early-onset sepsis; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; PMA, postmenstrual age; ROP, retinopathy of prematurity; UA, univariate analysis; MVA, multivariate analysis.
○ indicates the platelet parameters included in the multivariate regression ($P < 0.1$).
● indicates statistically significant ($P < 0.05$).
– indicates the platelet parameters excluded from the model or not statistically significant.

## 4. Discussion

This is the first comprehensive exploration of the possible relationship between initial platelet parameters at birth and the occurrence of complications in very preterm neonates. In our population, lower plateletcrit at birth was associated with EOS, severe IVH ≤7 days after birth, first-week mortality, and overall mortality.

A weak but significant negative correlation was observed between MPV and both GA and BW; however, there was no such correlation between platelet counts and GA. Our findings were consistent with those of previous studies and indicated that platelet counts were consistent among preterm neonates,[22] but MPV was slightly increased in neonates with a lower GA.[23,24] This negative MPV-GA correlation was expected given that preterm neonates have a higher percentage of reticulated platelets, which are larger than mature circulating platelets, than term infants,[25,26] and a greater MPV may reflect overall stress and subsequent platelet activation during preterm birth.[27,28]

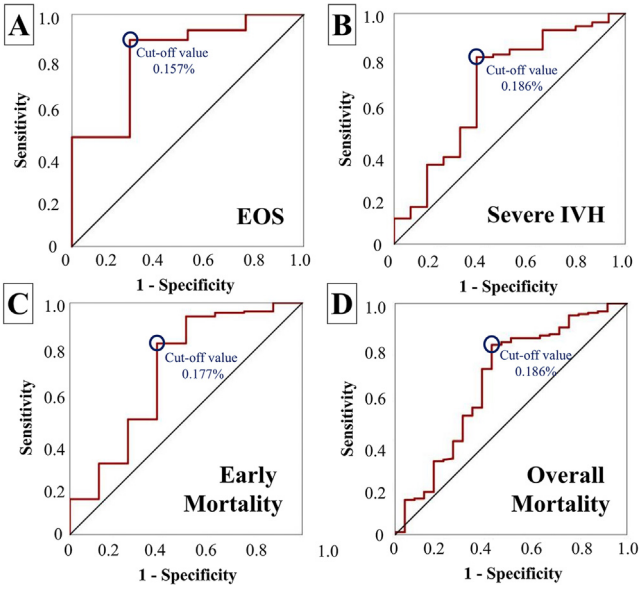


**Figure 3** ROC curves and cutoff values of plateletcrit in predicting (A) EOS (B) severe IVH ≤7 days after birth, (C) early mortality and (D) overall mortality, respectively. ROC, receiver operating characteristic; EOS, early-onset sepsis; IVH, intraventricular hemorrhage.

Lower platelet counts following excessive consumption and decreased production are associated with severe illness. Sepsis is a common cause of disseminated intravascular coagulation and neonatal thrombocytopenia, and severe sepsis contributes to mortality.[29] Furthermore, preterm neonates with lower platelet counts have been recognized as being at risk for IVH.[30] In our study, we found that lower platelet counts were associated with EOS, severe IVH ≤7 days after birth, and early and overall mortality, which was consistent with the previous studies. Since an insufficient response from bone marrow and lower platelet reactivity has been reported in preterm neonates,[31] platelet function has been suggested to be equally important in the balance of hemostasis, in addition to platelet counts. MPV could be an indicator of platelet function; however, as previously stated, the interpretation should be adjusted for GA. For example, we found that preterm neonates with RDS requiring surfactant administration had significantly lower platelet counts and larger MPV in the present study. The same association between RDS and MPV has been reported[12,13,32]; however, this association became insignificant after adjusting for GA. We subsequently examined the association between platelet counts, MPV, and plateletcrit with morbidities and mortality and found that only a lower plateletcrit remained an independent risk factor after adjusting for demographics. Therefore, we suggest that plateletcrit is a better marker for representing overall platelet activity, including counts and function.

Neonates with lower plateletcrit at birth may have a higher risk for severe IVH ≤7 days after birth. Various studies have investigated the relationship between postnatal first-day platelet parameters and IVH in preterm neonates. Although the findings varied, our results were consistent with several studies. One retrospective study found that plateletcrit <10th percentile at birth was associated with severe IVH and/or death in neonates weighing <1500 g.[33] Another cohort study demonstrated that a lower initial plateletcrit predicted the development of IVH within the first week in neonates born at a GA <32 weeks.[15] Based on our results, neonates with an initial plateletcrit <0.186% require careful monitoring for severe IVH.

Lower plateletcrit at birth was associated with EOS and mortality. Plateletcrit represents the total mass of platelets as a percentage of the platelet volume in whole blood. Therefore, platetecrit may act as a better indicator of overall platelet activity and inflammatory status than platelet count or MPV alone. A lower plateletcrit is the consequence of platelet consumption and/or the poor response of platelets to the inflammation cascade.[13] We attributed low plateletcrit to the result of severe inflammation and deterioration of the general health condition in the EOS and mortality group. One study suggested decreased platelet counts and plateletcrit at admission in term neonates with culture-proven sepsis.[34] Another study reported that plateletcrit was the most sensitive platelet parameter, which could be useful in predicting mortality in children with sepsis.[10] Plateletcrit has potential as a marker for EOS and early/overall mortality; however, additional studies are needed to confirm our findings.

Neonates with NEC requiring surgical intervention had higher platelet counts and plateletcrit at birth. However, the difference was small and within the reference range; thus, we suggest that it is clinically insignificant. Other studies have also reported no association between initial platelet count and NEC.[13,14]

Platelet parameters were not significantly associated with other morbidities in the present study. Platelet and thrombus formation have been recognized to play a critical role in the anatomical closure of the ductus arteriosus.[35] Although low platelet counts have been associated with PDA in preterm neonates, a recent systematic review considered low platelet counts as an epiphenomenon due to prematurity rather than as a contributing factor.[36] Regarding infants requiring oxygen demand on postnatal day 28 and at a PMA of 36 weeks, which implies bronchopulmonary dysplasia (BPD), our study showed a trend of a higher MPV. Similar results also suggest that a higher MPV may reflect the risk of BPD development in extremely preterm neonates.[14,37] This may be because the reactivity of larger platelets at birth could favor fibrin deposition in the alveoli of the lungs with insufficient fibrinolysis in preterm neonates with severe RDS,[38] which is related to future BPD development. The association between platelet parameters and ROP has recently gained interest, but our results and those of several previous studies have not found an association.[14,39]

This study has some limitations. First, this was a retrospective study; therefore, the occurrence of morbidities may have been underestimated due to the lack of a priori-defined screening protocol. To reduce bias, we restricted the morbidities to more severe forms (e.g., RDS requiring surfactant, EOS with culture-proven bacteremia, PDA needing treatment, and NEC requiring surgery). The association between platelet parameters and milder morbidities necessitates further investigation. In addition, owing to the limited number of neonates with some morbidities, a larger cohort would be beneficial. Second, platelet parameters were analyzed only on the first day. Exploration of longitudinal changes in platelet parameters during the disease course may be of great help in clinical assessment. Moreover, we noted that the cutoff values of plateletcrit for morbidities and mortality were within the reference range, and further investigations are required to explore their clinical significance. Third, certain maternal conditions that may influence neonatal platelets (e.g., immune-mediated thrombocytopenia and placental insufficiency) were not included in the current study but should be included. Finally, we included only MPV to represent platelet function. As there are other clinical tools to investigate platelet function,[40] future studies should test more platelet parameters to predict morbidities in preterm neonates.

In conclusion, we found that MPV was negatively correlated with GA in preterm neonates and suggested the plateletcrit as an indicator of overall platelet activity. A lower platelet count within 24 h of birth was associated with EOS, severe IVH ≤7 days after birth, and first-week and overall mortality. Future studies with larger sample sizes may provide better insights.

## Declaration of competing interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.06.009.