ORIGINAL RESEARCH

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Evaluation of Neutrophil/Lymphocyte and Thrombocyte/Lymphocyte Ratios in Cases of Preterm Premature Rupture of Membranes

Preterm Prematür Membran Rüptürü Olgularında Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranlarının Değerlendirilmesi

Yağmur Özkan[1], Simten Genç[2], Yücel Kaya[3], Damla Yenlik Kaya[4], Veli Mihmanlı[2]

[1]Bahçelievler State Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Perinatology, Antalya, Turkey
[4]İstanbul Medipol University, Health Care Practice and Research Center, Esenler Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

Objective: There is no daily practical method for the diagnosis and follow-up of premature rupture of membranes (PPROM). In this study, we examined the association between PPROM and platelet/lymphocyte (PLR) and neutrophil/lymphocyte (NLR) ratios.

Method: Eighty women with a diagnosis of PPROM between the 24th and 34th weeks of gestation were included in the study. Eighty-three women without membrane rupture between the same gestational weeks constituted the control group. Information about the women included in the study was collected retrospectively from hospital medical records. For each patient, gravida, parity, age, week of gestation, week of birth, and mode of delivery were examined. To evaluate perinatal outcomes, sex, 1st and 5th minute Apgar scores, birth weight, and neonatal death were examined. The patients' white blood cells, lymphocyte neutrophil, and platelet counts, PLR, NLR ratios, hemoglobin, and C-reactive protein values were examined.

Results: The mean NLR of the PPROM group was 30.96±2.55 [mean ± standard deviation (SD)] and mean PLR was 148.06±72.18 (mean ± SD). In the control group, these values were calculated as 30.91±2.43 (mean ± SD) and 126.74±45.85 (mean ± SD), respectively. Both rates were higher in the PPROM group (p=0.026).

Conclusion: PLR and NLR ratios were higher in the study group. Therefore, PLR and NLR can be used in the management of PPROM.

Keywords: Neutrophol/lymphocyte ratio, platelet/lymphocyte ratio, preterm premature rupture of fetal membranes

Öz

Amaç: Preterm prematür membran rüptürü (PPROM) tanı ve takibinde günlük pratik bir yöntem bulunmamaktadır. Biz çalışmamızda PPROM ile platelet/lenfosit (PLR) ve nötrofil/lenfosit (NLR) oranları arasındaki ilişkiyi incelemeyi amaçladık.

Yöntem: PPROM tanısı alan 24-34 gebelik haftaları arasında olan 80 kadın çalışmaya dahil edildi. Kontrol grubunu ise aynı haftalar arasındaki 83 sağlıklı gebe oluşturdu. Çalışmaya katılan kadınlara ait bilgiler retrospektif olarak hastanenin tıbbi kayıtlarından elde edildi. Her hastanın yaşı, gravidası, paritesi, gebelik haftası, doğum haftası ve doğum şekli incelendi. Perinatal sonuçları değerlendirmek için cinsiyet, 1. ve 5. dakika Apgar skorları, doğum ağırlığı ve yenidoğan ölümü incelendi. Hastaların beyaz kan hücresi, lenfosit, nötrofil ve trombosit sayıları, nötrofil/lenfosit, trombosit/lenfosit oranları ve hemoglobin, C-reaktif protein değerlerine bakıldı.

Bulgular: PPROM grubunun ortalama NLR'si 30,96±2,55 [ortalama ± standart sapma (SS)] ve ortalama PLR'si 148,06±72,18 (ortalama ± SS) idi. Kontrol grubunda ise bu değerler sırasıyla 30,91±2,43 (ortalama ± SS) ve 126,74±45,85 (ortalama ± SS) olarak hesaplandı. Her iki oran da PPROM grubunda daha yüksekti (p=0,026).

Sonuç: PLR ve NLR oranları çalışma grubunda anlamlı derecede yüksekti. Bu nedenle PPROM'nin yönetiminde NLR ve PLR kullanılabilir.

Anahtar kelimeler: Nötrofil/lenfosit oranı, platelet/lenfosit oranı, preterm prematür membran rüptürü

Address for Correspondence: Yağmur Özkan, Bahçelievler State Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
E-mail: yagmurolmez92@hotmail.com **ORCID:** orcid.org/0000-0003-0568-9575 **Received:** 19.01.2024 **Accepted:** 11.02.2024

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Introduction

Premature rupture of membranes (PPROM) is the loss of amniotic fluid due to damage to the chorioamniotic membranes before labor begins. If this condition occurs before the 37th week of pregnancy, it is referred to as preterm PPROM (1). The week of gestation at birth is inversely proportional to neonatal morbidity and mortality (2). Although the main causes of preterm birth include PPROM, preterm birth due to maternal or fetal indications, and multiple pregnancies, the cause of some preterm births cannot be explained. PPROM causes 30-35% of all preterm births (3). Preterm birth is the most frequently observed cause of neonatal morbidity and mortality. Approximately 560,000 preterm births occur in the USA every year, and approximately 150,000 preterm births are complicated by PPROM (2). PPROM has a complex pathophysiology that includes inflammation and oxidative stress. Although there are many factors that increase the risk of PPROM, the reason for this is not fully understood.

Fetal membranes act as a barrier against the ascending infection. When fetal membranes are damaged, both the mother and fetus are at risk of infection and other complications. Major maternal complications include chorioamnionitis, placental abruption, and cord prolapse. In PPROM, intraamniotic infection develops at a rate of 13-60% and postpartum endometritis develops at a rate of 2-13% (4). The most important factor in neonatal complications is the gestational age. Polymicrobial intraamniotic infection, which occurs in 15-30% of patients with PPROM, has been associated with 3-20% neonatal death and intraventricular hemorrhage (IVH). Severe oligohydramnios that develop in PPROM cause an increase in the incidence of cord compression at birth and unreliable fetal tests, leading to a further increase in the risk of birth by cesarean section. Factors such as infection and cord accidents carry a 1-2% risk of intrauterine fetal death (5). Although respiratory distress syndrome is the leading complication of PPROM, necrotizing enterocolitis, IVH, and sepsis are other important causes of morbidity (6).

The clinical evaluation and management approach for patients with PPROM is controversial. Management is based on the assessment of gestational age, relative risks of delivery, and possible complications of the expectant approach (1). Although tests such as the fern test, nitrazine test, and Amnisure are available to confirm the diagnosis of PPROM, no method is available to reliably predict PPROM (3). Many studies have been conducted to evaluate fetal well-being by measuring inflammatory mediators in amniotic fluid and cervicovaginal secretions and maternal blood. There is still no practical method suitable for daily monitoring. The use of markers such as C-reactive protein (CRP) and white blood cell count remains controversial. Complete blood count is a cheap and simple laboratory test. It has been shown in many studies that platelet increase in peripheral blood is associated with inflammatory conditions, various malignancies, and infections. Recently, platelet/lymphocyte (PLR) and neutrophil/lymphocyte (NLR) ratios have been identified as new markers associated with poor outcomes in various pathological conditions (7). The goal of this study was to evaluate the usability of PLR and NLR ratios as markers for the diagnosis and follow-up of PPROM.

Materials and Methods

Between April 2017 and April 2021, 196 patients between 24 and 34 weeks of gestation at the University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Gynecology and Obstetrics Clinic were included in the study. Twenty of these patients were excluded from the study because of chronic hypertension and preeclampsia, 10 because of diabetes mellitus, and 3 because of active systemic infection. Eighty women diagnosed with PPROM formed the study group, and 83 healthy women between 24 and 34 weeks of gestation who were not diagnosed with PPROM formed the control group.

Data on the patients were obtained by retrospectively scanning the patient files and the hospital electronic information system. Patients with maternal chronic diseases, such as diabetes mellitus, hypertension, and preeclampsia, were not included in the study because they may affect the neutrophil, lymphocyte, and platelet values investigated. For each patient, age, gravida, parity, week of gestation, week of birth, and mode of delivery were examined. To evaluate perinatal outcomes, birth weights, gender, 1st and 5th minute Apgar scores, and neonatal mortality were examined. The patients' white blood cell, neutrophil, lymphocyte, and platelet counts, neutrophil/lymphocyte, PLR ratios, hemoglobin, and CRP values were examined. Laboratory values during hospitalization were included in the study to ensure that the treatments applied did not change the data.

Statistical Analysis

In the evaluation of the data, in addition to descriptive statistical methods [mean, standard deviation (SD), median, interquartile range], the distribution of the variables was examined using the Shapiro-Wilk normality test. The independent t-test was used to compare pairwise groups of

variables with normal distribution, and the Mann-Whitney U test was used to compare pairwise groups of variables that did not show a normal distribution. The chi-square test was used to compare qualitative data. Univariate and multivariate logistic regression analyses were performed to separate the effective factors in the presence of PPROM. For the differential diagnosis of the presence of PPROM, the areas under the ROC curve were calculated, and the sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of the variables were determined. The results were evaluated at a significance level of $p<0.05$.

Results

In total, 163 patients were examined in our study. Eighty three patients constituted the control group and 80 patients constituted the PPROM group. The mean maternal age was 27.43±6.71 (mean ± SD) in the PPROM group and 27.99±5.79 (mean ± SD) in the control group. It was not found that there was a difference in groups in gravida and parity values. The mean gestational week in the PPROM group was 30.91±2.5 (mean ± SD). In addition to the mean week of birth being significantly lower in the study group (p=0.001), cesarean deliveries were more frequent in this group (p=0.0001). The 1st and 5th minute Apgar scores and average newborn weight were observed to be lower in the PPROM group (p=0.0001) (Table 1).

No significant difference was found when the hemoglobin, platelet, lymphocyte, and CRP values were examined. The mean leukocyte count was 11.49±3.04 (mean ± SD) in the PPROM group and 10.34±1.77 (mean ± SD) in the control group, and this difference was significant (p=0.004). While the mean neutrophil count of the study group was 8.93±2.87 (mean ± SD), it was calculated as 7.66±1.79 (mean ± SD) and similarly, this difference was also significant (p=0.001) (Table 2).

Table 1. Baseline demographic features and distribution of patients between PPROM (-) and PPROM (+)

		PPROM (-)		PPROM (+)		p
Age	Mean ± SD	27.99±5.79		27.43±6.71		0.574
Gravidity	Mean ± SD	2.32±1.44		2.62±1.66		0.330
	Median (IQR)	2 (1-3)		2 (1-4)		
Parity	Mean ± SD	0.98±1.11		1.15±1.34		0.666
	Median (IQR)	1 (0-1)		1 (0-2)		
Gestation week	Mean ± SD	30.96±2.43		30.91±2.5		0.899
Birth week	Mean ± SD	36.17±2.75		32.07±2.69		0.0001
Type of birth	**Vaginal**	43	53.09%	26	32.10%	**0.007**
	C/S	38	46.91%	55	67.90%	
Birth weight	Mean ± SD	2820.74±629.73		1925.63±593.41		**0.0001**
Gender	**Boy**	44	54.32%	43	53.09%	0.875
	Girl	37	45.68%	38	46.91%	
1st minute Apgar score	Mean ± SD	7.36±1		6.38±1.39		**0.0001**
5st minute Apgar score	Mean ± SD	8.72±0.76		8.07±1.1		**0.0001**

PPROM: Premature rupture of membranes, SD: Standard deviation, IQR: Interquartile range

Table 2. Laboratory values of the patients

		PPROM (-)	PPROM (+)	p
Hemoglobin	Mean ± SD	11.18±1.47	11.31±1.3	0.575
Leukocyte	Mean ± SD	10.34±1.77	11.49±3.04	**0.004**
Platelet	Mean ± SD	226.8±54.49	235.1±63.37	0.373
Neutrophil	Mean ± SD	7.66±1.79	8.93±2.87	**0.001**
Lymphocyte	Mean ± SD	1.92±0.58	1.91±1.09	0.416
	Median (IQR)	1.8 (1.5-2.28)	1.82 (1.28-2.32)	
CRP	Mean ± SD	9.75±13.5	17.68±35.93	
	Median (IQR)	6.49 (3.07-10.11)	7.56 (4.06-15.11)	0.168

PPROM: Premature rupture of membranes, SD: Standard deviation, IQR: Interquartile range, CRP: C-reactive protein

When the NLR and PLR values of both groups were calculated, the mean NLR of the PPROM group was 30.96±2.55 (mean ± SD) and the mean PLR was 148.06±72.18 (mean ± SD). In the control group, these values were calculated as 30.91±2.43 (mean ± SD) and 126.74±45.85 (mean ± SD), respectively. Both rates were significantly higher in the PPROM group (p=0.026) (Table 3).

In the differential diagnosis of PPROM positivity, the area under the ROC curve of the NLR variable was 0.599 (0.519-0.675) and that of the PLR variable was 0.582 (0.502-0.659) (Figure 1).

While the cut-off value of the NLR variable was above 7.3, the sensitivity was determined to be 39.63, and the specificity was 95.06. When the cut-off value of the PLR variable was above 165, its sensitivity was 30.86 and its specificity was 87.65 (Table 4).

Discussion

PPROM is one of the most common causes of preterm birth, with serious maternal and fetal complications. Today, premature birth still has an important place in neonatal mortality and morbidity. Although the pathogenesis of PPROM is not clearly clear, factors such as maternal infection, genetic conditions, smoking, and maternal chronic diseases are blamed. The best method for detecting intrauterine infection is amniocentesis. However, amniocentesis is an invasive method and may result in various procedure-related complications, such as a 0.5% risk of fetal loss. Therefore, non-invasive methods are required. Different studies have shown that PLR and NLR have prognostic and predictive importance in various diseases, including preeclampsia and gynecological malignancies (8,9).

The major findings of our study are as follows: (1) The mean PLR, NLR, and cesarean deliveries were higher in the PPROM group (2). The 1st and 5th minute APGAR scores were lower in the PPROM group (3). There was not difference between the CRP values of both groups.

Toprak et al. (10) investigated the relationship between PPROM and PLR and NLR values in 96 pregnant patients with spontaneous preterm labor and 121 pregnant patients with PPROM. They did not detect any significant difference between the two groups in terms of age, gravida, parity, gestational week, and lymphocyte values, similar to our study. Again, in this study, they found that the mean NLR was higher in the PPROM group and that there was a relationship between the increase in PLR values and neonatal complications (10). In our study, we also found

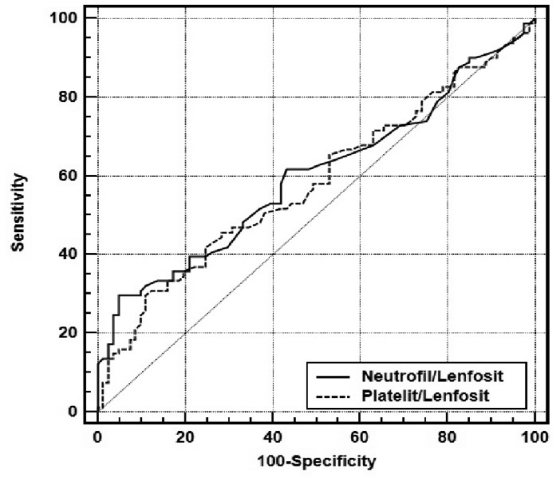

Figure 1. ROC curve in terms of NLR and PLR in the diagnosis of PPROM

PPROM: Premature rupture of membranes, NLR: Neutrophil/lymphocyte, PLR: Platelet/lymphocyte, ROC: Receiver operating characteristic

Table 3. NLR and PLR values of the patients

		PPROM (-)	PPROM (+)	p
NLR	Mean ± SD	30.91±2.43	30.96±2.55	**0.029**
	Median (IQR)	3.9 (3.25-5.15)	4.62 (3.2-7.9)	
PLR	Mean ± SD	126.74±45.85	148.06±72.18	**0.026**

PPROM: Premature rupture of membranes, SD: Standard deviation, IQR: Interquartile range, NLR: Neutrophil/lymphocyte, PLR: Platelet/lymphocyte

Table 4. NLR and PLR cut-off points

	Cut-off value	Sensitivity	Specificity	PCP	NCP	LR (+)
NLR	**>7.3**	39.63	95.06	85.7	57.5	4.00
PLR	**>165**	30.86	87.65	71.4	55.9	2.50

PCP: Positive predictive value, NCP: Negative predictive value, LR: Likelihood ratio, NLR: Neutrophil/lymphocyte, PLR: Platelet/lymphocyte

a lower Apgar score in preterm birth and newborns in the PPROM group and higher PLR and NLR values in the PPROM group.

Ekin et al. (11) investigated the risk factors associated with the latent period and perinatal outcomes in patients with PPROM. Maternal age, parity, mode of conception, maternal disease, PPROM history, previous cesarean section history, antenatal bleeding history, tobacco use, week of gestation with PPROM, amniotic fluid index, latent period, week of birth, and maternal blood parameters (CRP, platelet, leukocyte, lymphocyte and neutrophil) data. They calculated the NLR and PLR values. No differences were observed between the two groups regarding maternal age, fetal gender, tobacco use, and mode of conception. It was observed that there was an increased risk of abruptio placentae, emergency cesarean delivery, cord prolapse, and chorioamnionitis in the group with a latent period of over 72 h. They found that there was no relationship between the latent period and the NLR and PLR values between the groups (11).

Ozel et al. (12) found in their study that the mean NLR of patients diagnosed with PPROM was higher than that of the healthy group and the group with threatened preterm birth. They also stated that the predictive value of NLR was 5.14 (12). In our study, we calculated the predictive value of NLR to be 7.3.

Lakshmi and Sravani (13) examined the predictive values of PLR and NLR for PPROM. Researchers found that the mean hemoglobin value was lower and the neutrophil count, mean PLR, and NLR were higher in the PPROM group than in the control group. The mean birth weight in the PPROM group was also found to be lower. These results were similar to those of our study.

Conclusion

Consequently, in our study, we detected that PLR and NLR values were higher in patients diagnosed with PPROM. Therefore, PLR and NLR may be used as a cost-effective method in the diagnosis and follow-up of PPROM because they are non-invasive values that can be easily calculated by complete blood count. More studies are needed to determine the routine use of these parameters in the management of PPROM.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research. This study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, with protocol number 48670771-514.10, on May 24, 2021.

Informed Consent: Our study is retrospective and was carried out on data processing data without using patient names.

Authorship Contributions

Concept: V.M., Y.Ö., Design: V.M., Y.Ö., Data Collection or Processing: Y.Ö., Y.K., Analysis or Interpretation: Y.Ö., D.Y.K., Drafting Manuscript: S.G., D.Y.K., Critical Revision of Manuscript: Y.Ö., Y.K., V.M., Final Approval and Accountability: Y.Ö., S.G., Y.K., D.Y.K., V.M., Technical or Material Support: Y.Ö., Y.K., Supervision: D.Y.K., S.G., Writing: Y.Ö., S.G., Y.K., D.Y.K., V.M.

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