ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 27(4): 513-518, 2022
DOI: 10.5505/ejm.2022.34545

# Can Platelet Count, Platelet Mass Index and Mean Platelet Volume Be Parameters In Retinopathy of Prematurity?

**Ibrahim Deger[1*], Sabahattin Ertuğrul[1], Irfan Kemal Kaya[2], Sibel Tanrıverdi Yılmaz[1], Ilyas Yolbaş[2]**

*[1]Dicle University School of Medicine, Department of Pediatric, Division of Neonatology, Diyarbakir, Turkey*
*[2]Dicle University School of Medicine, Department of Pediatric, Diyarbakir, Turkey*

**ABSTRACT**

Platelet parameters such as platelet count (PLT), mean platelet volume (MPV) and platelet mass index (PMI) are associated with physiological and pathological functions in various inflammatory diseases. The aim of the present study was to investigate whether platelet parameters were related to retinopathy of prematurity (ROP) in premature newborns.
We retrospectively evaluated the platelet count, platelet mass index, and MPV parameters measured on the first day and 28th day, which belonged to patients, who were examined for retinopathy of prematurity at neonatal intensive care unit. Among 343 patients enrolled by the study, 52.8 % (181) were male and 47.2 %(162) were female. The PLT level studied on the first day was 231.6±84(x1000/mm3) in the ROP group and 207.8±81.6(x1000/mm3) in the non ROP group, and the PLT level studied on the 28th day was 409.9±179.4(x1000/mm3) in the ROP group and 350.7±140.4(x1000/mm3) in the non ROP group. There was a significant difference between the two groups regarding both PLT levels (p=0.007, p=0.006, respectively). The PMI level studied on the first day was 1854.1±774.7 in the ROP group and 1638.2±753.3 in the non ROP group, and the PMI level studied on the 28th day was 3784.5±1797.4 in the ROP group and 3302.8±1452.9 in the non ROP group.
This study showed that platelet count and platelet mass index measured on the first and 28th days are important parameters in patients who undergo ROP examination, and these parameters measured prior to examination will guide clinicians in diagnostic process.

**Keywords:** ROP, MPV, PMI, platelet count.

## Introduction

Retinopathy of prematurity (ROP) is a disease related to vascular and capillary proliferation of the retina that is receiving oxygen therapy and particularly affects small premature infants (1). Retinopathy of prematurity is the most common cause of treatable blindness that is particularly more common in underdeveloped and developing countries (2). Its incidence is higher in premature infants with incomplete retinal vascularization (1). In premature infants, particularly those who are born at 32nd gestational week or earlier, early diagnosis of ROP is highly important due to its increased risk (1). American Academy of Pediatrics' current ROP guideline recommends examination of all premature infants for ROP depending on patient characteristics and the quality of neonatal care, particularly those who are born at gestational age of 30 weeks or earlier or with a birth weight of 1500 g or less (3). Local release of proangiogenic or antiangiogenic factors that are responsible for angiogenesis plays a critical role in the pathogenesis of ROP (1). Some studies have stressed the role of platelets in angiogenesis (2,4,5). However, it is not unclear that elucidated whether platelet counts or function acts on angiogenesis. Platelets store, carry, and release various substances including vascular endothelial growth factor (VEGF) regulating angiogenesis (e.g. epidermal growth factor (EGF), platelet-derived growth factor (PDGF)), which play a crucial role in the pathogenesis of ROP (6-9). Platelet mass index (PMI) is obtained by multiplying platelet count by mean platelet volume (MPV) (6). Widely used in clinical practice, MPV, platelet mass index, and platelet count have been shown to be useful biomarkers for platelet activity

***Corresponding Author:** Ibrahim Deger, Assist. Prof. of Dicle University School of Medicine, Department of Pediatric, Division of Neonatology, Diyarbakir, Turkey
**E-mail:** drdeger@gmail.com, **Phone:** +90 505 271 01 58, **Fax:** +90 (412) 248 85 23
**ORCID ID: Ibrahim Deger:** 0000-0001-8093-5583, **Sabahattin Ertuğrul:** 0000-0003-0903-6520, **Irfan Kemal Kaya:** 0000-0002-1492-7902, **Sibel Tanrıverdi Yılmaz:** 0000-0001-5556-1866, **Ilyas Yolbaş:** 0000-0001-9978-9694
**Received:** 10.03.2022, **Accepted:** 17.08.2022

(2,10,11). The aim of this study was to evaluate the relationship with MPV, platelet count, and PMI with ROP, an inflammatory disease, in premature neonates with a birth weight less than 1500 g and/or born at 32 weeks of gestation or earlier.

## Materials and Methods

This study retrospectively examined the complete blood count parameters (PLT, MPV, and PMI) measured at the first and 28th days in patients who were treated at Neonatal Intensive Care Unit (NICU) between January 2016-December 2020. During this study, 4568 babies were admitted to the NICU, and 343 patients who met the criteria were included in the study. Retinopathy of prematurity examination of all cases included in the study was performed by the ophthalmologist on the postnatal 28th day and the results were recorded.

ROP is evaluated in 5 stages (12).

Stage I: Demarcation line in the form of a line between vascular and avascular

Stage II: Ridge; slightly raised neovascular proliferation from the surface

Stage III: Initiation of extraretinal fibrovascular proliferation in the back

Stage IVA: Partial retinal detachment (No macular involved)

Stage IVB: Partial retinal detachment (Macular involvement is present)

Stage V: Total retinal detachment.

Those with stage 1 or stage 2 ROP with plus disease in zone 1, stage 3 ROP in zone 1, stage 2 or stage 3 ROP in zone 2 and plus disease were treated. The follow-up examination of the patients in whom retinal vessels reached zone III and retinal vascularization was completed was terminated (12).

*Study inclusion criteria:*

Patients who were admitted to and treated at neonatal intensive care unit

Infants born at gestational week ≤32

Infants born with birth weight ≤1500 g

*Study exclusion criteria*

Infants with multiple congenital anomalies, cyanotic congenital heart disease, infants born at gestational week >32 and >1500 g, diagnosed with neonatal alloimmune thrombocytopenia and neonatal immune thrombocytopenia, born to a mother with immune thrombocytopenia, bone marrow failure, and infants who received thrombocyte transfusion were excluded.

The medical records of patients who were admitted to NICU and examined for ROP within the specified time window were obtained. The medical data of the study patients were obtained from their medical records kept in the hospital's archive unit. A form was prepared for each case, which included the infants' demographic characteristics, birth weight, birth week, gender, length of hospital stay, ROP examination findings, as well as platelet count, MPV (mean platelet volume) in the first 24 hours and on the 28th day. PMI was obtained by multiplying platelet count and MPV (PMI=mean platelet volume x platelet count/1000) that were obtained from complete blood count (CBC) results.

*Blood samples*

Blood samples were collected from a peripheral vein or umbilical cord to determine PLT, MPV, and PMI in all newborns. CBC samples were collected on the first day (first measurement) and on 28th day (second measurement) for each patient. Platelet count and MPV level were studied in Sysmex XN-1000 sampling unit (Sysmex, Kobe, Japan). The study was approved by local Ethics Committee (22.04.2021/265).

**Statistical Analyses**: The data obtained for the newborn patients enrolled by the study were analyzed using Statistical Package for Social Sciences (SPSS) statistical software package for Windows 10 v18.0.0. Descriptive statistics were given as mean and standard deviation. Student's t-test was used to compare normally distributed quantitative variables between study groups. The Kolmogorov-Smirnov normality test was utilized to determine whether the data had normal distribution. A $p$ value less than 0.05 was statistically significant for all statistical tests.

## Results

The study included 343 patients, of whom 52.8% (181) were male and 47.2% (162) were female. Among patients with ROP, 51.9% (70) were male; the mean birth weight was 914.3±243.3 grams; and the mean gestational age at birth was 26.1±2.1 weeks. In the non ROP group, 53.4% (111) of the patients were male; the mean birth weight was 1048.7±325.4 g; and the mean gestational age at birth was 27.3±2.3 weeks. When birth weight and gestational week were compared (p=0.01 and 0.01), there was a statistically significant increase in the non-ROP group, but there was no

**Table 1.** Comparison of Platelet, MPV and PMI values between cases with and without ROP

| Parameters | Non-ROP (n=208) | ROP (n=135) | p |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Platelet count (x1000/mm3) (First day) | 207.8±81.6 | 231.6±84.1 | 0.041 |
| Platelet count (x1000/mm3) (28th day) | 350.7±140.4 | 409.9±179.4 | 0.001 |
| MPV(fL) (First day) | 7.96±2.09 | 8.19±2.13 | 0.313 |
| MPV(fL) (28th day) | 9.31±2.44 | 9.48±2.49 | 0.464 |
| PMI (fL/nL) (First day) | 1638.2±753.3 | 1854.1±774.7 | 0.032 |
| PMI (fL/nL) (28th day) | 3302.8±1452.9 | 3784.5±1797.4 | 0.024 |

MPV: Mean platelet volüme, P<0.05; values are statistically significant, PMI: Platelet mass index, ROP: Retinopathy of prematurity, SD: standart deviation

significant difference in terms of gender in both groups (p=0.82). Platelet count and PMI studied on the first day and on the 28th day were statistically significantly higher in the ROP group than the non-ROP group whereas no significant difference was found between the MPV levels of both groups (Table 1, Figure 1, Figure 2).

## Discussion

Our study found no significant difference between the study groups with respect to MPV level for the prediction of ROP although both groups showed a significant difference regarding platelet count and platelet mass index studied both on the first and 28th days. This finding suggested that platelet count and PMI may be important predictors of ROP.

Severe neonatal inflammatory reactions play an important role in the pathogenesis of ROP (13). The first stage in the development of ROP is the cessation of retinal vessel growth, and the second stage is the formation of retinal neovascularization (2). In order to adequately perfuse the hypoxic retina, various hormones and growth factors (such as VEGF, growth hormones, and insulin-like growth factor-1) are secreted excessively (2). The release of these factors is thought to trigger abnormal vascularization in ROP (1,13-16).

Although the role of platelets in angiogenesis is not fully known, they are thought to contain both angiogenic and antiangiogenic factors (14). Platelets secrete potent proinflammatory substances (15). In addition to toxic oxygen radicals and proinflammatory cytokines, various lipid mediators and potent proteases may be responsible for abnormal retinal vascularization (15,16). Platelets store and carry various substances such as PDGF, EGF, matrix metalloproteinases, and VEGF (2,17). Alterations in platelet count and platelet volume may play a role in the physiopathology of ROP (2,17). Young platelets are usually larger, and an increased number of young platelets indicates that their production has increased in response to increased consumption of them (18,19). It is thought that larger platelets show a better enzymatic activity and function in hemostasis compared with smaller platelets (18,19). It is thought that MPV can inform clinicians about possible coagulation disorders, increased inflammatory response, and oxidative stress in premature infants (18,19). It is known that inflammatory response is highly correlated to adverse clinical outcomes in intensive care patients (18,19). Platelet parameters such as MPV are markers of platelet activation mediated by inflammatory processes (20). Therefore, elevated MPV can be an indicator of oxidative stress in the newborn (18). It is thought that elevated MPV is a marker of advanced ROP since larger platelets are more active than smaller ones in transporting and storing VEGF (1,17). While Çekmez et al. (21) and Okur et al. (11) found no significant correlation between ROP and MPV, Tao et al. (2) found a correlation between elevated MPV and ROP. Go et al. (19) showed that low MPV levels were associated with increased mortality in premature infants. Similar to the studies by Çekmez et al. (21) and Okur et al. (11), our study found no correlation between ROP and MPV levels measured on the first and 28th days. Thrombocytopenia is a common hematological disorder and linked to increased mortality and morbidity in the newborn (11,22). Platelet count decreases in the first week of life and increases over the next few weeks (23). Zi Di Lim et al. (23) showed that a low mean platelet count observed in infants with ROP is dependent on other processes (particularly culture-proven sepsis, blood transfusion, and bronchopulmonary

**Fig. 1.** Platelet count distribution measured on the first day between cases with and without ROP

dysplasia) increasing their susceptibility to ROP, adding that there was no difference between the mean platelet counts of the groups with and without ROP. Çakır et al. (24), in a mouse ROP model, demonstrated that any thrombocytopenia episode at ≥30 weeks of postmenstrual age (PMA) was associated with severe ROP. Jensen et al. (25) showed that thrombocytopenia was associated with severe ROP at a period from birth to postmenstrual 34 weeks. Şahinoğlu et al. (26) evaluated the platelet counts of infants in the first week after birth; they showed that a low platelet count was a risk factor for developing ROP. Okur at al. (11) found a lower 1st-day platelet count in patients with ROP compared with controls. In contrast to the study reported by Okur et al. (11), our study found a higher platelet count in the ROP group compared with the control group. Similarly, platelet count measured on 28th day was significantly higher in the ROP group than the controls. Our study did not investigate whether or not the patients developed thrombocytopenia during follow-up. Platelet count plays a role in neovascularization; we thus suggest that increased platelet count in both phases of inflammation effectively initiated proinflammatory processes and it may be a marker of ROP.

Recent studies have provided evidence suggesting that platelet functions rather than platelet count may be more closely related to mortality and morbidity (6,11,19). Based on those studies, the use of MPV, PMI, PCT, and PDV, in addition to platelet count, has been gradually increasing. It has been shown that as PMI decreases, platelet activity is reduced (6). Several studies have shown that PMI has a greater role than PLT count and MPV level in demonstrating the hemostatic efficacy of a platelet plug (11,17). Some other

**Fig. 2.** Platelet count distribution measured on day 28 between cases with and without ROP

studies have also shown that PMI may be a better predictor of neonatal morbidities than MPV (6,11,27). Thus, it is believed that comparing the effects of platelet count and markers of platelet function would provide an important insight into ROP's course (6). Korkmaz et al. (6) suggested that PMI was a better marker than platelet count; while they found no significant difference regarding PMI levels in the first stage of ROP, they reported a significantly higher PMI in patients who underwent laser photocoagulation in the second stage (6). In our study, there was only two patients that underwent laser photocoagulation, and the PMI levels were significantly higher in the ROP group than the control group on both the first and 28th days. Since our study included all patients diagnosed with ROP, we consider that this difference is even more significant. We are of the opinion that PMI levels calculated from platelet count and MPV level may guide physicians in predicting ROP.

**Limitations**: Our study has some limitations. Some analyses are missing owing to its retrospective nature. In the present study, which was conducted in a single center and with a limited number of patients, measurements were performed in all patients on 28th day but outcomes at postnatal 32-34th weeks were not evaluated. Furthermore, whether patients developed thrombocytopenia, a well-known risk factor for ROP, and whether they were administered thrombocyte suspensions during the study period were not investigated. Retinopathy of prematurity is a multifactorial condition, and other risk factors for ROP, such as intraventricular hemorrhage, necrotizing enterocolitis, and

bronchopulmonary dysplasia were not investigated.

**Conclusion**: Based on our study results, we believe that platelet count and PMI levels indicating platelet activity may provide convenience in the diagnosis of ROP considering that proinflammatory and anti-inflammatory processes start with birth in the development of ROP. Additionally, based on the hypothesis that platelet count and PMI measured on 28th day affect vascular endothelium especially during ROP examination, we reached the conclusion that they can be used to predict ROP. For neonatologists and ophthalmologists, it may be a simple, complementary minimally invasive method allowing a more precise diagnosis of ROP in preterm newborns at risk for ROP. We think that large studies involving large numbers of patients are needed in order to apply the standard use of these tests.

## References


1. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv Ophthalmol. 2018; 63: 618-637.
2. Tao Y, Dong Y, Lu CW, Yang W, Li Q. Relationship between mean platelet volume and retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2015; 253: 1791-1794.
3. Fierson WM; American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening Examination of Premature Infants for Retinopathy of Prematurity. Pediatrics 2018; 142(6):e20183061.
4. Palmblad J. Platelets and angiogenesis: novel aspects. Expert Rev Hematol. 2009; 2: 1-2.
5. Patzelt J, Langer HF. Platelets in angiogenesis. Curr Vasc Pharmacol. 2012; 10: 570-577.
6. Korkmaz L, Baştuğ O, Özdemir A, Korkut S, Karaca Ç, Akın MA, et al. Platelet mass index can be a reliable marker in predicting the prognosis of retinopathy of prematurity in very preterm infants. Pediatr Neonatol. 2018; 59: 455-463.
7. Italiano JE Jr, Richardson JL, Patel-Hett S, Battinelli E, Zaslavsky A, Short S, et al. Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet alpha granules and differentially released. Blood. 2008; 111: 1227-1233.
8. Vinekar A, Hegde K, Gilbert C, Braganza S, Pradeep M, Shetty R, et al. Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity? Retina. 201; 30: 20-23.
9. Jensen AK, Ying GS, Huang J, Karp K, Quinn GE, Binenbaum G. Thrombocytopenia and retinopathy of prematurity. J AAPOS. 2011; 15: e3-e4.
10. Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost. 2010; 8: 148-156.
11. Okur N, Buyuktiryaki M, Uras N, Oncel MY, Ertekin O, Canpolat FE, et al. Platelet mass index in very preterm infants: can it be used as a parameter for neonatal morbidities? J Matern Fetal Neonatal Med. 2016; 29: 3218-3222.
12. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021; 128: e51-e68.
13. Hu YX, Xu XX, Shao Y, Yuan GL, Mei F, Zhou Q, et al. The prognostic value of lymphocyte-to-monocyte ratio in retinopathy of prematurity. Int J Ophthalmol. 2017; 10: 1716-1721.
14. Folkman J. Angiogenesis: an organizing principle for drug discovery? Nat Rev Drug Discov. 2007; 6: 273-286.
15. Kaplanski G, Farnarier C, Kaplanski S, Porat R, Shapiro L, Bongrand P, Dinarello CA. Interleukin-1 induces interleukin-8 secretion from endothelial cells by a juxtacrine mechanism. Blood. 1994; 84: 4242-4248.
16. Leviton A, Dammann O, Engelke S, Allred E, Kuban KC, O'Shea TM, et al. The clustering of disorders in infants born before the 28th week of gestation. Acta Paediatr. 2010; 99: 1795-1800.
17. Akyüz Ünsal Aİ, Key Ö, Güler D, Kurt Omurlu İ, Anık A, Demirci B, et al. Can Complete Blood Count Parameters Predict Retinopathy of Prematurity? Turk J Ophthalmol. 2020; 50: 87-93.
18. Mohsen L, Akmal DM, Ghonaim EKE, Riad NM. Role of mean platelet volume and ischemia modified albumin in evaluation of oxidative stress and its association with postnatal complications in infants of diabetic mothers. J Matern Fetal Neonatal Med. 2018; 31: 1819-1823.
19. Go H, Ohto H, Nollet KE, Takano S, Kashiwabara N, Chishiki M, et al. Using Platelet Parameters to Anticipate Morbidity and Mortality Among Preterm Neonates: A Retrospective Study. Front Pediatr. 2020; 8: 90.
20. 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; 99: e21649.
21. 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: 134-137.

22. Sancak S, Toptan HH, Gokmen Yildirim T, Karatekin G, Ovali F. Thrombocytopenia as a risk factor for retinopathy of prematurity. Retina. 2019; 39: 706-711.
23. Lim ZD, Pheng E, Min ETL, Van Rostenberghe H, Shatriah I. Comparison of Mean Platelet Counts in Preterm Infants with and without Retinopathy of Prematurity. Int J Environ Res Public Health. 2021; 18: 3783.
24. Cakir B, Liegl R, Hellgren G, Lundgren P, Sun Y, Klevebro S, et al. Thrombocytopenia is associated with severe retinopathy of prematurity. JCI Insight. 2018; 3: e99448.
25. Jensen AK, Ying GS, Huang J, Quinn GE, Binenbaum G. Longitudinal study of the association between thrombocytopenia and retinopathy of prematurity. J AAPOS. 2018; 22: 119-123.
26. Şahinoğlu Keşkek N, Gülcan H, Yılmaz G, Akkoyun İ. Impact of Platelet Count in Retinopathy of Prematurity. Turk J Ophthalmol. 2020; 50: 351-355.
27. Kahvecioglu D, Erdeve O, Alan S, Cakir U, Yildiz D, Atasay B, et al. The impact of evaluating platelet transfusion need by platelet mass index on reducing the unnecessary transfusions in newborns. J Matern Fetal Neonatal Med. 2014; 27: 1787-1789.