Special Focus on Retinopathy of Prematurity, Original Article

Correlation between systemic immune-inflammation index and routine hemogram-related inflammatory markers in the prognosis of retinopathy of prematurity

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Purpose: To evaluate the prognostic potential of systemic inflammatory index in the course of retinopathy of prematurity (ROP). **Methods:** This is a retrospective case-control study. 303 infants with a gestational age of ≤35 weeks were screened with and without ROP at birth and 1 month after the birth of complete blood counts (CBC) were included in this study. Serum neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte (PLR), and systemic immune-inflammation index (SII) was calculated at birth and one month after. LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. NLR and PLR were determined by dividing the absolute neutrophil count or the absolute platelet count by the absolute lymphocyte count, respectively. The SII was calculated by the formula = neutrophilxplatelet/lymphocyte. All statistical analyses were performed using SPSS 22 (SPSS for Windows, version 22.0; SPSS, Inc. Chicago, IL, USA). **Results:** A total of 303 infants were included 145 with ROP and 158 without ROP. The NLR, LMR, PLR and SII values were 0.56 ± 1.17/0.51 ± 1.04 (P = 0.997), 13.7 ± 18/9.49 ± 13.1 (P = 0.014), 31.69 ± 68/24.1 ± 37.7 (P = 0.268), 131.42 ± 326/124.66 ± 267 (P = 0.935) in with ROP and without ROP infant at birth respectively. The NLR, LMR, PLR, and SII values were 0.68 ± 1.27/0.34 ± 0.99 (P = 0.001), 2.58 ± 6.01/2.46 ± 14.5 (P = 0.706), 47.5 ± 78.33/33.55 ± 42.4 (P = 0.035), and 253 ± 681/114 ± 345 (P = 0.001), respectively in with ROP and without ROP infant at 1 month after birth. **Conclusion:** The NLR, PLR, and SII seem an independent predictor of the development of ROP.

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Retinopathy of prematurity (ROP) is a leading cause of visual impairment and blindness in preterm neonates worldwide.[1,2] ROP is a vasoproliferative disease characterized by retinal ischemia as well as neovascularization and proliferative retinopathy which are the main factors limiting the development of retinal vessels in premature infants.[3] Many studies reveal that retinal neovascularization and fibrosis take a pioneering role in the formation and development of ROP.[4,5] Today, the increasing survival rates of premature infants thanks to the developing intensive care conditions have led to an increase in the frequency of ROP.[2]

Recent studies report that inflammation is associated with ROP.[6-8] In addition, it has been revealed that systemic inflammation impairs retinal vascular development and induces pathological characteristics of ROP in newborn animal models.[9] In the evaluation of inflammation, the ratios of white blood cells (WBC) have been proposed as the markers of general inflammatory responses.[10]

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are cost-effective inflammatory markers that do not require additional cost. Ocular disorders, which also develop in ROP as in other ischemic diseases such as age-related macular degeneration and diabetic retinopathy, have been reported to be correlated with these ratios.[11-14] Systemic immune-inflammation index (SII) is a new marker calculated from lymphocyte, neutrophil, and platelet count and shows immune balance.[15,16]

Therefore, the purpose of this study is to evaluate the prognostic potential of systemic immune-inflammation index in patients with ROP. For this purpose, a retrospective cohort study was conducted.

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Methods

303 infants with a gestational age of ≤35 weeks who available hemogram data were screened retrospectively. 158 of the infants had without ROP while 145 infants had ROP at various stages. Birth and 1-month hemogram values were screened in SBU Bursa Yuksek Ihtisas Training and Educational Hospital between February 2016-February 2018. The study received non-drug clinical study approval from the SBU ethics committee (2011-2018/08.06), and the Helsinki Declaration criteria were followed.

The infants with sepsis proven in blood culture, necrotizing enterocolitis, and hematological disease and the infants receiving blood product transfusion or steroid treatment before their exclusion from the ROP screening were excluded from the study. All ophthalmological examinations were performed by the same ophthalmologist and all images were recorded in the Archimed VGA system (Pronova, Ankara).

After dilatation, the pupils of the infants (0.5% tropicamide [Tropamid, Bilim, Turkey] and 2.5% phenylephrine [Mydfrin, Alcon, USA]) were screened by indenting the whole peripheral retina by using a 28D lens and indirect ophthalmoscope (Omega 500, Heine, Germany). In the classification, the zone was determined according to the localization and distribution of plus (In at least two quadrants of the retina, there is enlargement of the veins and an increase in the arterioles It is indicated by the "p+" sign), pre-plus (pp) (It is a situation in which retinal vessels are not normal, but do not change as much as the plus disease. It should be followed up, plus may progress to the disease over time)[17] and lesion based on the severity of the ROP disease.[18] In addition, birth weights, weeks, genders, lengths of intensive care stay, and follow-up durations of the infants were recorded in their files.

Peripheral venous blood (1 mL) was collected in tubes containing dipotassium ethylene diamine tetraacetate (EDDA-2K). Complete blood counts were evaluated by an automated hematology analyzer. This is a retrospective case-control study. By screening from 550 infant files (n = 550), 303 infants with and without ROP and with a gestational age of ≤35 weeks were identified, the infants whose CBC were measured at birth and 1 month after birth were included in the study. Serum NLR, lymphocyte-to-monocyte ratio (LMR), PLR, and SII were calculated at birth and 1 month after birth. LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. NLR and PLR were determined by dividing the absolute neutrophil count or the absolute platelet count by the absolute lymphocyte count, respectively. The SII was calculated by the formula: neutrophil × platelet/lymphocyte.

Statistical analysis

Statistical analyses were performed by using SPSS 22.0 (SPSS for Windows, version 22.0; SPSS, Inc., Chicago, Ill, USA). Descriptive statistics (mean, standard deviation) were used to evaluate all data. The values for non-normally distributed variables were given with interquartile ranges (IOR).

Unpaired t-test or Mann-Whitney nonparametric U test was used for the comparisons.

Univariate analysis was performed to evaluate other potential risk factors regarding the presence of ROP such as NLR1, NLR2, LMR1, LMR2, PLR1, PLAR2, SII1, and SII2. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated for each possible risk factor. Receiver operating characteristics (ROC) curve analysis was performed to show sensitivity and specificity. P value of <0.05 was considered statistically significant.

Results

A total of 303 infants as 158 infants without and 145 with ROP, who were born at gestational 35 weeks or earlier and whose CBC was calculated within <72 h of age and whose hemogram data for the 1st month were obtained, were included in this study. Demographic characteristics of the infants with and without ROP and their birth and 1-month blood values [Table 1].

There was a negative correlation between gestational week (r = -370, P = 0.001) and birth weight (r = -474, P = 0.001) in the development of ROP. The positive correlation was between the duration of incubation (r = +515, P = 0,001) and follow-up time (r = +623, P = 0,001) in the development of ROP. While 51 (in 6 pp (+)) (35.1%) of the infants with ROP had stage 1 ROP, 43 (in 20 pp, 10 p +) (29.6%) had stage 2 ROP, 24 (all in pp, p +) (16.5%) had stage 3 ROP, 27 (18.6%) infants had aggressive posterior ROP (APROP).[19] No infant in group 1 was treated. In group 2, 14 babies received intravitreal low/ultralow dose bevacizumab treatment. Low-dose bevacizumab and/or laser photocoagulation were administered to all babies in groups 3 and 4 either alone or simultaneously or intermittently.

When the blood count values were examined, it was seen that birth and 1-month WBC values were 11.1 (IQR5)/10.7 (IQR9) P = 0.014, 9.9 (IQR3)/11.9 (IQR6) P = 0.001 [Table 1]. These values were significant at a lower level in the infants who developed ROP at birth and they were significant at a higher level in the 1st month when ROP developed. The platelet count was determined as 345 ± 126/359 (IQR247) P = 0.001 in the 1-month period when ROP developed and was found to be significantly low in the infants with ROP compared to the infants without ROP. Also, when the 1st-month platelet count of group 1 (stage 1 ROP) and group 4 (APROP) babies were compared, it was 360 ± 136 in group 1 and 324 ± 199 in group 4, and the difference was statistically significant (P = 0.034). Conversely, when the 1-month neutrophil count was examined, it was detected as 2.3 (IQR1.5)/3 (IQR3.7) P = 0.040, and this value was significantly higher in the infants with ROP. The birth lymphocyte count was significantly low in infants with ROP compared to control group (P = 0,010).

The NLR, LMR, PLR and SII values were 1.07 (IQR1.1)/0.61 (IQR1.1) P = 0.997, 4.1 (IQR9)/7.2 (IQR13) P = 0.014, 56 (IQR51)/44 (IQR39) P = 0.268, 124 (IQR320)/131 (IQR208) P = 0.935 in the infants with ROP and without ROP at birth, respectively. The NLR, LMR, PLR and SII values were 0.4 (IQR0.4)/0.6 (IQR0.9) P = 0.0001, 2.1 (IQR1.6)/2.5 (IQR2.8) P = 0.706, 62 (IQR48)/54 (IQR45) P = 0.035, 130 (IQR194)/183 (IQR342) P = 0.0001 in the infants without ROP and with ROP one month after birth, respectively.

In the subgroup analysis (Conover test), the difference between the Group 1 and 4 between NLR (P = 0.0011) and SII (P = 0.003) values was found to be significant in the 1st month. Other values were not found to be different between Group 1

Table 1: Demographic characteristics and birth and 1-month blood values of infants with and without ROP

Variables	ROP (-) (*n*=158)	ROP (+) (*n*=145)	*P*
Sex (M/F)	81 (%52)/77 (%48)	81 (%56)/64 (%44)	0.648
Gestational age (w)	31.8 (26-35) (IQR3)	30 (23-35) (IQR4.2)	0.013[a]
Birth weight (g)	1717 (840-2830)(IQR640)	1215 (490-2850) (IQR662)	0.018[a]
Incubator day	16.5 (0-120)(IQR20)	44.5 (6-120) (IQR42)	0.001[a]
Following week	42 (38-50)(IQR2)	48 (38-73) (IQR8)	0.001[a]
WBC count at birth (x10^9/L)	11.1 (IQR5)	10.7 (IQR9)	0.014
WBC count one month (x10^9/L)	9.9 (IQR3)	11.9 (IQR6)	0.001
Platelet count at birth (x10^9/L)	242 (IQR85)	224±80	0.681
Platelet count one month (x10^9/L)	359 (IQR247)	345±126	0.001
Neutrophil count at birth (x10^9/L)	3.95 (IQR4)	3 (IQR5)	0.116
Neutrophil count one month (x10^9/L)	2.3 (IQR1.5)	3 (IQR3.7)	0.040
Lymphocyte count at birth (x10^9/L)	4.7±2.6	4.45 (IQR3.6)	0.010
Lymphocyte count one month (x10^9/L)	5.3±1.7	5.5 (IQR3.2)	0.503
Monocyte count at birth (x10^9/L)	0.9 (IQR1)	0.75 (IQR1.5)	0.037
Monocyte count one month (x10^9/L)	1.1 (IR0.7)	1.4 (IR1.2)	0.841
NLR at birth	1.07 (IQR1.1)	0.61 (IQR1.1)	0.997
NLR one month	0.4 (IQR0.4)	0.6 (IQR0.9)	0.000
PLR at birth	56 (IQR51)	44 (IQR39)	0.268
PLR one month	62 (IQR48)	54 (IQR45)	0.035
LMR at birth	4.1 (IQR9)	7.2 (IQR13)	0.014
LMR one month	2.1 (IQR1.6)	2.5 (IQR2.8)	0.706
SII at birth	124 (IQR3209	131 (IQR208)	0.935
SII one month	130 (IQR194)	183 (IQR342)	0.000

WBC; white blood cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII; systemic immune-inflammation index. *P*<0.05, statistically significant

and 4 as well as among other groups [Table 2]. ROC analysis between groups and groups 1 and 4 [Figs. 1-3].

Discussion

SII values were found to be highly significant in the development period of ROP. The difference was significant in early-stage ROP, APROP, and advanced stage ROP.

When reviewed in the literature, it is seen that this is the first study showing the relationship between SII and the development of ROP. Systemic Immune-Inflammation (SII) is a new index defined in recent years and shows the immune balance calculated from the number of lymphocyte neutrophil, monocyte, and platelet.[15,16] In the literature, many studies have revealed that SII values can be used as prognostic markers in malignancies.[16] In our study, the fact that SII was determined as higher in the infants with ROP compared to the infants without ROP in the 1-month period, when ROP developed, and the same value was distinctively high in early-stage ROP and advanced stage ROP indicates that this value can be an independent predictor.

Other inflammatory markers as well as SII were found to be significantly different in the infants with ROP. This is consistent with the findings stating that the risk of ROP increases when both the mother and infant encounter inflammation.[7] Tremblay *et al*.[6] state that severe systemic perinatal inflammation provokes microglia activation in the retina and causes vascular anomalies similar to the ones observed in ROP.

The immune systems of neonates, especially those born very prematurely, are immature. Therefore, they are sensitive to infection.[20] Factors related to postnatal and prenatal inflammation in neonates are known to be associated with ROP.[21]

There is evidence that exposure of preterm neonate to inflammatory mediators is associated with an increased risk of ROP.[5]

There are studies revealing that the lymphocyte count decreases in infants with ROP in the first 24 hours after birth.[12] Also, in our study, while the first 24-hour lymphocyte count was significantly lower in the infants with ROP compared to the infants without ROP, this value was found to be significantly higher in favor of the infants with ROP in the values of the first month when ROP developed. In the infants who developed ROP at birth, significantly low lymphocyte values can be evaluated as the lack of maturation in their immune systems at birth or due to corticosteroid treatment that the mother may have received prepartum, while the 1-month high values can be evaluated as a positive correlation between ROP and inflammation. There are studies revealing that mothers of infants with low birth weights and APGAR scores have significantly lower leukocyte counts in their cord blood.[22]

Neutrophils are among the most important components of the immune system in many infections, especially bacterial infections. When the neutrophil values in our study were examined, the difference was not significant in the infants with

Table 2: Comparison of stage 1 ROP (+) with advanced stage and APROP infants

	Stage 1 ROP	Advanced stage-APROP	*P*
WBC count at birth (x10⁹/L)	11±7	7.6±4.5	0.157
WBC count 1 month (x10⁹/L)	11±4	13±4	0.558
Platelet count at birth (x10⁹/L)	222±80	217±81	0.913
Platelet count 1 month (x10⁹/L)	360±136	324±199	0.034
Neutrophil count at birth (x10⁹/L)	5±5	3±4	0.491
Neutrophil count 1 month (x10⁹/L)	3±2	6±3	0.032
Lymphocyte count at birth (x10⁹/L)	4±3	3.5±2.5	0.580
Lymphocyte count 1 month (x10⁹/L)	5±2	4.1±1.6	0.130
Monocyte count at birth (x10⁹/L)	1.6±2.2	0.69±0.5	0.079
Monocyte count 1 month (x10⁹/L)	1.3 (IQR0.8)	1.8 (IQR1.9)	0.001
NLR at birth	0.68 (IQR1.1)	0.52 (IQR0.69)	0.652
NLR 1 month	0.56 (IQR0.79)	1.34 (IQR2)	0.001
PLR at birth	82±18	66±12	0.159
PLR 1 month	65.3 (IQR57)	58.6 (IQR102)	0.063
LMR at birth	15±3	8±1.6	0.008
LMR 1 month	2.3 (IQR2)	2.8 (IQR4)	0.000
SII at birth	120 (IQR269)	105 (IQR180)	0.953
SII 1 month	184 (IQR269)	411 (IQR717)	0.001

WBC; white blood cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio ; LMR: lymphocyte-to-monocyte ratio; SII; systemic immune-inflammation index. *P*<0.05, statistically significant

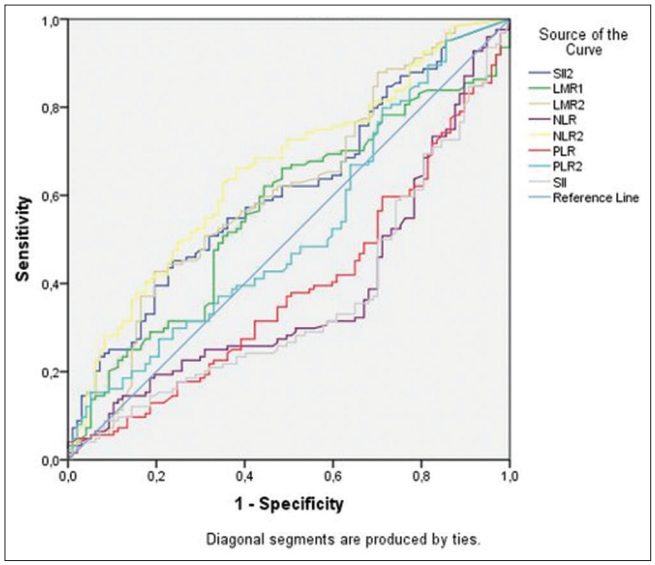

Figure 1: Receiver operating characteristics (ROC) analysis between groups and group 1 and 4

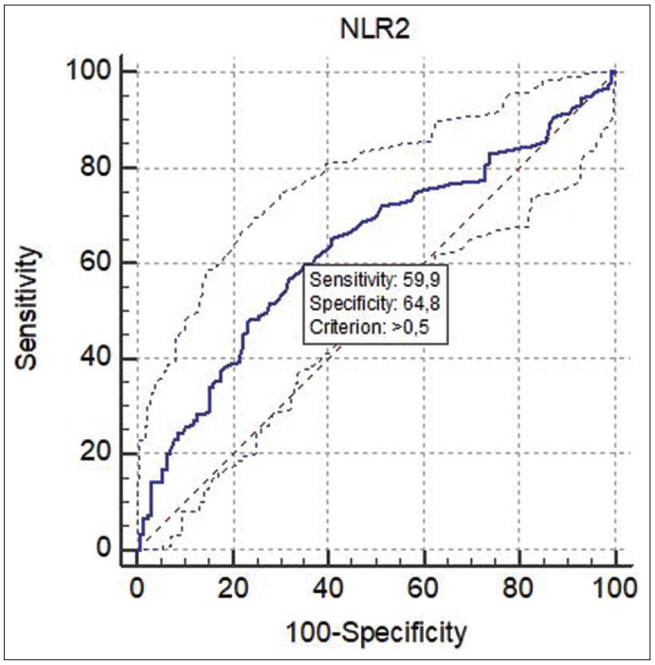

Figure 2: ROC analysis NLR2 between groups and group 1 and 4

and without ROP at birth, while the 1-month neutrophil count was significantly higher in the infants with ROP. It is known that systemic inflammation can increase the development of ROP by affecting retinal angiogenesis directly or indirectly. These values also support the close relationship between inflammation and ROP.

Today, the ratios of WBC cells such as NLR, LMR, and PLR have been suggested as a general inflammatory response in many diseases including retinal diseases.[11,16,23]

In the literature, it is suggested that age-related macular degeneration and diabetic retinopathy are associated with inflammatory indices calculated from complete blood count while this relationship is now fully known in ROP.[13,14] While some studies conducted on NLR reveal that NLR is not an independent determinant in the development of ROP, others suggest that low lymphocyte values in the first 24 hours of birth are determinant for ROP.[12] When the data of our study are analyzed, it is seen that WBC values were significantly lower in the infants with ROP at birth and the high level of these values in the period when ROP developed can be evaluated as the

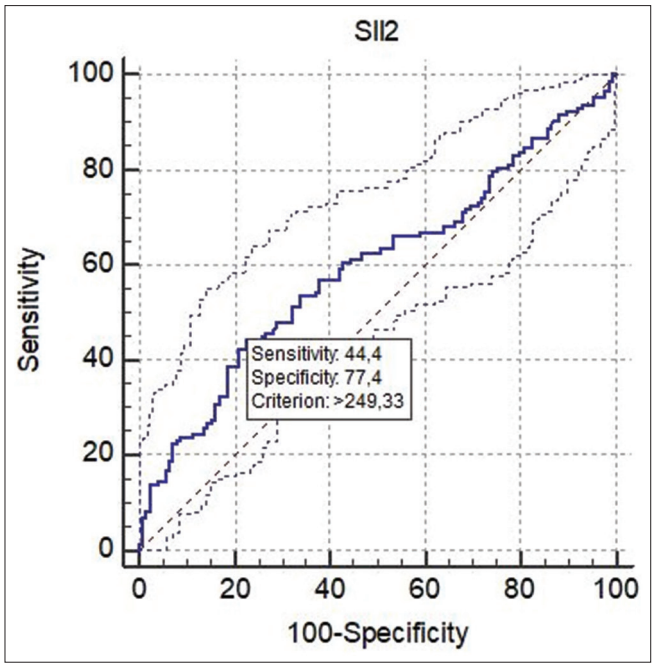

Figure 3: ROC analysis SII2 between groups and group 1 and 4

relationship between ROP and inflammation. Furthermore, the fact that in 1-month blood values, WBC values were higher in favor of the infants with ROP compared to the infants who did not develop ROP can be accepted as another finding showing the role of postnatal inflammation in the development of ROP. Recent studies also support this.[5,21,22,24-26]

Prenatal and postnatal inflammation-related risk factors for retinopathy of prematurity.[27]

Inflammatory factors such as cytokines, chemokines, growth factors, leukocytes, monocytes, and macrophages are implicated in the control of angiogenesis and contribute to the developing vasculature in ROP.[6,9,22,27]

Considering the WBC-related inflammation markers, when the NLR, LMR, and PLR values were examined in the infants with and without ROP at birth, LMR was high only in the infants who developed ROP at birth, and no significant difference was found in terms of other ratios. These values were found to be consistent with the literature.[11,12]

However, while NLR was significantly high in the infants with ROP in the 1-month period when ROP developed, PLR values were significantly low in favor of those with ROP. These values explain the development of inflammation and angiogenesis in ROP. Indeed, angiogenesis is regulated by pro-angiotic and anti-angiotic factors released locally from platelets. These factors play a critical role in the development of angiogenesis in ROP.[28] On the other hand, it is known that thrombocytopenia is associated with bacterial, fungal infection and necrotizing enterocolitis. MPV is a potential marker showing platelet activity. There are studies showing the relationship between increased MPV values of the infants at the advanced stage and with APROP and thrombocytopenia and APROP.[28]

Similar to Tao *et al*.[27] in our study, the difference between the number of platelets was not significant at birth, while in the 1-month period when ROP developed, the infants with ROP were found significantly lower than the infants without ROP. These values may be determinant for the place of platelets in angiogenesis, inflammation, and ROP development.[28]

In another study, Akyüz *et al*. found no difference in platelet counts between the ROP group (n = 99) and the non-ROP (n = 43) groups in the postnatal 4th week.[29]

As a result, postnatal inflammation-related factors were associated with severe ROP more strongly than prenatal factors. The association between prenatal inflammation-related factors and ROP was explained by earlier gestational age in infants exposed to prenatal inflammation.

The fact that this is a retrospective study is a limitation of this study. The second limitation of the study is the absence of any other parameters related to inflammation, such as CRP, in the files of the infants. In addition, the hemogram values were obtained for clinical indications unrelated to the study that may lead to selection bias. It is not possible to determine whether the marker levels evaluated in our study caused ocular changes or related to the systemic condition of the babies which further affects the development of ROP.

Supporting these data with prospective controlled studies will strengthen this study.

Conclusion

In the light of our data, WBC ratios such as NLR, LMR, PLR and especially monthly SII values that we obtained can be accepted as independent predictors of the development of ROP.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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