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The role of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP) and fibrinogen in predicting the latent period after preterm premature rupture of membranes between 24 and 34 weeks

Mevlut Bucak[1], Zeynep Seyhanli[1], Betul Tokgoz Cakir[1], Can Ozan Ulusoy[1], Gulsan Karabay[1], Gizem Aktemur[1], Fatih Akkus[2], Zehra Vural Yılmaz[1]

[1]*Ankara Etlik City Hospital, Department of Perinatology, Ankara, Turkiye*
[2]*Necmettin Erbakan University, Departmant of Perinatology, Konya, Turkiye*

Abstract

Objective: In this study, we aimed to identify patients with PPROM between 24 and 34 weeks of gestation who had high potential for delivery before 72 hours of gestation based on systemic inflammatory parameters.

Methods: In this retrospective study, 101 patients with preterm prelabor rupture of membranes (PPROM) between 24 and 34 weeks of gestation were evaluated. Patients were divided into two groups: those who delivered within 72 hours (n = 51) and those who delivered after 72 hours (n = 50). Demographic data, inflammatory markers (NLR, PLR, CRP, fibrinogen), and neonatal outcomes were compared between the groups. Statistical analyses were performed to assess the predictive value of inflammatory markers for delivery within 72 hours.

Results: Among the inflammatory markers examined, CRP, fibrinogen, NLR, and PLR levels were significantly higher in patients who delivered within 72 hours (p = 0.034, p = 0.015, p = 0.020, and p = 0.028, respectively). In multivariate analysis, cervical dilatation (p = 0.004) and PLR (p = 0.008) were identified as independent predictors of delivery within 72 hours. Cervical dilatation had a specificity of 86.0%, while PLR had a sensitivity of 66.6%, with an AUC of 0.627.

Conclusion: PLR was identified as a moderate predictor for delivery within 72 hours in PPROM cases. However, it should be used in conjunction with other clinical factors to improve decision-making.

Keywords: Preterm premature rupture of membranes, C-reactive protein, Fibrinogen, NLR, PLR

Introduction

Preterm premature rupture of membranes (PPROM) is the term used to describe the spontaneous rupture of fetal membranes before 37 weeks of pregnancy. This condition occurs in approximately 3% of all pregnancies.[1] Management is influenced by factors such as gestational age, clinical infection, abruptio placenta, labor, or abnormal fetal tests. It is generally accepted that PPROM, which usually occurs at 24-34 weeks of gestation, should be managed conservatively to improve neonatal outcomes in the absence of maternal or fetal contraindications.[1] The exact underlying mechanisms of PPROM are not fully understood, but they are thought to result from a variety of different pathological processes. The contributing factors to this condition include intraamniotic infection, previous history of PPROM, a shortened cervical length, bleeding during the second and third trimesters, low body mass index, low socioeconomic status, smoking, and drug use.[2,3] Many studies have reported an association between PPROM and inflammatory markers.[4–9]

Various invasive and noninvasive methods can be used to assess maternal and fetal inflammation. Due

Correspondence: Mevlut Bucak, Ankara Etlik City Hospital, Department of Perinatology, Ankara, Turkiye, **e-mail:** mevlutbucak@gmail.com , **Received:** May 30, 2024 **Accepted:** October, 03, 2024

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ORCID ID: M Bucak 0000-0002-5035-8727; Z Seyhanli 0000-0003-3924-3723; B Tokgoz Cakir 0000-0003-0202-4981; CO Ulusoy 0009-0005-7931-5172; G Karabay 0000-0003-2567-2850; G Aktemur 0000-0003-3696-1287; F Akkus 0000-0001-7037-9165; Z Vural Yılmaz0000-0002-8719-1879

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to its practicality and noninvasiveness, the estimation of inflammation using maternal complete blood count parameters has gained widespread use.[10] In addition, C-reactive protein (CRP) and fibrinogen, which are acute-phase reactants, have been shown to increase inflammation during pregnancy.[11] Low albumin levels inhibit platelet proliferation and lead to inflammatory and oxidative damage. The C-reactive protein (CRP)/albumin ratio (CAR) has the potential to determine a patient's inflammatory status. Fibrinogen levels are thought to initiate inflammation by releasing growth factors and stimulating endothelial cell damage. Reports suggest that the fibrinogen/albumin ratio (FAR) is more effective than individual assessments of fibrinogen and albumin.[12] The fibrinogen/CRP ratio (FCR) is intended to increase its diagnostic power by accounting for physiologic changes in fibrinogen.[13] The platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are recently discovered markers of inflammation that have been linked to adverse outcomes in various pathological conditions.[8]

At least half of patients with PPROM have been shown to deliver within 1 week of membrane rupture.[14] Approximately 75% of perinatal deaths occur in premature babies.[15] The prediction of the time of delivery after PPROM is very important for neonatal intervention. PPROM cases between 24-34 weeks of gestation in this group are also important in terms of neonatal complications. Therefore, there is a need for markers that can predict the time of delivery in PPROM patients. In this study, considering the role of inflammation in the pathophysiology of PPROM, we aimed to investigate the role of fibrinogen, CRP, the NLR, the PLR, the CAR, the FAR, and the FCR in predicting the time of delivery and to identify patients with a high potential to deliver <72 hours.

Methods

The study included 101 patients who underwent treatment at the Perinatology Clinic of Ankara Etlik City Hospital from 2022 to 2023. These patients were diagnosed with preterm prelabor rupture of membranes (PPROM) between 24 and 34 weeks of gestation. The study was conducted in compliance with the principles outlined in the Helsinki Declaration. The local ethics committee granted ethical approval with the approval number AESH-EK1-2023-603. Patient data were gathered from both medical records and the hospital information management system.

The inclusion criteria for the study were singleton pregnancies diagnosed with preterm prelabor rupture of membranes (PPROM) occurring between 24-34 weeks of gestation and delivery at our institution. PPROM was defined as a membrane rupture that occurred before the onset of regular uterine contractions before 37 weeks of gestation. We performed cervical and vaginal examinations using a sterile speculum in all patients. A PPROM diagnosis was established through the visualization of amniotic fluid loss and/or the results of the placental alpha microglobulin-1 protein assay.[16] Following hospital admission, all participants underwent a series of laboratory tests, which included a complete blood count, serum biochemistry, sedimentation rate, and C-reactive protein (CRP) levels, prior to receiving any medication. Given the retrospective nature of this study, microbiological cultures were not routinely obtained as part of the study protocol, as the primary focus was on inflammatory markers and their correlation with delivery latency. All patients were managed in accordance with the guidelines provided by the American College of Obstetricians and Gynecologists (ACOG). Patients with PPROM beyond 34 weeks of gestation were promptly delivered according to guidelines.[1] Antibiotic prophylaxis was administered to all patients with PPROM.[1] Upon admission to the hospital, the patient received oral azithromycin (1 gram) and intravenous ampicillin (2 gram) every 6 hours for the first 48 hours of hospitalization. Subsequently, oral amoxicillin (875 mg) was administered every 12 hours for an additional 5 days.[17] All patients were scheduled to receive a standard regimen of two 12 mg intramuscular doses of betamethasone, administered 24 hours apart, as

part of the corticosteroid protocol to enhance fetal lung maturity. However, if delivery occurred within 24 hours of the first dose, the second dose was not administered.[1] Neuroprotective magnesium sulfate was administered to patients who delivered before 32 weeks of gestation.[1] The delivery of the fetus was deferred to approximately 34 weeks of gestation, as was feasible. However, in the presence of clinical signs or symptoms indicative of chorioamnionitis or fetal distress, delivery was promptly performed.

Patients who had acute or chronic inflammatory conditions such as gestational diabetes and preeclampsia, systemic diseases, multiple pregnancies, polyhydramnios, disorders of the hematopoietic system, fever of unknown origin, urinary tract infections, malignancies, or PPROM between 34 and 37 weeks were not included in the study. Patients exhibiting symptoms of acute infection, such as pain, fever, or vaginal discharge, were not included in the study (Figure 1).

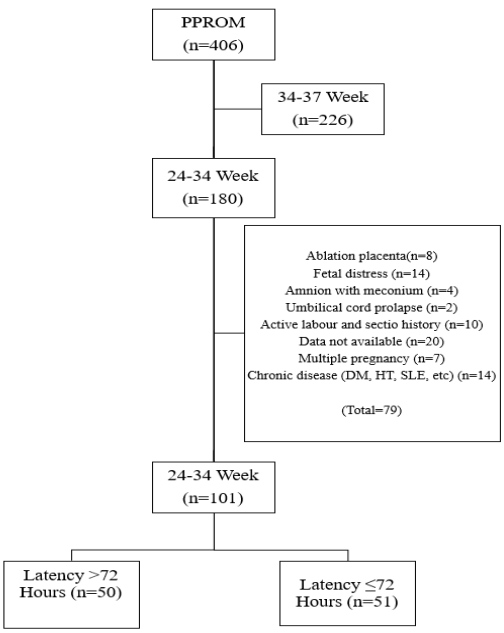

Fig 1. Selection of study patients

According to the interval between membrane rupture and delivery, we divided patients with PPROM into two groups: those with a latency period ≤72 hours and those with a latency period >72 hours. Maternal age, gravidity, parity, gestational age at presentation, week of PPROM, week of delivery, interval between PPROM and delivery, birth weight, neonatal intensive care unit admission rate, neonatal sepsis, and neonatal outcomes were recorded from medical records. Neonatal sepsis was diagnosed based on clinical records available from the hospital database. However, specific details regarding microbiological culture results and the antibiotic treatments administered in the NICU were not available for this study.

The inflammatory scores were calculated as follows: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; CAR = CRP/albumin; FAR = fibrinogen/albumin; and FCR = fibrinogen/CRP.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA). Normality of the data was assessed using the Kolmogorov-Smirnov test and histograms. An independent sample t test was used for pairwise comparisons of normally distributed data, and the results are presented as mean ± standard deviation. A Mann-Whitney U test was used for pairwise comparisons of non-normally distributed data, and the results were expressed as median (minimum-maximum). A Chi-square test or Fisher's exact test was used to compare categorical data, and the results are presented as percentages (n%). In the univariate analysis, the ability of each independent variable to predict delivery within 72 hours was assessed separately and then included in the multivariate logistic regression analysis. Multivariate analysis was performed to assess the ability of the independent variables to predict labor together, and the results are presented as odds ratios (β) and p significance values.

Receiver operating characteristic (ROC) analy-

sis was performed to assess the ability of PLR and cervical length to predict the occurrence of labor within 72 hours of PPROM. The area under the ROC curve (AUC) was calculated for each parameter to assess its diagnostic efficiency. Performance is reported as sensitivity, specificity, PPV, and NPV with confidence intervals. Confidence intervals for all variables were determined using the Wilson score method. Results are presented as two-tailed p values at a significance level of 0.05.

Results

The study was completed with a total of 101 patients: 50 patients in the group with a birth interval of more than 72 hours and 51 patients in the group with a birth interval of 72 hours or less.

Maternal and birth characteristics

There was no significant difference between the two groups in terms of maternal age, gravidity, parity, live birth, abortion rate, BMI, or week of hospitalization ($p > 0.05$). However, significant differences were observed between the two groups with regard to cervical dilatation (p=0.011), birth time (p=0.012), and birth interval (p=0.001) (Table 1).

Table 1. Comparison of maternal and birth characteristics between birth intervals longer and shorter than 72 hours

Variable	Latency >72 Hours (n=50)	Latency ≤72 Hours (n=51)	p-value
Age(year)	28.2 ± 5.8	27.2 ± 5.6	0.383[α]
Gravidity	2 (1 - 13)	2 (1 - 6)	0.274[β]
Parity	1 (0 - 5)	0 (0 - 4)	0.206[β]
Living Children	1 (0 - 5)	0 (0 - 4)	0.152[β]
Abortion	0 (0 - 9)	0 (0 - 3)	0.903[β]
BMI(kg/m²)	28.2 ± 4.8	27.3 ± 5.1	0.399[α]
Cervical Dilation (cm)	1 (0 - 4)	1 (0 - 5)	0.011[β]
Hospitalization Week	30.2 ± 2.3	30.4 ± 3.0	0.643[α]
Birth Time (weeks)	32.0 ± 2.1	30.6 ± 3.0	0.012[α]
Interval (days)	8 (4 - 55)	1 (0 - 3)	0.001[β]
Smoking	1 (2.0%)	1 (1.9%)	0.989[γ]
PTL history	2 (4.0%)	0 (0.0%)	0.149[γ]
Cesarian section history	14 (28.0%)	12 (23.5%)	0.607[γ]

[α] Independent t-test (mean ± SD), [β] Mann-Whitney U test [median (min-max)], [γ] chi-square test n (%). BMI: Body mass index, PTL: Preterm Labor.

Laboratory Values

CRP (p = 0.034), fibrinogen (p = 0.015), NLR (p = 0.020), and PLR (p = 0.028) were significantly different between the groups. Other laboratory parameters, including WBC, hemoglobin, neutrophil, lymphocyte, monocyte, platelet, albumin, CAR, FAR, FCR, and MLR, were not significantly different ($p > 0.05$) (Table 2).

able 2. Comparison of laboratory values between birth intervals longer and shorter than 72 hours

Variable	Latency >72 Hours (n=50)	Latency ≤72 Hours (n=51)	p-value
WBC (x10³/mm³)	12.51 ± 3.14	13.97 ± 5.52	0.105[α]
Hemoglobin (g/dl)	11.44 ± 1.48	11.91 ± 1.17	0.079[α]
Neutrophils (x10³/mm³)	8.75 (4.88 - 89.60)	9.43 (4.82 - 32.52)	0.151[β]
Lymphocytes (x10³/mm³)	2.05 (0.64 - 4.49)	1.75 (0.68 - 4.64)	0.074[β]
Monocytes (x10³/mm³)	0.70 (0.12 - 1.48)	0.70 (0.08 - 2.53)	0.820[β]
Platelets (x10³/mm³)	256.8 ± 62.8	266.5 ± 66.9	0.451[α]
Albumin (g/L)	36.92 ± 2.26	37.83 ± 2.87	0.081[α]
CRP (mg/L)	6.97 (0.67 - 47.30)	11.57 (0.63 - 87.89)	0.034[β]
Fibrinogen (mg/dL)	493 (271 - 751)	536 (322 - 776)	0.015[β]
NLR	4.16 (1.98 - 54.30)	5.34 (1.90 - 17.44)	0.020[β]
PLR	121.11 (43.56 – 345.31)	138.00 (50.77 – 426.92)	0.028[β]
CAR	0.18 (0.02 – 1.30)	0.27 (0.01 - 2.28)	0.068[β]
FAR	13.52 ± 2.69	14.45 ± 3.10	0.114[α]
FCR	70.85 (11.23 - 686.57)	47.15 (8.16 – 574.60)	0.060[β]
MLR	0.32 (0.10 – 0.58)	0.35 (0.08 - 1.24)	0.429[β]

[α] Independent t-test (mean ± SD), [β] Mann-Whitney U test [median (min-max)].
WBC: White blood cell, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CAR: CRP to albumin ratio, FAR: Fibrinogen to albumin ratio, FCR: Fibrinogen to CRP ratio, MLR: Monocyte to lymphocyte ratio.

Neonatal Outcomes

Cesarean section rate (p=0.189), sex distribution (p=0.276), birth weight (p=0.132), NICU admission rate (p=0.365), TTN (p=0.900), there was no significant difference between the groups (p>0.05), neonatal sepsis (p=0.130), or RDS (p=0.149). However, the percentage of patients with APGAR scores less than 7 at 5 minutes was significantly greater in the group with a birth interval of less than 72 hours (p = 0.025) (Table 3).

Table 3. Comparison of Neonatal Outcomes between birth intervals longer and shorter than 72 hours

Variable		Latency >72 Hours (n=50)	Latency ≤72 Hours (n=51)	p-value
Caesarean section rate		31 (62.0%)	25 (49.0%)	0.189[γ]
Gender	Female	25 (50%)	20 (39.2%)	0.276[γ]
	Male	25 (50%)	31 (60.8%)	
Birth weight		1875.1 ± 493.7	1700.9 ± 646.3	0.132[α]
APGAR 1.Minute		8 (0 – 9)	7 (0 – 9)	0.153[β]
APGAR 5.Minute		9 (1 – 10)	9 (0 – 10)	0.051[β]
APGAR 5.Min. Score <7		5 (10.0%)	14 (27.5%)	0.025[γ]
NICU admission		45 (78.9%)	42 (85.7%)	0.365[γ]
TTN		19 (38.0%)	20 (39.2%)	0.900[γ]
Neonatal sepsis		6 (12.0%)	12 (23.5%)	0.130[γ]
RDS		12 (24.0%)	19 (37.3%)	0.149[γ]

[α] Independent t-test (mean ± SD), [β] Mann-Whitney U test [median (min-max)], [γ] chi-square test n (%).
RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit, TTN: Transient tachypnea of the newborn.

Predictors of Delivery Within 72 Hours: Univariate and Multivariate Analysis

In the univariate analysis, cervical dilatation, CRP, fibrinogen, and PLR were identified as significant predictors of giving birth within 72 hours. Cervical dilatation demonstrated a robust correlation (β=1.70, p=0.007), indicating that with each unit increase in dilatation, the probability of giving birth within the specified time frame exhibited a notable increase. Furthermore, the univariate model indicated that CRP (β=1.03, p=0.020) and fibrinogen (β=1.00, p=0.023) also exhibited predictive value. Furthermore, PLR was found to be marginally significant (β=1.06, p=0.047), indicating a potential role in predicting near labor.

In the multivariate analysis, cervical dilatation and PLR remained significant, with cervical dilatation demonstrating an even stronger association (β=1.918, p=0.004). Furthermore, PLR remained statistically significant (β=1.126, p=0.008) and demonstrated an enhanced predictive capacity when other variables were considered. It is noteworthy that BMI, age, NLR, CRP, and fibrinogen did not retain statistical significance in the multivariate model. This suggests that the predictive values may be influenced by other factors. The results indicate that cervical dilatation and PLR are strong predictors for identifying women at risk of giving birth within 72 hours (Table 4).

Table 4. Results of univariate and multivariate analyses for predicting pregnant women with the potential to give birth within 72 hours

Predictor	Univariate Analysis			Multivariate Analysis		
	β	SE	p-value	β	SE	p-value
Age	0.97	0.03	0.379	1.024	0.04	0.573
BMI	0.96	0.04	0.395	0.929	0.05	0.145
Cervical Dilation	1.70	0.19	0.007	1.918	0.22	0.004
CRP	1.03	0.01	0.020	1.038	0.02	0.087
Fibrinogen	1.00	0.01	0.023	1.002	0.01	0.441
NLR	1.02	0.03	0.452	0.924	0.03	0.106
PLR	1.06	0.03	0.047	1.126	0.04	0.008

BMI: Body mass index, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio.

Diagnostic Performance

In the ROC curve analysis, cervical dilatation and PLR were evaluated as predictors for delivery within 72 hours (Figure 2). The area under the curve (AUC) for cervical dilatation was 0.639 (95% CI: 0.531-0.747, p=0.016), indicating a moderate predictive value. The optimal cut-off value for cervical dilatation was 3 cm, with a sensitivity of 39.2% (95% CI: 27.03% to 52.91%), a specificity of 86.0% (95% CI: 73.81% to 93.05%), a positive predictive value (PPV) of 74.0% (95% CI: 55.32% to 86.83%), and a negative predictive value (NPV) of 58.1% (95% CI: 46.74% to 68.68%).

The AUC for PLR was 0.627 (95% CI: 0.518-0.735, p=0.028), indicating a moderate predictive capacity. A cut-off value of 125.5 for PLR yielded a sensitivity of 66.6% (95% CI: 52.97% to 78.03%), a specificity of 54.0% (95% CI: 40.40% to 67.03%), a positive predictive value (PPV) of 59.6% (95% CI: 46.70% to 71.38%), and a negative predictive value (NPV) of 61.3% (95% CI: 46.62% to 74.28%). While both cervical dilatation and PLR demonstrated notable predictive capacity, cervical dilatation exhibited higher specificity, whereas PLR demonstrated higher sensitivity (Figure 2, Table 5).

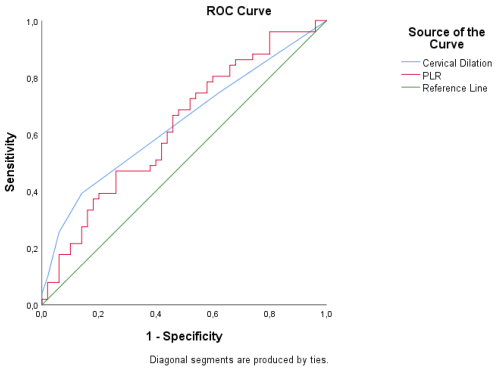

Figure 2. ROC Curve for Cervical Dilatation and PLR in Predicting Labor before 72 Hours

Table 5. Comparison of performance of variables for prediction of labour before 72 hours

	Cut-off	Sensivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	95% CI	p value
Cervical Dilatation	3	39.2	86.0	74.0	58.1	0.639	0.531-0.747	**0.016**
PLR	125.5	66.6	54.0	59.6	61.3	0.627	0.518-0.735	**0.028**

Discussion

The primary conclusions of our investigation are as follows: the NLR, PLR, CRP, and fibrinogen were significantly greater in the group of patients who experienced PPROM and delivered within 72 hours. In the multivariate analysis, cervical dilatation and PLR were identified as independent predictors of delivery within 72 hours. However, while both PLR and cervical dilatation were statistically significant predictors, the analysis suggests that these markers alone are insufficient for accurate prediction. Multiple studies have investigated the effectiveness of assessing maternal complete blood count parameters and indices in predicting negative obstetric outcomes. Although microbiological cultures were unavailable to confirm infection or sepsis, the elevated inflammatory markers in our cohort suggest a potential underlying inflammatory process that warrants further investigation.

Under systemic inflammatory conditions, the neutrophil count increases and the lymphocyte count decreases. The NLR is a parameter that may play a role in inflammatory processes. The NLR is known to increase rapidly after infection. Patients with unexplained fever and infection were not included in our study. Studies have shown that elevated NLR levels are associated with an increased incidence of sepsis. Various studies have shown the prognostic and predictive value of increased NLR in cancers such as lung cancer and hepatocellular carcinoma.[18,19] Furthermore, the NLR has been found to be significantly altered in pregnant patients with several conditions, including preeclampsia, gestational diabetes, intrahepatic cholestasis, SLE, and acute appendicitis.[20–25] Two studies in the literature reported that the NLR was greater in the group with PPROM than in the control group. Although our study initially revealed elevated NLR levels in the group with a latency period of ≤72 hours, consistent with previous studies linking NLR to PPROM prediction, it did not retain significance in the multivariate analysis.[6,26] This suggests that, although NLR may play a role in inflammatory processes associated with PPROM, it may not be a strong independent predictor of delivery latency when considered alongside other factors.

CRP levels increase in response to both acute and chronic inflammation resulting from diverse factors, including inflammatory conditions. Minimal increases in CRP levels detected by highly sensitive

assays can also occur in relation to metabolic stresses in the absence of acute or chronic inflammatory conditions, as commonly observed.[4] In the study by Moghaddam Banaem et al., maternal CRP levels were greater in patients with PPROM and preterm labor than in those without PPROM and preterm labor.[27] Ryu et al. reported that high CRP levels were an independent risk factor for delivery within 72 hours in the PPROM patient group.[28] Point et al. reported that despite low sensitivity, elevated CRP levels shorten the latent period.[29] This finding suggested that inflammatory pathways play an important role in PPROM. The mean CRP levels were slightly greater during pregnancy in pregnant women than in nonpregnant women. Although CRP levels were higher in the group of PPROM patients who delivered within 72 hours, multivariate analysis did not confirm CRP as an independent predictor of delivery within this time frame. This suggests that, while CRP may reflect underlying inflammatory processes, it may not be a strong independent factor in predicting delivery latency when considered alongside other variables.

Fibrinogen is an acute-phase reactant. It is subject to hepatic expression and high amounts of circulating protein under inflammatory conditions.[12,13] Keren-Politansky et al. measured fibrinogen levels between preterm labor and control groups and found no significant difference.[30] This may be related to the primary function of fibrinogen in the coagulation cascade. In some studies, the ratios of fibrinogen to albumin and CRP were used to increase the significance of fibrinogen.[12,13] In our study, we observed that fibrinogen levels were significantly greater in patients who delivered during the first 72 hours after PPROM. However, we observed that the FAR and FCR were not significant predictors of delivery in patients with PPROM.

The PLR, a commonly utilized biomarker, has demonstrated its ability to predict thrombotic events, inflammatory conditions, and malignancies. Prior research has consistently shown elevated PLRs in patients with malignancies, including colorectal cancer and endometrial cancer. Furthermore, studies conducted on pregnant women have examined the PLR in patients with gestational diabetes, acute pancreatitis, preeclampsia, systemic lupus erythematosus, and PPROM.[6,7,21,25,31] Ekin et al. designed a study to investigate the relationship between the PLR and PPROM in relation to the latent period. The study revealed no significant difference in the PLR between 72 hours before and 72 hours after surgery.[7] Toprak et al. compared PPROM patients with a control group in their study. High PLR values in the PPROM group were found to be significantly different.[6] In our study, multivariate analysis confirmed the independent predictive value of PLR for delivery within 72 hours in PPROM patients. While the AUC of PLR (0.627) indicated moderate diagnostic performance, PLR can still play a role in risk stratification for managing PPROM cases.

Our hospital is a tertiary center, and the total number of births is approximately 12,500 per year. The follow-up and treatment of PPROM patients were performed in the perinatology clinic at our hospital. Accurate prediction of the time of labor before 34 weeks in pregnant women with PPROM allows for the implementation of interventions that can significantly improve neonatal outcomes. Therefore, it is important to identify easily applicable and noninvasive methods to predict the time of labor.

The limitations of this study include its retrospective design and small sample size. In addition, the lack of difference in neonatal outcomes between the groups may be explained by the fact that we are a tertiary center, our neonatal intensive care unit is of sufficient size, and we have a permanent perinatology and neonatology specialist in our center. Another limitation is that cervical dilatation was used as the primary measure of cervical status, as data on cervical length and Bishop score were unavailable.

Although PLR and cervical dilatation are statistically significant predictors, further analysis indicates that these markers alone are insufficient as predictors of delivery within 72 hours and demonstrate only moderate predictive capacity. To enhance ac-

curacy, further validation and combination with other clinical markers are required.

Conclusion

Accurately predicting the time of delivery in pregnancies with PPROM before 34 weeks is crucial for improving neonatal outcomes and ensuring timely care. Our study found that both PLR and cervical dilatation are moderate predictors for delivery within 72 hours, but neither marker alone is sufficient. These should be considered alongside other clinical factors for better risk assessment. Further research is needed to develop more accurate tools or combinations of markers for predicting early delivery in PPROM cases.

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