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Predictive Value of Maternal Systemic Inflammatory Markers in Treatment-Requiring Retinopathy of Prematurity

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Abstract

The aim of the study was to investigate the predictive value of maternal systemic inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), systemic immune-inflammatory index (SII), platelet mass index (PMI) and mean platelet volume (mPV) in treatment-requiring retinopathy of prematurity (TR-ROP). In this retrospective study, 19 mothers whose preterm infants required treatment (intravitreal injection) for ROP were included in the TR-ROP group. Twenty-one mothers whose preterm infants did not require treatment for ROP were included in the control group. Birth weights (BWs) and gestational age (GA) were recorded. Maternal complete blood count samples obtained within 3 days before delivery were analyzed. Maternal NLR, PLR, LMR, SII, PMI and mPV data were calculated and statistically compared. All data were analyzed using statistical package for the social sciences, version 22.0 (SPSS, Chicago, IL, USA). There was no significant difference between the groups in terms of BW (p=0.108). The GA was significantly lower in the TR-ROP group compared to the control group [28 (24-33), 30 (27-32), p=0.04, respectively]. NLR, PLR, LMR and SII values were 5.9/4.2 (p=0.02), 143.8±26.3/123.1±36.2 (p=0.02), 2.06/3.01 (p=0.001), 1279/1040 (p=0.05) between the TR-ROP and control groups, respectively. In the TR-ROP group, when these values were corrected according to the GA in logistic regression analysis, the NLR, PLR, and SII were not statistically significant (p=0.11, p=0.83 and p=0.13), but there was an increase in the LMR [p=0.02, odds ratio=0.38 95% confidence interval (0.16-0.88)]. The relationship of maternal SII, PMI and mPV parameters with TR-ROP was shown for the first time in this study. Maternal LMR in the prenatal period may be helpful in predicting TR-ROP. Additional studies are needed before these conclusions can be applied to daily clinical practice.

Keywords: Inflammatory markers, maternal lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) is a sight-threatening disease that affects premature infants with arrested retinal vascularization. It is a leading cause of childhood blindness worldwide. The two most well-known risk factors in the pathophysiology of ROP are premature birth and low birth weight (BW). Numerous studies have shown that retinal ischemia, neovascularization and fibrosis are important factors in the development and progression of ROP, particularly in ROP requiring therapy (TR-ROP), which can lead to severe visual impairment if not diagnosed and treated early[1,2].

In recent studies, inflammation has been associated with age-related macular degeneration and diabetic retinopathy and ROP[3-6]. Several studies have investigated whether hematologic inflammatory biomarkers are potential predictors of an increased inflammatory response in ROP[7-11]. However, the majority of these studies have focused on infant inflammatory biomarkers, with limited exploration of maternal inflammatory biomarkers. Given that maternal health and intrauterine conditions influence fetal development, understanding the potential role of maternal inflammation in the pathogenesis of ROP may provide new insights into early risk assessment and prevention.

While extensive research has examined inflammatory biomarkers in infants, the potential impact of maternal biomarkers during pregnancy remains largely unexplored. Identifying maternal inflammatory biomarkers associated with ROP may allow for earlier interventions and improved neonatal outcomes. Therefore, our objective was to assess the predictive power of complete blood count (CBC) parameters and maternal blood inflammatory biomarkers for TR-ROP.

Highlights

- **Maternal inflammatory markers:** This study is the inaugural investigation into the correlation between maternal systemic inflammatory markers, including systemic immune-inflammatory index (SII), platelet mass index, and mean platelet volume, and treatment-requiring retinopathy of prematurity (TR-ROP).
- **Lymphocyte/monocyte ratio (LMR):** A significant association was observed between maternal LMR in the prenatal period and TR-ROP, suggesting that this parameter may serve as a predictive marker.
- **Predictive values:** Although the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and SII were elevated in the TR-ROP group, they became non-significant after adjusting for gestational age.
- **Novel findings:** These findings underscore the potential utility of maternal inflammatory biomarkers in predicting TR-ROP.
- **Clinical implications:** LMR may serve as an early, non-invasive indicator for identifying infants at an elevated risk for TR-ROP

Material and Method

Erciyes University Department of Ophthalmology is the site of this retrospective study and ethical approval was granted by Erciyes University Clinical Research Ethics Committee (approval number: 2023/116, date: 08.02.2023).

ROP screening was performed according to the latest national ROP screening guideline[12]. The study enrolled preterm infants with gestational age (GA) less than 34 weeks or BW less than 1,700 g and preterm infants with GA greater than 34 weeks or BW greater than 1,700 g who received cardiopulmonary support. The infants were grouped according to their condition, with the mothers assigned to each group accordingly: those who needed treatment for ROP and those who did not. Conditions including gestational diabetes, pre-eclampsia, systemic infections and clinical chorioamnionitis are known to cause systemic inflammation and significantly alter maternal inflammatory markers. To avoid these confounding factors that may affect the interpretation of our results, mothers with these conditions were excluded from the study. In addition, mothers who received antenatal steroids were not included in this study.

The newborns had their first ophthalmological examination at 31 weeks' GA for those born before 27 weeks, and at the fourth week after birth for those born after 27 weeks. The examination was performed according to the guidelines of the international classification of ROP[13]. A binocular indirect ophthalmoscope, a twenty-diopter lens, an infant speculum, and a pediatric scleral depressor were used for retinal examination. All infants were examined 1 hour after the instillation of 1% phenylephrine and 0.5% tropicamide. Treatment choices were based on the early treatment for ROP study criteria[14]. Patients who received vascular endothelial growth factor (VEGF) [0.625 mg in 0.025 mL Bevacizumab (Avastin®)] inhibitors were administered intravitreally for zone I and posterior zone II type 1 disease. Treated infants were defined as the TR-ROP group, and infants with ROP not requiring treatment were defined as the control group. In the study period, some patients received laser for zone 2 or 3 ROP and aiming a homogenous study population for disease severity and treatment modality those were excluded from the study. These treatment options were discussed with families and applied accordingly after informed consent. None of the infants had stage 4 or 5 ROP. The same ophthalmologist examined the infants and performed the intravitreal injections.

Maternal CBC samples, which were collected within 3 days before delivery, were analyzed. Electronic health records were screened to obtain the required data. White blood cell (WBC), lymphocyte, neutrophil, monocyte, platelet counts, and C-reactive protein (CRP) levels were recorded. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), systemic immune-inflammatory index (SII) (neutrophil x platelet/lymphocyte), platelet mass index (PMI) [platelet count x mean platelet volume (mPV)], and mPV were calculated and recorded. The results of the groups were contrasted. All measurements were

performed in the same laboratory using the same method. This standardized approach aimed to minimize variability between samples, prevent potential laboratory-induced errors, and enhance the comparability of results.

Statistical Analysis

The data was analyzed using the statistical package for the social sciences (SPSS, Chicago, IL, USA) application, version 22.0. The data's normality was examined using the Shapiro-Wilk test. Parametric methods were applied for normally distributed numerical data, and results were expressed as mean ± standard deviation. Non-parametric methods were used for data that did not follow a normal distribution, and results were presented as median (minimum-maximum) or interquartile range (25^{th}-75^{th} percentile). To ascertain if the means of the two independent groups differed, the Mann-Whitney U test (for non-normally distributed data) and the Student's t-test (for regularly distributed data) were employed. Using logistic regression, the significant independent risk factors linked to the existence of ROP were calculated. The adjusted odds ratio (OR) and 95% confidence interval (CI) were estimated for each potential risk factor. The area under the curve (AUC) was calculated for each plot. In addition, sensitivity, specificity, and cut-off values were determined based on the LMR value and expressed via receiver operating characteristic (ROC) curve analysis. A p-value below 0.05 was considered statistically significant.

Results

A total of 40 mothers of infants with ROP were included in the study. Nineteen premature infants with ROP were treated with an intravitreal injection and represented the TR-ROP group, while 21 premature infants with ROP were followed without any treatment and represented the control group. Infants in the TR-ROP group had stage 3 ROP in 15 patients and aggressive ROP in 4 patients. The control group had stage 1 or 2 ROP that eventually resolved without treatment. **Table 1** shows the GA, BW, and maternal age data. The groups' differences in mother age and body weight of infants were not statistically significant. GA was lower in the TR-ROP groups (p=0.04).

Table 2 summarizes each group's maternal CBC parameters. The lymphocyte count was significantly lower in the TR-ROP group than in the control group (1.69±0.5 and 2.23±0.89 respectively, p=0.01). The TR-ROP group did not differ statistically significantly from the control group in terms of mPV, CRP, neutrophil count, platelet count, or monocyte count (p=0.08, p=0.345, p=0.405, p=0.649, p=0.127, respectively). NLR, PLR, and SII were increased and LMR was decreased in the TR-ROP group compared to the control group [NLR=5.9 (3.2-12.9) in TR-ROP group and 4.2 (0.9-11.8) in control group, p=0.02; PLR=143.8±26.3 in TR-ROP group and 123.1±36.2 in control group, p=0.02; SII=1,279 (826-4625) in TR-ROP group and 1040 (219-2401) in control group, p=0.05; LMR=2.06 (1.1-4.2) in TR-ROP group and 3.01 (1.2-5.9) in control group, p=0.001]. PMI was comparable between groups (p=0.260).

Table 1.
Comparison of maternal age, gestational age and birth weight of infants between groups

	TR-ROP group (n=19)	Control group (n=21)	p-value
Maternal age	31.2±5	28.7±5	0.156
Gestational age (wk)	28 (24-33)	30 (27-32)	**0.04***
Birth weight (gr)	1.176.9±353.9	1.357±343.1	0.108

TR; Treatment-requiring, ROP; Retinopathy of prematurity, *; Statistically significant

Table 2.
Comparison of maternal hemogram parameters

Maternal hemogram parameters	TR-ROP group n=19	Control group n=21	p-value
CRP (µg/mL)	12.1 (2.3-123.7)	6.43 (0.49-48.3)	0.345
WBC (x10³/mcL)	12.46 (1.06-29.13)	13.64 (8.15-21.77)	0.893
Platelets count (x10³/mcL)	227 (158-358)	234 (170-386)	0.649
Neutrophils count (x10³/mcL)	9.06 (6.7-25.58)	9.19 (1.56-18.88)	0.405
Lymphocytes count (x10³/mcL)	1.69±0.5	2.23±0.89	**0.01***
Monocytes (x10³/mcL)	0.84±0.24	0.71±0.27	0.127
MPV (fL)	10.6 (9.4-12.6)	10.7 (9.4-12.7)	0.08
NLR	5.9 (3.2-12.9)	4.2 (0.9-11.8)	**0.02***
LMR	2.06 (1.1-4.2)	3.01 (1.2-5.9)	**0.001***
SII	1.279 (826-4.625)	1.040 (219-2.401)	0.05
PLR	143.8±26.3	123.1±36.2	**0.02***
PMI	2.466±570	2.703±688	0.260

The mean was used to express normally distributed data (standard deviation), and the median (min-max) was used to express non-normally distributed data
WBC; White blood cell, NLR; Neutrophil-to-lymphocyte ratio, LMR; Lymphocyte-to-monocyte ratio, PLR; Platelet-to-lymphocyte ratio, CRP; C-reactive protein, SII; Systemic immune-inflammatory index (neutrophil x platelet /lymphocyte), PMI; Platelet mass index (platelet count x MPV), MPV; Mean platelet volume, TR; Treatment-requiring, ROP; Retinopathy of prematurity *; Statistically significant

Table 3 shows the variable logistic regression analysis of NLR, PLR, SII, and LMR. When these results were adjusted using logistic regression analysis based on week of birth for TR-ROP, the NLR, PLR, and SII were not statistically different (p=0.11, p=0.83, and p=0.13, respectively). However, only LMR was found to be a significant independent predictor for TR-ROP among all variables examined. [p=0.02, OR=0.38, 95% CI (0.16-0.88)].

For maternal LMR, a ROC test was carried out. It is shown in **Table 4** and **Figure 1**. The ROC analysis showed a cut-off value of 2,807, a sensitivity of 0.73, and a specificity of 0.71, with an area AUC of 0.807 (0.66-0.94) (95% CI).

Discussion

ROP is a multifactorial retinal vascular disease whose pathogenesis consists of two phases. The initial stage is characterized by postnatal hyperoxia, which arrests normal retinal vascularization. In the latter stage, the retina experiences hypoxia as a result of the increased demand of the growing retinal cells afterward. Increased levels of mediators including VEGF, erythropoietin, and insulin-like growth factor-1 cause neovascularization to start[15]. Studies also show a "pre-phase" due to placental inflammation that develops in the mother during the intrauterine period[11]. Studies have shown that neonatal and maternal systemic inflammatory responses are essential in the etiology of ROP[2,16].

To date, inflammatory markers from CBC have been suggested as potential markers of inflammation in various diseases, including bronchopulmonary dysplasia and kidney disease[17,18]. In addition, peripheral blood and biomarker studies are ongoing to predict or detect preterm delivery or ROP. With the increasing importance of the role of inflammation in ROP, studies in this area have increased in recent years. However, a number of different conditions, including normoblasts, earlier or later cord clamping, labor stress, and antenatal administration of steroids, can lead to discordant pediatric CBC results in the early stages of a newborn's life[19,20]. Prenatal maternal inflammation may also influence the pathogenesis of ROP. This study evaluated the potential of maternal inflammatory markers to predict TR-ROP.

The study by Çelik et al.[10] evaluated the CBC parameters of preterm infants treated for ROP treatment and their mothers. While maternal WBC was markedly more elevated in the TR-ROP group, maternal NLR, LMR, PLR, and PCI were not significantly different (maternal WBC AUC=0.69). In addition, infant WBC was significantly lower in the TR-ROP group. Woo et al.[21] found that clinical chorioamnionitis (excluding histological chorioamnionitis) and increased levels of the mother's WBC were a significantly important risk predictor for developing ROP at any stage. We found a significant reduction in maternal lymphocyte count in the TR-ROP. However, GA may affect the results when interpreting neonatal CBC results. Previous studies have reported that neutrophil abnormalities and lymphocyte maturation are altered in GA[22,23]. When the lymphocyte counts adjusted for GA were evaluated, the groups did not significantly differ from one another (p=0.06).

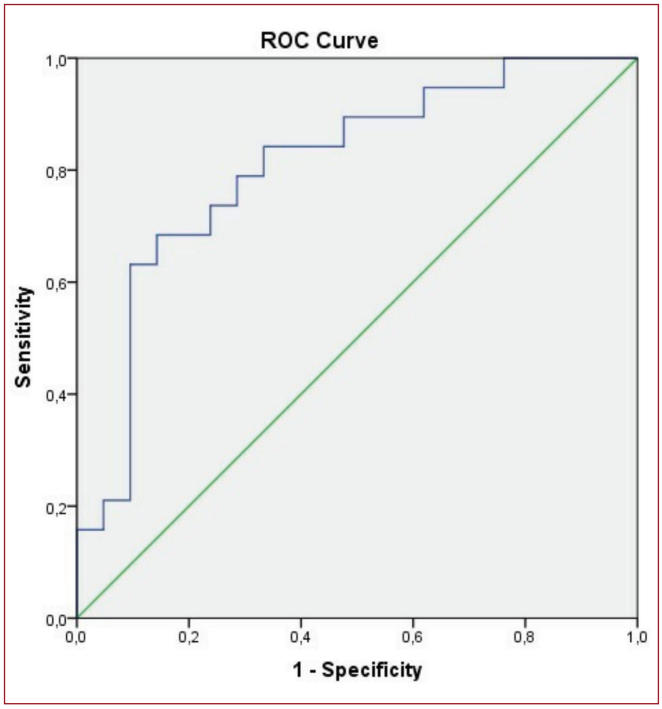

Figure 1. ROC curve for maternal LMR in predicting TR-ROP

ROC; Receiver operating characteristic, LMR; Lymphocyte/monocyte ratio, TR-ROP; Treatment-requiring retinopathy of prematurity

Table 3.
Logistic regression analysis

	OR	%95 CI		p-value
		lower	upper	
NLR	1.19	0.95	1.48	0.11
LMR	0.38	0.16	0.88	**0.02***
SII	1.00	1.00	1.00	0.13
PLR	1.01	0.99	1.04	0.83

NLR; Neutrophil-to-lymphocyte ratio, LMR; Lymphocyte-to-monocyte ratio, PLR; Platelet-to-lymphocyte ratio, SII; Systemic immune-inflammatory index (neutrophil x platelet /lymphocyte), OR; Odds ratio, 95% CI; 95% confidence interval, *; Statistically significant

Table 4.
ROC analyses of maternal parameters

Maternal parameters	AUC (%95)	cut off	p-value	Sensitivity %	Specificity %
LMR	0.807 (0.669-0.94)	2.807	**0.001***	73.7	71.4

AUC (%95); Area under the curve with 95% confidence intervals, LMR; Lymphocyte-to-monocyte ratio, *; Statistically significant

Novel inflammatory biomarkers generated from the infants' peripheral blood, including the NLR, PMI, LMR, and PLR, have been determined for predictive ability regarding developing ROP[7,8,24]. A LMR may reflects a suppressed adaptive immune response with heightened inflammation, which has been linked to poor outcomes in several conditions. Hu et al.[7] reported that infants with increased LMR have an independent risk factor for ROP. They suggested that ROP development is substantially and independently correlated with LMR. In a study by Peng et al.[25], maternal PLR was significantly higher in spontaneous preterm birth than in full-term controls, whereas maternal LMR did not differ between groups. In light of these findings, in the prenatal period, PLR may be helpful for predicting preterm delivery, while LMR may be useful for predicting TR-ROP. Furthermore, maternal LMR may be helpful in detecting TR-ROP during screening for ROP. Using ROC analysis, we determined threshold level of maternal LMR for predicting TR-ROP and found that the optimal level was 2.807. These findings suggest that preterm infants whose mothers' LMR is greater than 2.807 are at risk for TR-ROP. The significant inverse association between maternal LMR and TR-ROP in our study suggests that systemic maternal immune dysregulation during pregnancy may contribute to postnatal ROP development. Given its predictive potential, maternal LMR could be integrated into prenatal and perinatal risk assessment strategies for ROP. Maternal LMR measurement during pregnancy could be incorporated into routine prenatal care, particularly in high-risk pregnancies (e.g., preterm births, gestational diabetes, preeclampsia). In addition, infants born to mothers with high LMR could receive enhanced postnatal care, including optimized oxygen therapy, nutritional interventions (e.g., vitamin A, docosahexaenoic acid, and insulin-like growth factor-1 support), and anti-inflammatory strategies to mitigate ROP risk. Nevertheless, the findings require further prospective studies to provide robust support.

The SII is a new immune marker[26]. It has been widely studied in oncology, cardiovascular diseases, and neonatal disorders. Elevated SII levels have been demonstrated to be associated with worse outcomes in various cancers, as a high neutrophil and platelet count with a low lymphocyte count indicates tumour-associated inflammation[27]. Moreover, high SII levels correlate with increased cardiovascular risk, including atherosclerosis and myocardial infarction[28]. The formula for determining this was as follows: neutrophil x platelet/lymphocyte. Akdoğan et al.[8] reported the only study in the literature on the association of SII and ROP, and the present study is the initial to examine the association of the TR-ROP link with maternal SII. They reported that during the one-month observation period, infants with ROP had a greater SII value compared to newborns who did not present with ROP. They also stated that SII may be an independent predictor for ROP. According to our findings, there was no discernible variation in maternal SII between the groups. The data from the current study also showed that the prediction of TR-ROP by SII was not significant.

PMI has been the focus of research in a range of inflammatory and thrombotic conditions, given its established role in platelet function, vascular integrity, and coagulation[29]. In addition, Korkmaz et al.[9] compared premature infants who received laser photocoagulation therapy with premature infants who did not receive treatment. In the 1st phase of ROP, they did not find any variation in PMI levels across the groups; however, in the second phase of ROP, they discovered a substantial difference between the study groups. Their findings suggested that PMI levels during the 2nd stage of ROP might be significant for ROP follow-up. They stated that PMI levels may also rise in association with the rise in VEGF in the 2nd phase of ROP, as platelets play a role in the delivery, retention, and secretion of VEGF. mPV has been shown to be a reliable measure of the average size of platelets and serves as an indirect indicator of platelet activation. Increased platelet volume is frequently associated with an elevated risk of thrombosis, while lower mPV levels may be indicative of impaired platelet production. Research has demonstrated that mPV and PMI levels may be subject to alteration in the context of inflammatory bowel disease activity, underscoring their significance in chronic inflammation, Fournier's gangrene, and necrotizing soft tissue infection[30-32]. The relationship between ROP development and mPV values was examined. Özkaya[33] reported no difference in further platelet values such as PMI, mPV, platelet number, and platelet distribution width between the groups. Similar results were obtained in our study, and maternal mPV, platelet count, and PMI values did not differ across the groups.

Study Limitations

There are various limitations to this study. The retrospective design of this study is its primary limitation. The second is the study's low number of participants. The results of the ROC analysis may have been affected by this small sample size. Third, some maternal stress conditions (such as subclinical chorioamnionitis) that may affect systemic inflammatory markers could not be excluded.

Conclusion

The relationship of maternal SII, PMI, and mPV parameters with TR-ROP was shown for the first time in this study. Maternal LMR in the prenatal period may help predict TR-ROP. Additional studies are needed before these conclusions can be applied to daily clinical practice.

Ethics

Ethical Approval: Ethical approval was granted by Erciyes University Clinical Research Ethics Committee (approval number: 2023/116, date: 08.02.2023).

Informed Consent: These treatment options were discussed with families and applied accordingly after informed consent.

Footnotes

Author Contributions: Polat OA: Surgical and Medical Practices; Karaca Ç, Özer F: Consept; Polat OA, Özer F: Design; Polat OA, Özer F: Data Collection or Processing; Polat OA, Özer F: Analysis or Interpretation; Karaca Ç: Literature Search; Karaca Ç, Polat OA, Özer F: Writing.

Conflict of Interest: The authors declare no conflicts of interest.

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