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ORIGINAL ARTICLE

Association between Platelet to Lymphocyte ratio and Intraventricular hemorrhage in extremely immature infants

İleri derecede immatür bebeklerde Trombosit Lenfosit oranı ile İntraventriküler kanama arasındaki ilişki

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ABSTRACT

Aim: Intraventricular hemorrhage (IVH) is a serious complication of premature births, especially in newborns with very low birth weight. It's important to be able to predict IVH. In this study, the relationship between thrombocyte lymphocyte ratio (TLR) and intraventricular hemorrhage in premature infants born under 28 weeks was examined.
Materials and Methods: In the last 5 years, the medical records of infants with less than 28 weeks of gestational age (n=78) born in our hospital have been retrospectively examined. Obtained parameters from the whole blood count, especially the relationship between TLR and IVH were examined.
Results: White blood cell and lymphocyte counts were significantly higher in severe IVH (grade 3-4), while TLR was found to be significantly lower (16048±5265 & 11972±10915, p=0.043; 10705±4537 & 6329±8101, p=0.007; 36.9±22.7 & 56.7±37.9 p=0.012, respectively). When the white blood cell, lymphocyte count, and TLR's diagnostic performance in predicting severe IVH were evaluated by ROC curve analyses, it was observed that the strongest performance belonged to the TLR (Area under the curve, AUC for WBC: 0.644; ALS: 0.687; TLR: 0,691, respectively). TLR can estimate severe IVH with 94% sensitivity and 43% specificity at a cut-off value below 55.84.
Conclusion: TLR can be used as a valuable marker for predicting IVH in extremely premature infants.

Keywords: Intraventricular hemorrhage; platelet lymphocyte ratio; premature infants.

ÖZ

Amaç: İntraventriküler hemoraji (IVH), özellikle çok düşük doğum ağırlıklı yeni doğanlarda prematüre doğumların ciddi bir komplikasyonudur. IVH'yi tahmin edebilmek oldukça önemlidir. Bu çalışmada 28 hafta altında doğan prematüre bebeklerde doğumda bakılan trombosit lenfosit oranı (TLO) ve intraventriküler hemoraji (IVH) arasındaki ilişki incelenmek istenmiştir.
Gereç ve yöntem: Son 5 yılda hastanemizde yatan 28 hafta altı prematüre bebeklerin (n=78) dosyaları geriye dönük incelendi. Doğum sonrası bakılan tam kan verilerinden elde edilen parametreler ve özellikle TLO ve IVH arsındaki ilişki incelendi.
Bulgular: Beyaz küre ve lenfosit sayıları ciddi IVH'de (grade 3-4) anlamlı yüksek bulunurken, TLO anlamlı düşük bulunmuştur (sırasıyla 16048±5265 & 11972±10915, p=0,043; 10705±4537 & 6329±8101, p=0,007; 36,9±22,7 & 56,7±37,9 p=0,012). Beyaz küre, lenfosit sayısı ve TLO'nun ciddi IVH'i öngörmede tanısal performansları ROC eğrisi analizleri ile değerlendirildiğinde en güçlü performansın TLO'ya ait olduğu gözlemlendi (sırasıyla eğri altında kalan alan WBC: 0,644; ALS: 0.678; TLO:0,691). TLO kesme değeri 55,84 altındaki değerlerde %94 sensitivite ve %43 spesifite ile ağır IVH'i tahmin ettirebilir.
Sonuç: TLO ileri derecede immature bebeklerde ciddi IVH'iöngörmede değerli bir belirteç olarak kullanılabilir.

Anahtar kelimeler: Intraventriküler kanama; Trombosit lenfosit oranı; prematüre

Introduction

Intraventricular hemorrhage (IVH) is one of the most important complications of this high-risk group, causing mortality and long-term sequelae in severely immature infants. In studying the etiology of IVH, it is known to be multifactorial (1) and related to both prenatal and postnatal factors (2). The occurrence of IVH may be due to many environmental and medical risk factors. These include assisted reproductive techniques (IVF), non-administration of antenatal steroids, antenatal maternal bleeding, maternal medical risk factors, chorioamnionitis, external birth, prematurity/low birth weight, low APGAR scores, male gender, early sepsis, hypoxemia, hypercapnia, hypocapnia, pneumothorax, pulmonary hemorrhage, respiratory distress syndrome (RDS), and treatment with vasopressors (3-6). TLR is an indicator of the balance between inflammation and thrombosis. Inflammatory conditions in the body lead to increased production of megakaryocytes and associated thrombocytosis. Furthermore, it is recognised that increased platelet counts and

decreased lymphocyte counts are associated with both aggregation and inflammation and are therefore risk indicators for inflammation (7-10). Lymphopenia is common in childhood and the neonatal period and can be included among the etiologic factors under the main headings such as infections, genetic causes, iatrogenic causes, and systemic diseases. A lymphocyte count of less than 2500 /mm3 in the neonatal period is generally considered lymphopenia (18).

Whole blood indices related to platelets, which are indicators of inflammation in the neonatal period, have been evaluated in relation to neonatal and especially preterm morbidities. There are studies suggesting that there is an association between platelet-related markers including platelet mass index, mean platelet volume and IVH (11).
Here, TLR was calculated in whole blood samples collected at the first hospitalization of preterm infants younger than 28 weeks, and the relationship between IVH was to be investigated.

Materials and Methods

This single-centre, retrospective study was conducted at Başkent University, Konya Application and Research Centre, Konya, Turkey. This study was approved by the Ethics Committee of Başkent University (project number: KA19/70). The medical records of 78 preterm low birth weight infants treated in the neonatal intensive care unit of our hospital during the last 5 years were retrospectively reviewed. Preterm infants with a gestational age of less than 28 weeks and a birth weight of less than 1200 g were included in the study.

Clinical data and demographic information, including week of gestation, sex, weight; prenatal steroid administration, respiratory distress syndrome (RDS), oxygen consumption days; bronchopulmonary dysplasia (BPD), maximum oxygen demand in the first three days of life, intraventricular hemorrhage; hemodynamically significant patent ductus arteriosus, complete blood count on admission, parenteral nutrition days, necrotizing enterocolitis (NEC); The incidence of sepsis and ROP and length of hospital stay were obtained from the medical records of the admitted infants. Patients admitted to the neonatal intensive care unit later than the third day of life, infants with genetic anomalies and other severe congenital malformations were excluded from the study. Infants included in the study underwent cranial usg by postnatal day 7 (usually postnatal day 3) and were classified into grades 1-4 according to the Papilla classification (12). Grade 1: bleeding from germinal matrix, Grade II: intraventricular hemorrhage, Grade III: intraventricular hemorrhage and dilatation, Grade IV: intraventricular and intraparenchymal hemorrhage. Of the 78 cases, 7 cases were not included in the study due to lack of data on early exitus and IVH. A total of 71 cases were divided into 2 groups, one group with severe IVH (grade 3-4, n=17) and the other group with mild IVH or no IVH (grade 1-2 or no IVH, n=54). TLR and neutrophil-to-lymphocyte ratio (NLR) were calculated from complete blood count data on day 1.

Descriptive statistics of scale variables are presented as mean ± standard deviation (SD) or median (range), as appropriate. Demographic and clinical continuous variables were compared using 2 independent T tests for normally distributed values and the Mann-Whitney U test for nonnormally distributed values. Parameters that did not conform to the normal distribution were transformed to the normal distribution using the two-step approach defined by Garry Templeton (13). Z-scores for kurtosis and skewness and Kolmogorov-Smirnov statistics were used to determine whether continuous variables were normally distributed. Categorical variables were compared using the Fisher'sExact test. ROC (Reciever operating charactheristic) curves and area under the curve were evaluated to assess the diagnostic performance of complete blood count values and indices for IVH. Optimal cut-off values were calculated by the Youden method using the web-based interactive system developed by Goeksulluk Göksulluk et al (17). The statistical significance level was set as $p < 0.05$ for all tests. SPSS (Chicago, Illinois, USA) version 26 was used for all data analyses.

Results

Data were collected from a total of 78 cases under 28 weeks. The mean gestational week and birth weight were 26.1 ± 1.2 weeks and 844 ± 206 grams, respectively. 52% of the cases were female and 48% were male. When examined for IVH, the data of 7 cases could not be obtained due to death or other reasons. There were 17 cases in the group with severe IVH and 54 cases in the other group. There were no significant differences between the groups in terms of gestational week, birth weight, sex, mode of delivery, administration of surfactant and antenatal steroids (Table 1). On evaluation of intubation status, it was found that intubation rate was higher in the group with severe IVH, however this was not statistically significant (47% & 33%). However, it was found that the intubation time was significantly longer in the severe IVH group than in the mild IVH group (5(0-21) & 1.5 (0-51), p=0.031). This statistical difference was considered an effect rather than a cause. There was no difference between groups in duration of nasal Cpap use, total time of oxygen exposure, maximum oxygen demand in the first 3 days, and total length of hospital stay. The mortality rate was slightly higher in the severe IVH group (47% & 25%), although there was no statistically significant difference between the groups. There was no difference in neonatal early and late morbidities between groups in terms of ROP requiring laser treatment, advanced stage NEC and BPD at any stage, while hemodynamically significant PDA was about three times more common in the severe IVH group (62.5% & 26.9%.) p=0,016) (Table 1). When complete blood count parameters were examined on the first day of admission, no difference was observed between the groups in terms of absolute neutrophil count (ANC), hemoglobin levels, neutrophil to lymphocyte ratio (NLR) and platelet count. While

white blood cell count (16048±5265 & 11972±10915, p=0.043) and absolute lymphocyte count (ALC) (10705±4537 & 6329±8101, p=0.007) were significantly higher in the severe IVH group, TLR was significantly lower in the severe IVH group (36.9±22.7 & 56.7±37.9; p=0.012) (Table 2). The diagnostic performance of whole blood parameters WBC, ALC and TLR in predicting severe IVH was evaluated by ROC curve analysis. When the diagnostic performance of white blood cell, lymphocyte count and TLR in predicting severe IVH was evaluated by ROC curve analyzes, the strongest performance was observed for TLR (area under the curve AUC: WBC: 0.644 (95% CI: 0.520-0.768) ; ALS: 0.687(95% CI: 0.563-0.811); TLR: 0.691(95% CI: 0.562-0.820)) (Table 3). According to the analysis of ROC, values below the cut-off value of 55.84 for TLR were considered predictive of severe IVH with a sensitivity of 94% and a specificity of 43% (Figure 1).

Figure 1: ROC curve showing the diagnostic performance of TLR values in predicting severe IVH

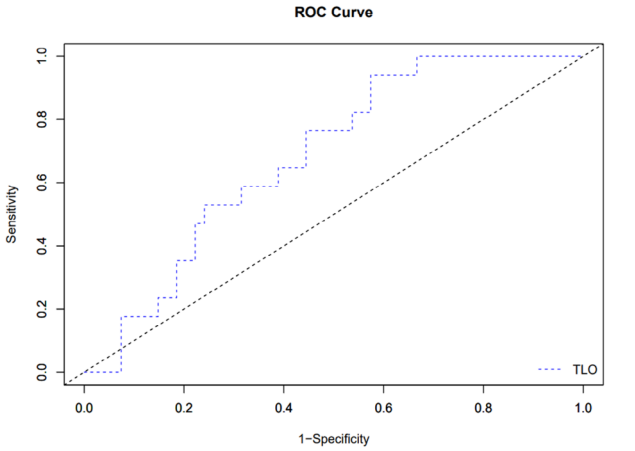

Figure caption: Area under the curve AUC: 0.691 (CI 95 %: 0.562-0.82) Optimal cut-off value: 55.84; sensitivity: %94, specificity: %43.

Discussion

While IVH is primarily responsible for the increase in mortality in extremely low birth weight preterm infants, it is associated with neurological deficits that can affect lifelong social life in surviving cases. This study shows a moderate correlation between TLR, calculated from first admission blood, and severe IVH (grade 3-4) in low birth weight infants. Because it helps predict which infants are more likely to have severe IVH, it will help clinicians provide these patients with better hemodynamic balance that can influence IVH, control fluctuations in cerebral perfusion pressure, and take additional measures to maintain optimal blood gas parameters.

In a recent study investigating the risk factors for IVH, 495 preterm infants less than 29 weeks of age were studied, and it was found that the rate of IVH at any stage was 24.4%, while the rate of severe IVH was reported to be 9.7% (14). In our study, the rate of severe IVH was 23.9% (17/71) in our group of patients. We think that this high rate is related to inadequate perinatal care and high number of outpatient admissions in our unit. While the mean gestational week and birth weight of the severe IVH group were similar to our study, it was observed that the antenatal steroid rates in our study group were quite low (41% & 66%) compared to this study. This study mainly investigated the risk factors related to the association between IVH and PDA treatment. They showed that medical treatment of PDA with indomethacin in the early phase significantly reduced severe IVH, although the association with whole blood indices was not studied. Similarly, in our hospital, we start medical management of hemodynamically significant PDA by echocardiographic examination of preterm infants between the postnatal 48-72 hours before the appearance of clinical findings. In our study group, hemodynamically significant PDA was observed about 3 times more frequently in the group with severe IVH than in the group without IVH. This and, as evidenced by our study, the association between hemodynamically significant PDA and IVH is related to fluctuations in cerebral perfusion pressure and a phenomenon called steal phenomenon. At patient admission, cases with a TLR value below the cut-off value are considered to be at high risk of IVH, and approaches may be brought to the fore by earlier evaluation of echocardiography or prophylactic PDA closure treatments. There are also significant associations between prenatal steroids and hemodynamically significant PDA. Better postnatal lung development, lower surfactant requirements, less or shorter intubation, better oxygenation, better blood gas levels, and less hemodynamically significant PDA are observed in patients given prenatal steroids. The cumulative result of these data can be interpreted as better hemodynamics. When studies examining the relationship between TLR and intracranial hemorrhage were reviewed in the literature, it was found that high TLR levels were associated with worsening Glasgow Coma Scale scores and neurological impairment in a study conducted in adult patients. The authors explained the underlying scientific fact by proposing that secondary brain damage after cerebral hemorrhage is associated with inflammation (15). The need for numerous external interventions (central line, intubation, and surfactant applications) for preterm infants to be open to infection and survive leaves this fragile population alone with inflammation and cytokines. The difference between our study and this study is that the TLR of our patients was lower in the group with severe IVH. This could be related to the different bone marrow responses of preterm infants to inflammation, or to the predominance of lymphocytes in the complete blood count in the first 4 years of childhood, or to the higher likelihood of low platelet levels in preterm infants compared with adults. Also, in a study examining neonatal outcomes in preterm infants with maternal TLR, it was found that mothers with high prenatal maternal TLR levels had a higher rate of delivery of infants less than 1500 g and a higher rate of intracranial hemorrhage in preterm infants. Although the prenatal blood results of the mothers of our babies were not included in our

Table 1: Baseline characteristics of the groups

	Grade 3-4 IVH	No IVH or Grade 1-2	P value
GW; Mean. ±SD	25,94± 1,144	26,44± 1,144	,118
BW; Mean. ±SD	838,24 ±160	884,72 ±198	,384
Sex; male, n (%)	9(52,9)	25(46,3)	,782
Delivery mode; C/S, n (%)	13(76,5)	44(81,5)	,730
Antenatal steroid use; n (%)	7(41,2)	22(40,7)	1
Surfactant application; n (%)	15(88,2)	51(94,4)	,587
Intubation rate, n (%)	8(47,1)	18(33,3)	,389
Intubation duration; median (min-max)	5(0-21)	1,5(0-51)	**,031**
Max Fio2 requirement first 3 DOL, median (min-max)	40(23-90)	35(25-100)	,131
O2 duration median (min-max)	21(4-153)	43,5(2-286)	,427
Cpap duration, median (min-max)	10(0-40)	14(0-59)	,331
Exitus n (%)	8 (47,1)	14 (25,9)	,134
Hospital stay length (min-max)	56(4-153	63,5 (1-190)	,582
HsPda, n (%)	10(62,5)	14(26,9)	**,016**
Culture proven sepsis, n (%)	8(47,1)	26 (48,1)	1
Laser requiring ROP n (%)	5 (41,7)	8(19,5)	,140
BPD any stage; n (%)	8 (80)	36(87)	,612
Advanced stage NEC; n (%)	4(23,5)	11(20,4)	,745

Abbreviations: IVH: Intraventricular hemorrhage; **GW**: gestational week; **BW**: Birth weight; **Cpap**: Continuous positive airway pressure; **HsPDA**: Hemodynamically significant patent ductus arteriosus; **ROP**: Retinopathy of prematurity; **BPD**: Broncopulmonary dysplasia; **NEC**: Necrotizing enterocolitis

Table 2: IVH and complete blood count parameters on first admission

	Grade 3-4 IVH	No IVH or Grade 1-2	P value
Transformed WBC; Mean ± SD	16048± 5265	11972± 10915	**,043**
Hgb Mean ± SD	15,8±2,5	16,7±2,4	,162
Transformed ANC Mean ±SD	3652±4904	4072±5411	,777
Transformed ALC Mean ±SD	10705±4537	6329±8101	**,007**
Transformed NLR Mean ±SD	0,69±1,1	0,90±1,4	,583
Transformed TLR Mean ±SD	36,9±22,7	56,7±37,9	**,012**
Transformed PLT Mean ±SD	212490±53417	230915±51058	,205

Abbreviations: **IVH**: Intraventricular hemorrhage; **WBC**: White blood cell; **ALC:** Absolute lymphocyte count; **TLR:** Thrombocyte lymphocyte ratio; **ANC**: Absolute neutrophil count; **NLR**: Neutrophil to lymphocyte ratio; SD: Standard deviation

Table 3: ROC (Receiver operating Curve) analysis results showing the diagnostic performance of WBC, ALS and TLR variables in predicting Grade 3-4 IVH

Area Under the Curve						
Test Result Variable(s)	Area	Std. Error a	Asymptotic Sig.b	Asymptotic 95% Confidence Interval		
				Lower Bound	Upper Bound	
N_dist_WBC	0,644	0,063	0,076	0,52	0,768	
N_dist_ALS	0,687	0,063	0,021	0,563	0,811	
N_dist_TLO	0,691	0,066	0,019	0,562	0,82	

Abbreviations: **WBC:** White Blood Cell; **ALC:** Absolute lymphocyte count; **TLR:** Thrombocyte lymphocyte ratio.

data set, maternal inflammation (chorioamnionitis) may have caused changes in the postnatal blood count and TLR may be a postnatal reflection of the prenatal events. In the intrauterine period, mother and child are one unit, prenatal situations cause transient and permanent changes in many infants. Affecting the fetus is considered as a part of the systemic inflammatory response syndrome. Maternal diabetes, chorioamnionitis and premature rupture of membranes can be given as examples. Looking at the studies on antenatal events and neonatal outcomes in the literature, conditions such as maternal chorioamnionitis are known to be responsible for preterm birth and neonatal sepsis in the short postnatal period and bronchopulmonary dysplasia, periventricular locomalacia and cerebral palsy in the long term (19).

In their study investigating the correlation between maternal whole blood parameters and neonatal whole blood parameters, Akgün et al. evaluated the results of 783 pregnant women who had no maternal risk factors and they showed that there was a negative correlation between maternal TLR, delivery week and birth weight (20). Although the relationship between maternal whole blood data and infant whole blood data was not evaluated in this study, the correlation between maternal TLR and birth weights and birth weeks suggests that an inflammatory process induces labor and causes preterm birth and low birth weights. We also did not analyze maternal whole blood data in our study, but we found a weak positive correlation between birth week and birth weights and TLR. The association between antenatal steroid use and TLR was not statistically examined because studies were generally not included more studies or as exclusion criteria because of concerns that antenatal steroid use might have an impact on whole blood indices. However, in our data set, we found no statistical difference between the first day TLR of babies whose mothers received a full dose of antenatal steroid and those whose mothers did not. The lack of this difference could be related to the intrauterine environment, stress, and active maternal steroidogenesis causing preterm birth of very immature babies in our study group. Studies in which maternal steroid hormone levels are also measured and maternal adrenocortical hormone biosynthesis can be assessed are needed to evaluate this relationship.

The relationship between other whole blood indices such as MPV, plateletcrit (thrombocrit), platelet mass index, PDW and morbidity in preterm infants less than 32 weeks was studied (16). It was found that the thrombocyte parameters can be a significant indicator for the assessment of IVH stage. We did not measure plateletcrit in our study, but we found no similar significant difference between severe and mild IVH in terms of platelet count, one of the platelet parameters studied.

Considering the important aspects and limitations of the study: first, we could not find any study that investigated the association between TLR and severe intracranial hemorrhage in extremely premature infants. We think that this aspect is important. The limitations are the inability to perform logistic regression modeling to determine risk factors and the inability to understand whether TLR is an independent risk factor because it is a retrospective study with a small sample size and only 17 cases of severe IVH.
Consequently, TLR values measured on the first day of patient admission are a useful and cost-effective indicator that can be used to predict severe IVH in extremely preterm infants less than 28 weeks. If clinicians can predict severe IVH, they should also be more careful not to expose highly fragile immature babies to additional risks that may affect intracranial hemorrhage, such as hemodynamic instability, uncontrolled carbon dioxide fluctuations in blood gas. To understand whether TLR is an independent risk factor for predicting severe IVH in extremely immature infants, well-designed, prospective, randomized, large-scale, multicenter, guideline-based studies are needed in which hemodynamic monitoring and respiratory management are regulated with strict protocols, especially in the first 3 days of life which IVH is frequently observed.

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