Are The Neutrophil-to-lymphocyte, Platelet-to-lymphocyte And Monocyte-to-lymphocyte Ratios Predictive Factors For The Retinopathy Of Prematurity?

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Abstract

Purpose: In this study, we aimed to evaluate the possible relationship between the neutrophil-to-lymphocyte, monocyte-to-lymphocyte and platelet-to-lymphocyte ratio and retinopathy of prematurity (ROP).

Method: The data of 348 patients who applied to Erzincan University Ophthalmology Unit for screening the retinopathy of prematurity were analyzed retrospectively. One hundred sixty seven patients who were collected CBC samples within the first 72 hours after delivery and who met the inclusion criteria were included in the study. Infants with a gestational age of ≤35 week were screened for ROP. Pateints were divided into two groups. Group 1 was involved the patients with the diagnosis of ROP and group 2 was involved the normal patients (no ROP). The levels of NLR, PLR and MLR were determined in two groups.

Results: Fifty nine patients who were detected ROP are in group 1 and 108 patients who were not seen ROP are in group 2 in the study. The mean gestational age at birth of the patients was 30,4 ± 2,1 [26-34] weeks in group 1 and 33,7 ± 1,7 [27-35] weeks in group 2.(P =0.004) The mean gestational weigth at birth was 1927,2 ± 158,4 [1690-2300] gram in group 1 and 2169,1 ± 283,1 [1750-3100] gram in group 2. (P <0.001) With the result of logistic regression analysis, gestational age [Odds Ratio(OR): 0.531, 95%CI: 0.388-0.726, P <0.001], NLR [OR:34.849, 95%CI: 2.091-580.779, P :0.013] and PLR [OR: 1.067, 95%CI: 1.034-1.110, P <0.001] were detected the independent risk factors for ROP.

Conclusion: Our study revealed that higher NLR and PLR which are evaluated with in first 72h after birth is an independent predictor of ROP.

Background

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disease characterized by an interception of normal retinal vascular development and subsequent disorganized vascular growth. ROP is a primary cause of preventable vision loss worldwide in children and affects thousands of infants.[1,2] The progression of ROP has been connected to different factors such as angiogenic factors, cytokines, and neuroprotective and oxidative growth factors.[3] In recent years, inflammatory factors have also been stated to be associated with ROP. [3–6]

Complete blood count (CBC) is an easy, economical, and commonly used principal hematological test comprising the quantitative determination of white blood cells (WBC), red blood cells (RBC), and platelets. WBC contain neutrophils, lymphocytes, monocytes, eosinophils and basophils. WBC are found in blood, lymphatic fluid and all tissues of the body. Leukocyte count in the blood is an important indicator especially in infectious diseases.[7,8] In healthy humans, the most plenty white blood cells are neutrophils, which play important roles during acute and chronic inflammatory reactions. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are the respective proportions of absolute neutrophil to lymphocyte, platelet to lymphocyte, and monocyte to

lymphocyte counts obtained from the evaluation of the CBC test. As markers of inflammation, many studies have shown the relationship between NLR, PLR and MLR and many diseases, such as inflammatory and cardiovascular diseases, and cancer.[7–10] The ratios of WBC have been recommended as indicators of general inflammatory reactions. [11] In this retrospective study, we purposed to evaluate the correlation between NLR, MLR and PLR and ROP.

Methods

The data of 348 infants that were referred to the Ophthalmology Unit of Erzincan University, Turkey between June 2018 and July 2019 for the screening of ROP were retrospectively analyzed. A total of 167 patients, from whom CBC samples were collected within the first 72 hours after birth and who met the inclusion criteria were included in the study. Fifty-nine patients were found to have ROP on the first examination, but none had the severe form of the disease. This study was created in accordance with the Declaration of Helsinki, and verbal informed consent was taken from the parents of each patient before the study. All infants were participants who applied for ROP screening and had blood tests available. Performing the study no extra blood sample were needed and all of the parents accept including in the study of the babies. All the infants had CBC samples which were collected in intensive care unit for newborns. The approval of the Institutional Ethics Committee of Erzincan University was also obtained.

Clinical evaluation:

Infants with a smaller gestational age than 35 weeks were examined for ROP after administering tropicamide 1% (Tropamid®, Bilimilaç®,Gebze, Turkey) eye drops and phenylephrine hydrochloride 0.5% (Mydfrin®, Alcon®, Fort Worth, TX) eye drops for three times for pupillary dilatation. The ROP examination was performed by the same experienced eye professional using a binocular indirect ophthalmoscope combined with a sclera depressor after administering proparacaine hydrochloride 0.5% (Alcaine®, Alcon®, Fort Worth, TX)eye drops as the topical anesthetic. The ROP status was graded according to the international classification of ROP in all infants. The ROP status was noted including the stage, zone and extent of the disease, and the presence or absence of plus disease for each infant.[12] Each infant was also graded according to the maximum stage of ROP examined in either eye.

All blood samples were gathered and investigated within the first 72 h after birth. Peripheral venous blood samples (1 mL) was gathered in tubes containing dipotassium ethylenediamine tetraacetate (EDTA–2K). CBC were investigated by an automated hematology analyzer. (Sysmex Corporation, Kobe 651–0073, Japan). The NLR values were figured out by dividing the neutrophil count to the lymphocyte count, the PLR values by dividing the platelet count to the lymphocyte count, and the MLR values by dividing the monocyte count to the lymphocyte count.

The patients were seperated into two groups: Group 1 comprised those with the diagnosis of ROP and Group 2 consisted of patients without ROP. All patients accepted in the study were evaluated by fundoscopic examination at four weeks after birth. The patients were called for a control visit at an

appropriate time according to the stage and zone of ROP (after one, two, three or four weeks. Retinal vascularization reached the ora serrata in the follow-up of all the patients.

Exclusion criteria:

Infants born with hematologic disorders, received postnatal steroid therapy or a blood product transfusion before the ROP examination were excluded from the study. And also patients with respiratory distress syndrome (RDS), asphyxia neonatorum, neonatal pneumonia, premature rupture of membranes (PROM), necrotizing enterocolitis, hypoxic-ischemic encephalopathy (HIE) and blood culture-proven sepsis were excluded from the study. Infants who did not attend follow-up regularly and who had any other accompanying ocular or systemic diseases were excluded from the study.

Statistical analysis:

The SPSS (Statistical Package for the Social Sciences) version 22.0 statistical software package was used for statistical analyses. The Kolmogorov-Smirnov test was applied to observe the distribution of the parameters in the study groups. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. The chi-square test was used to analyze the categorical variables. Inter-group comparisons of the continuous variables were performed using Student's t-test in addition to the analysis of variation (ANOVA) for homogenous data and the Mann-Whitney U test for non-homogenous data. The Friedman variance analysis test was performed to compare the variables in repeated measures, Wilcoxon's signed rank test for the pairwise comparisons of these variables, and the Pearson and Spearman correlation tests for the assessment of the correlations between the variables. Logistic regression analysis was performed to predict the significant independent risk factors associated with the existence of ROP. Exact *P* values of <0.05 were considered statistically significant. The adjusted odds ratio (OR) and the 95% confidence interval (CI) for each possible risk factor were calculated. A receiver operating characteristic (ROC) curve analysis was applied to define the cut-off values of NLR and PLR in predicting the stage of ROP. All of the results were appraised at a confidence interval of 95% based on a significance level of $P < 0.05$.

Results

In Group 1, 34 patients of the 59 patients were male and 25 were female. In Group 2, 68 of the 108 patients were male and 40 were female. There wasn't any statistically significant difference between the two groups in terms of gender distribution ($P = 0.745$). The mean gestational age at birth was 30.4 ± 2.1 [26–34] weeks in Group 1 and 33.7 ± 1.7 [27–35] weeks in Group 2, and there was a statistically significant difference between the two groups ($P = 0.004$). The mean gestational weight at birth was 1927.2 ± 158.4 [1690–2300] and 2169.1 ± 283.1 [1750–3100] gram in Group 1 and 2, respectively ($P < 0.001$).

The CBC test results of the patients are shown in Table 1.

When the CBC test results of the patients were evaluated, the mean neutrophil count was 3.74 ± 1.85 (10^9/L) in Group 1 and 1.91 ± 0.87 (10^9/L) in Group 2. The difference in the neutrophil count between the two groups was statistically significant ($P < 0.001$). The average lymphocyte count was 4.86 ± 1.56 (10^9/L) in Group 1 and 5.22 ± 1.58 (10^9/L) in Group 2. There wasn't any statistically significant difference between the two groups in terms of the lymphocyte count ($P = 0.394$). The mean monocyte count was 1.43 ± 0.49 (10^9/L) in Group 1 and 0.86 ± 0.46 (10^9/L) in Group 2, with no significant difference between the two ($P = 0.088$). The average platelet count was 453.36 ± 121.96 (10^9/L) and 304.33 ± 117.58 (10^9/L) in Groups 1 and 2, respectively, and the difference was not statistically significant ($P = 0.744$).

The NLR value of the patients was 0.87 ± 0.59 in Group 1 and 0.39 ± 0.18 in Group 2. NLR was significantly higher in infants with ROP ($P < 0.001$). When the MLR of the patients was examined, this ratio was calculated as 0.32 ± 0.15 for Group 1 and 0.18 ± 0.11 for Group 2, and there was a significant difference between the two groups ($P = 0.009$). The PLR value of the patients was 98.94 ± 30.97 in Group 1 and 59.41 ± 18.97 in Group 2. PLR was significantly higher in Group 1 than in Group 2 ($P < 0.001$).

The logistic regression analysis was performed to determine the independent risk factors for ROP. According to the results of this analysis, gestational age (OR: 0.531, 95% CI: 0.388–0.726,$P < 0.001$), NLR (OR: 34.849, 95% CI: 2.091–580.779, $P = 0.013$), and PLR (OR: 1.067, 95% CI: 1.034–1.110, $P < 0.001$) were detected as the independent risk factors for ROP.

The ROC curve analysis was used to determine whether the cut-off values of NLR and PLR could be used to predict ROP. An NLR over 0.53 indicated higher risk of ROP with 81.4% sensitivity and 83.3% specificity while a PLR over 81.48 indicated higher risk of ROP with 71% sensitivity and 90% specificity.

Discussion

It is certain that systemic inflammatory responses of maternal immune system and vigorous neonatal inflammatory reactions play a significant role in the development of ROP.[12–15]Systemic inflammatory responses may affect the creation of abnormal retinal vascularization and promote the risk of ROP, independent of gestational age and weight or intensity of early systemic disease.[16] Woo et al.also informed that umbilical cord blood cytokine levels and perinatal factors were significantly associated with the pathogenesis of ROP.[17] NLR, PLR or MLR have been used in the prognostic diagnosis of cancer in many different branches of medicine and clinically significant results have been obtained.[18–21]

Previous studies indicated that increased neutrophil count and decreased lymphocyte count were associated with a systemic inflammatory response and physiological stress, respectively.[22–25] In our study, the neutrophil count was meaningfully higher in the ROP group, but the logistic regression analysis indicated that the neutrophil count was not an independent risk factor for ROP. No significant difference was observed between the lymphocyte values of the groups with and without ROP. In the logistic regression analysis, the lymphocyte count was not associated with ROP, as in the neutrophil count. Similarly, the number of monocytes was not associated with ROP.

Guida et al. found a relationship between sepsis and thrombocytopenia in babies with a very low birth weight, and they suggested that the pathogens that caused sepsis might affect the platelet kinetics.[26] In our study, no relationship was found between the presence of ROP and platelet count, and the exclusion of the infants with systemic problems, such as sepsis may have been effective in the emergence of this condition.

Several studies have shown that the NLR, PLR and MLR values, which are related to systemic inflammation, may be prognostic factors for ocular diseases, such as degenerative myopia, keratoconus and age-related macular degeneration.[27–29]

Kurtul et al. examined the relationship between ROP and NLR and found no independent risk relationship.[3] The authors only observed a relationship between the lymphocyte count and ROP. In the current study, the logistic regression analysis showed that PLR and NLR were independent risk factors for ROP. In addition, in the ROC analysis, the cut-off value was found to be 0.53 for NLR and 81.48 for PLR; however, no relationship was found between the lymphocyte count and ROP, unlike the results reported by Kurtul et al.

The major limitation of our study is that severe ROP cases were not included in the sample. Some postnatal conditions, such as oxygen support, intraventricular hemorrhage, anemia, apnea, and sepsis have been shown to be associated with ROP progression.[30] These accompanying pathologies are likely to affect the NLR, PLR and MLR values. Accordingly, the patients with severe ROP were excluded from the study group. In addition, the relatively low number of participants and the absence of an evaluation of other inflammatory markers can be considered as limitations. Studies involving large-scale patient groups and infants with severe ROP and systemic diseases may be important in evaluating the relationship of ROP with NLR and PLR.

Conclusion

Our study revealed that increased NLR and PLR evaluated within the first 72 h after birth are independent predictors of ROP. In premature babies, the detection of NLR and PLR can be helpful to predict the possible development of ROP.

Declarations

Ethics approval and consent to participate

Informed consent was taken from the parents of each patient before the study. The approval of the Institutional Ethics Committee of Erzincan University was obtained (33216249–604.01.02-E.24306). Verbal informed consent was taken from the parents of each patient before the study.

Consent for publication

Not applicable.

Availability of data and materials

All generated or analyzed data during this study are included in the supporting file.

Competing interests

In accordance with our ethical obligation as a researcher, all authors are reporting that we have not any financial or non-financial conflicts of interest in this research. (Authors: Adem Uğurlu MD, Erel Icel MD, Nurdan Gamze Tasli MD, Hayati Yılmaz MD, Turgay Ucak MD, Yucel Karakurt MD)

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Authors' contributions

AU and Eİ conceived and supervised this research. AU, NGT and HY collected and analyzed the data in the study. AU wrote the initial manuscript, revised by TU and YK. All authors critically reviewed the manuscript for significant intellectual content and approved the final version.

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Tables

Table 1. Clinical findings and laboratory measurements of the patients

	Group 1	Group 2	Total	p value
Number of patients	59 (35.3%)	108 (64.7%)	167 (100%)	-
Gender(male/female)	34 (57.6%) / 25 (42.4%)	65 (60.2%) / 43 (39.8%)	99 (59.3%) / 68 (40.7%)	0.745
GA	30.4 ± 2.1	33.7 ± 1.7	32.2 ± 2.3	***0.004***
GW	1927.2 ± 158.4	2169.1 ± 283.1	2083.6 ± 270.9	***<0.001***
Neutrophil	3.74 ± 1.85 (10^9/L)	1.91 ± 0.87 (10^9/L)	2,55 ± 1,56 (10^9/L)	***<0.001***
Lymphocyte	4.86 ± 1.56 (10^9/L)	5.22 ± 1.58 (10^9/L)	5.09 ± 1.57 (10^9/L)	0.394
Monocyte	1.43 ± 0.49 (10^9/L)	0.86 ± 0.46 (10^9/L)	1.06 ± 0.54 (10^9/L)	0.088
Platelet	453,36 ± 121,96 (10^9/L)	304,33 ± 117,58 (10^9/L)	356.98 ± 138.2 (10^9/L)	0.744
NLR	0.87 ± 0.59	0.39 ± 0.18	0.56 ± 0.44	***<0.001***
MLR	0.32 ± 0.15	0.18 ± 0.11	0.23 ± 0.14	***0.009***
PLR	98.94 ± 30.97	59.41 ± 18.97	73.38 ± 30.34	***<0.001***

GW: gestational weight GA: gestational age NLR: neutrophil to lymphocyte ratio

PLR: platelet to lymphocyte ratio MLR: monocyte to lymphocyte ratio

Table 2. Logistic regression analysis results for independent predictors of ROP.

Variable	OR	95% CI	*P* value
GW	0.998	0.996-1.001	0.281
GA	0.531	0.388-0.726	***<0.001***
Sex	0.654	0.213-2.008	0.458
Neutrophil	0.327	0.022-4.901	0.419
Lymphocyte	0.309	0.043-2.235	0.244
Monocyte	42.341	0.275-6524.413	0.145
Platelet	1.022	0.990-1.056	0.181
NLR	34.849	2.091-580.779	***0.013***
PLR	1.067	1.034-1.110	***<0.001***
MLR	0.641	0.005-81.611	0.857

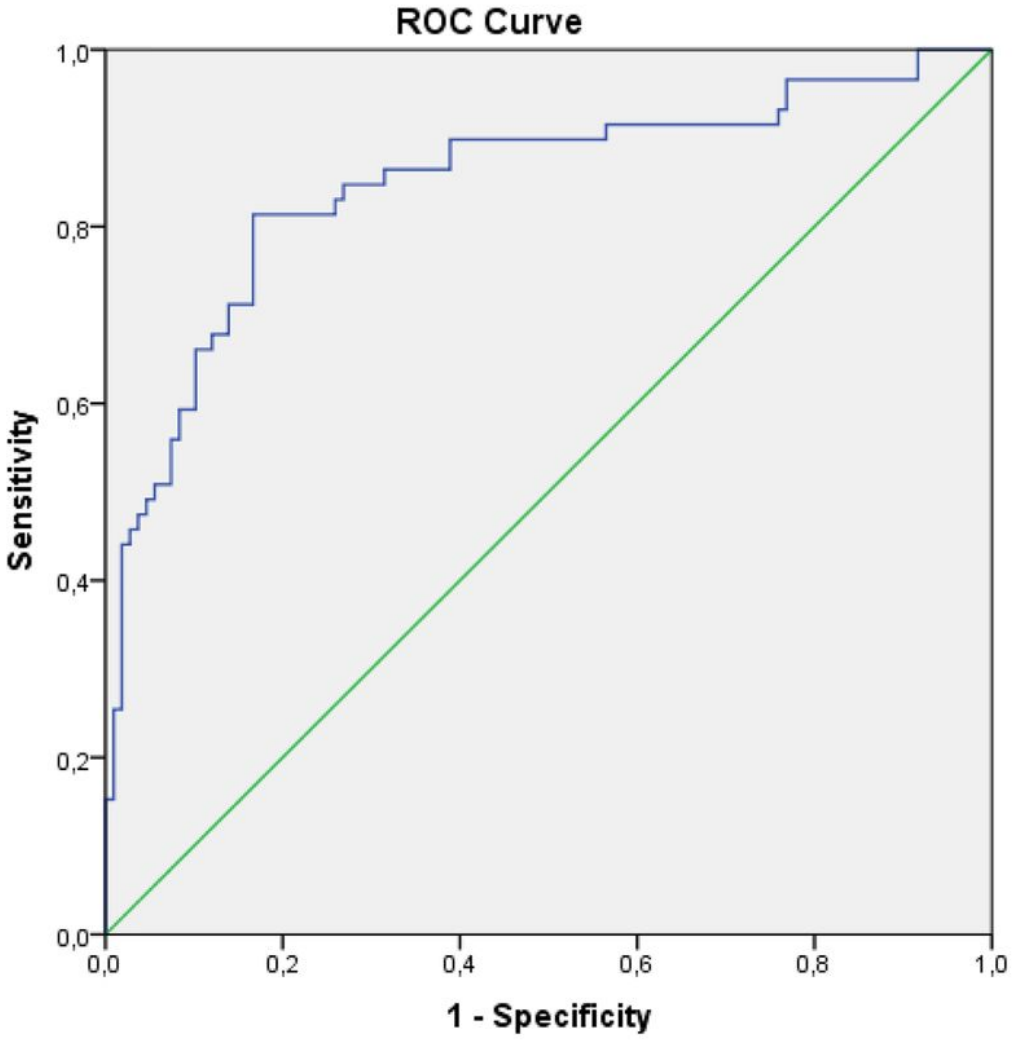
GW: gestational weight GA: gestational age OR: odds ratio

95% CI: 95% confidence interval NLR: neutrophil to lymphocyte ratio

PLR: platelet to lymphocyte ratio MLR: monocyte to lymphocyte ratio

Figures

Figure 1. ROC curve analysis for NLR



Area under curve (AUC)= 0.849 *P*= <0.001 SE= 0.034

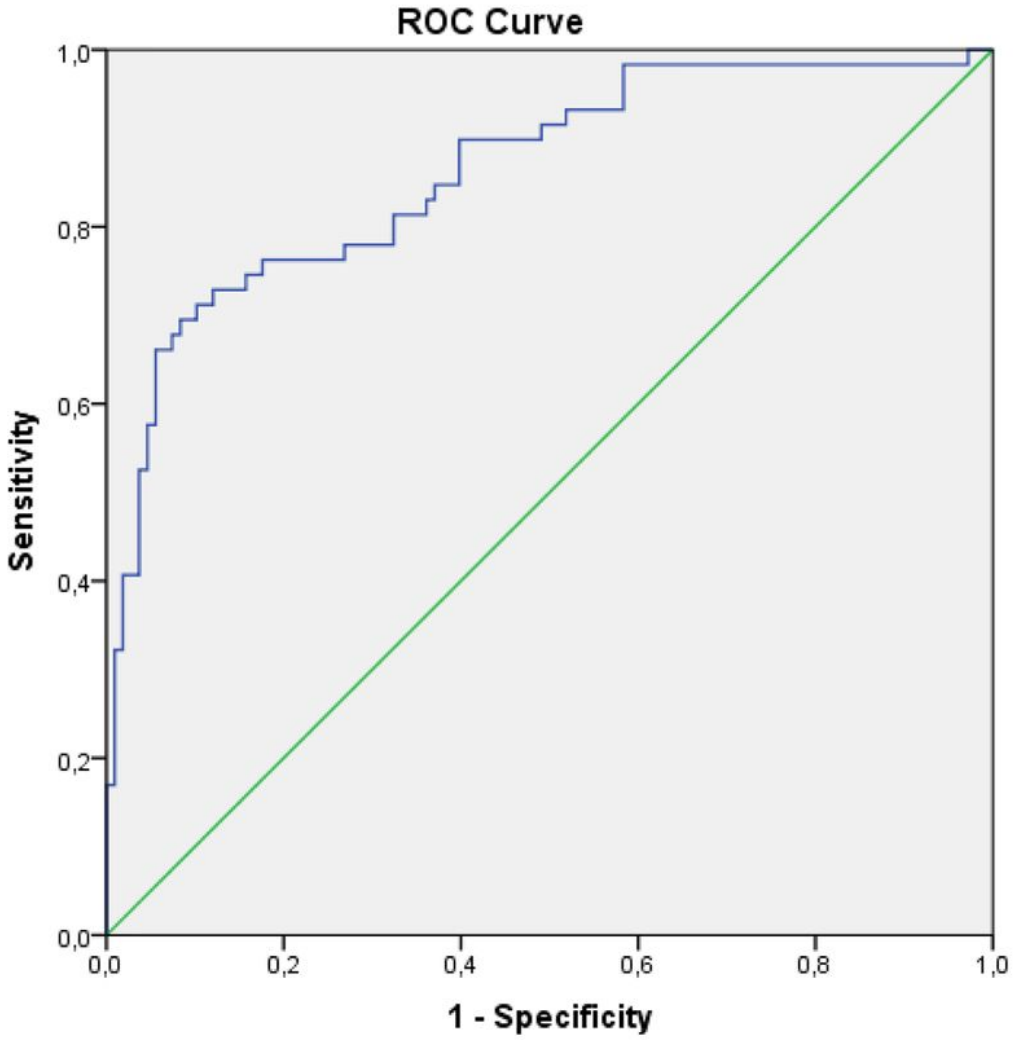
95% Confidence Interval (CI) = 0.782-0.916

Cut off value= 0.532

Sensitivity= 81.4% Specificity= 83.3%

Figure 1

Figure 2. ROC curve analysis for PLR



Area under curve (AUC)= 0.862 *P*= <0.001 SE= 0.031

95% Confidence Interval (CI)= 0.802-0.922

Cut off value= 81.48

Sensitivity= 71% Specificity= 90%

Figure 2