




# Predictive Value of Crp-Albumin and Neutrophil-Lymphocyte Ratio in Preterm Premature Rupture of Membranes

## Preterm Prematür Membran Rüptüründe Crp-Albümin Oranı ve Nötrofil-Lenfosit Oranının Prediktif Değeri

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### ÖZET

**Amaç:** Bu çalışmada, Crp-Albumin oranı (CAR), Nötrofil-Lenfosit oranı (NLR), Trombosit-Lenfosit oranı (PLR) ile Prematüre Preterm Membran Rüptürü (PPROM) arasındaki ilişkiyi değerlendirmeyi amaçladık.

**Gereçler ve Yöntem:** Bu prospektif çalışmanın örneklemini Ocak 2021 Temmuz 2021 tarihleri arasında Necmettin Erbakan Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniğine poliklinik veya acil servisten su gelmesi şikayeti ile başvuran ve 24-37. gebelik haftalarında Prematüre Membran Rüptürü tanısı ile doğum yapan 143 gebe oluşturmaktadır. Kontrol grubunu ise spontan preterm doğumu başlayan ve PPROM tanısı olmayan 108 gebe oluşturmaktadır. Demografik veriler, tam kan sayımı sonuçları kaydedildi ve karşılaştırıldı.

**Bulgular:** Hastaların temel demografik özelliklerini incelediğimizde gruplar arasında yaş, gravida, parite, gestasyonel yaş açısından istatistiksel olarak anlamlı fark saptanmamıştır (sırasıyla  $p=0.881$ ,  $p=0.888$ ,  $p=0.912$ ,  $p=0.916$ ). PPROM grubunda CAR ve NLR kontrol grubuyla kıyaslandığında istatistiksel olarak anlamlı derecede yüksek bulunmuştur (Her iki oran için de  $p<0.001$ ). CAR'ın PPROM'u teşhis etme yeteneği, ROC eğrisi analizi kullanılarak değerlendirildiğinde AUC 0,734'dür ( $p<0,001$ ). PPROM ve kontrol grubunda CAR için cut off değer %64,81 duyarlılık ve %73,97 özgüllükle 0.1433 olarak bulundu. NLR'nin PPROM'u teşhis etme yeteneği, ROC eğrisi analizi kullanılarak değerlendirildiğinde AUC 0,650'dir ( $p<0,001$ ). Gruplar arasında NLR için cut off değer %49,59 duyarlılık ve %87,67 özgüllükle 5,3937 olarak tespit edildi. PLR ise gruplar arasında karşılaştırıldığında anlamlı bir fark tespit edilmemiştir ( $p= 0.121$ ).

**Sonuç:** CAR ve NLR, maternal ve neonatal iyilik halinin sağlanmasına yardımcı olabilecek, PPROM'un erken teşhisi için kullanılabilir uygun maliyetli, kullanımı kolay ve pratik bir belirteç olabilir.

**Anahtar Kelimeler:** Albümin, CRP/albümin oranı, prematüre preterm membran rüptürü, nötrofil/lenfosit oranı, trombosit/lenfosit oranı

### ABSTRACT

**Objective:** This study aimed to evaluate the relationship between C-reactive protein to albumin ratio (CAR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and preterm premature rupture of membranes (PPROM).

**Materials and Methods:** This prospective study included 143 pregnant women diagnosed with PPROM between 24 and 37 weeks of gestation who presented with leakage of fluid to the Obstetrics and Gynecology Clinic of Necmettin Erbakan University Meram Faculty of Medicine between January 2021 and July 2021. The control group consisted of 108 pregnant women with spontaneous preterm birth without PPROM. Demographic data and complete blood count results were recorded and compared.

**Results:** There were no statistically significant differences between the groups regarding age, gravidity, parity, and gestational age ( $p=0.881$ ,  $p=0.888$ ,  $p=0.912$ ,  $p=0.916$ , respectively). CAR and NLR were significantly higher in the PPROM group compared to the control group ( $p<0.001$  for both ratios). The ability of CAR to diagnose PPROM, evaluated using ROC curve analysis, yielded an AUC of 0.734 ( $p<0.001$ ). The cut-off value for CAR was 0.1433 with 64.81% sensitivity and 73.97% specificity. The ability of NLR to diagnose PPROM, evaluated using ROC curve analysis, yielded an AUC of 0.650 ( $p<0.001$ ). The cut-off value for NLR was 5.3937 with 49.59% sensitivity and 87.67% specificity. There was no significant difference in PLR between the groups ( $p=0.121$ ).

**Conclusion:** CAR and NLR may be cost-effective, easy-to-use, and practical markers for the early diagnosis of PPROM, which could contribute to improved maternal and neonatal well-being.

**Keywords:** Albumin, CRP/Albumin Ratio, Preterm Premature Rupture of Membranes, Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio

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## INTRODUCTION

Premature rupture of membranes (PROM) is defined as the rupture of fetal membranes before the onset of uterine contractions, regardless of gestational age. Preterm premature rupture of membranes (PPROM) refers to rupture before 37 weeks of gestation. PPRM complicates approximately 5-10% of all pregnancies (1) and is responsible for 40% of spontaneous preterm births (2).

PPROM is the most common cause of premature birth requiring neonatal intensive care and neonatal complications. Common complications in preterm births due to PPRM include respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and sepsis. In neglected cases, maternal complications such as endometritis, sepsis, disseminated intravascular coagulopathy, adult respiratory distress syndrome, and renal failure can develop as a result of chorioamnionitis (3). The fetus is at greater risk than the mother for morbidity and mortality associated with PPRM (4).

Although the pathophysiological mechanism is speculative, infection and inflammatory processes play a significant role in the etiology of PPRM (5). The immune response to bacterial colonization of the endocervix and/or fetal membranes can lead to localized weakening of the fetal membranes and trigger numerous inflammatory cascades that can result in PPRM (6). The role of inflammation in PPRM has been evaluated in numerous studies, and a significant relationship has been reported between various inflammatory markers and PPRM (7-9). C-reactive protein (CRP), due to its short half-life, can be used as a marker in the early stages of inflammation. Several studies have shown that CRP is elevated in pregnant women with PPRM who have chorioamnionitis or intra-amniotic inflammation and can predict the time to delivery (latent period) (10,11).

In chronic inflammatory processes, megakaryocytic lineages progressively increase, and lymphocyte counts tend to decrease due to severe apoptosis. Consequently, markers such as the platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), obtained from complete blood counts, can be affected in severe chronic inflammatory diseases (12,13). Albumin, a negative acute-phase reactant synthesized by the liver, decreases in concentration during inflammation. Previous studies have shown that albumin levels are associated with inflammation severity, disease prognosis, and mortality (14,15).

Despite extensive research, an ideal marker that can predict the latent period and enable early detection of infection or chorioamnionitis in PPRM has not yet been translated into clinical practice. This study aimed to investigate the relationship between PPRM and C-reactive protein to albumin ratio (CAR), NLR, and PLR, which are increasingly researched and thought to be elevated due to inflammation, a key factor in the etiology of PPRM.

## MATERIALS AND METHODS

This prospective observational study included 143

pregnant women diagnosed with PPRM who presented with leakage of fluid to the Obstetrics and Gynecology Clinic of Necmettin Erbakan University Meram Faculty of Medicine between January 2021 and July 2021. The control group consisted of 108 pregnant women with spontaneous preterm birth without PPRM.

The study was initiated following approval from the Necmettin Erbakan University Meram Faculty of Medicine Clinical Research and Ethics Committee (Number: 2021/2996). All participating pregnant women were informed about the study, and their consent was obtained through written and verbal informed consent forms. The study was conducted in accordance with the latest principles of the Declaration of Helsinki.

Cases with PPRM diagnosed between 24 and 37 weeks of gestation and eligible for recording complete blood samples and other clinical perinatal findings were included in the study. The exclusion criteria included maternal systemic disease, hematological disease, malignancy, autoimmune disease, infection or acute febrile illness, any inflammatory disease of pregnancy such as gestational diabetes mellitus and preeclampsia, severe anemia (Hgb < 10 g/dL), fetal chromosomal disease, intrauterine growth restriction and stillbirth, any invasive procedure (amniocentesis, etc.), smoking or alcohol use, and use of steroid-containing or other medications that could affect blood parameters.

Age, gestational week, gravidity, and parity were recorded. Complete blood counts and biochemistry results from maternal antecubital vein blood samples taken upon admission were recorded. All biochemical parameters were analyzed from a single serum sample. Complete blood counts were tested using an Automated Blood Cell Analyzer (Pentra 120 Retic Hematology Analyzer, ABX, Montpellier, France). Biochemical parameters were determined by an Automated Biochemical Analyzer 7600-120 (Hitachi High Technologies, Japan).

Leukocyte, lymphocyte, neutrophil, monocyte, platelet, CRP, and albumin values were obtained from peripheral blood samples. NLR was calculated by dividing the neutrophil count by the lymphocyte count; PLR by dividing the platelet count by the lymphocyte count; and CAR by dividing the CRP level by the albumin level.

Healthy pregnant women in the control group with preterm labor and confirmed absence of premature rupture of membranes were selected to match the PPRM group in terms of age, gestational week, and body mass index (BMI). Since CRP levels are known to be affected by conditions involving endothelial damage and infectious inflammatory events, healthy pregnant women without any morbidity that could cause endothelial damage were included in the control group.

The PPRM group consisted of 143 pregnant women diagnosed with premature rupture of membranes who presented to our clinic with vaginal fluid drainage or perineal wetness, showed active leakage or pooling of fluid upon sterile speculum examination, and had a positive nitrazine test or Amnisure™ kit test based on PAMG-1 detection. All cases with confirmed PROM admitted to our clinic received antibiotic

prophylaxis. Antenatal corticosteroids (betamethasone, 12 mg intramuscularly, 2 doses 24 hours apart) were administered to all cases with gestational age less than 34 weeks.

### Statistical Analysis

All collected data were analyzed using the Statistical Package for the Social Sciences, version 23 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Normally distributed continuous variables were expressed as mean  $\pm$  standard deviation, non-normally distributed continuous variables as median (25th percentile - 75th percentile), and categorical variables as number (%). Student's t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used for non-normally distributed continuous variables. The chi-square test was used to compare categorical variables. Statistical significance was set at  $p < 0.05$ .

### RESULTS

There were no statistically significant differences between the groups in terms of age, gravidity, parity, and gestational age. The mean age was similar in both groups:  $28.3 \pm 5.4$  years in the PPRM group and  $28.6 \pm 5.4$  years in the control group ( $p=0.881$ ). The mean gestational age was also similar:  $33.8 \pm 3.1$  weeks in the PPRM group and  $34.8 \pm 1.1$  weeks in the control group ( $p=0.916$ ). Gravidity and parity were 2.0 (1.0, 4.0) and 1 (0, 2) for the PPRM group, and 2.0 (1.0, 3.5) and 1 (0, 1) for the control group, respectively ( $p=0.888$  and  $p=0.912$ ). (Table 1)

Regarding hematological parameters, the median leukocyte count was 11,550 (10,375-13,965)/ $\text{mm}^3$  in the PPRM group and 10,300 (8,790-11,500)/ $\text{mm}^3$  in the control group. Neutrophil counts were 8,665 (7,800-10,757)/ $\text{mm}^3$  and 7,550 (6,565-8,900)/ $\text{mm}^3$  in the PPRM and control groups, respectively. Statistically significant differences were observed between the groups for both neutrophil and leukocyte counts ( $p < 0.001$ ). Lymphocyte counts were 1,795 (1,375-2,420)/ $\text{mm}^3$  and 1,750 (1,460-2,330)/ $\text{mm}^3$ , and monocyte counts were 650 (500-860)/ $\text{mm}^3$  and 580 (485-755)/ $\text{mm}^3$  in the PPRM and control groups, respectively. There were no significant differences between the groups for lymphocyte and monocyte counts ( $p=0.510$  and  $p=0.154$ , respectively). While CRP values differed significantly between the groups [PPROM group: 7.9 (3.6, 12.6) mg/dL, control group: 3.3 (2.0, 5.4) mg/dL] ( $p < 0.001$ ), albumin values [PPROM group: 37.5 (33.4, 40.5) g/L, control group: 38.8 (36.4, 40.4) g/L] ( $p=0.069$ ) did not show a statistically significant difference.

The NLR was 4.6 (3.5, 7.2) in the PPRM group and 4.1 (3.7, 5.2) in the control group, showing a statistically significant elevation in the PPRM group ( $p < 0.001$ ). The CAR was 0.18850 (0.09003, 0.34868) in the PPRM group and 0.08097 (0.05601, 0.14917) in the control group, also significantly higher in the PPRM group ( $p < 0.001$ ). The PLR was 133.2 (105.4, 163.9) in the PPRM group and 117.7 (100.2, 143.0) in the control group, with no significant difference between the groups ( $p=0.121$ ). (Table 2)

The ability of CAR to diagnose PPRM was evaluated

**Table 1.** Comparison of Demographic Characteristics of the Groups

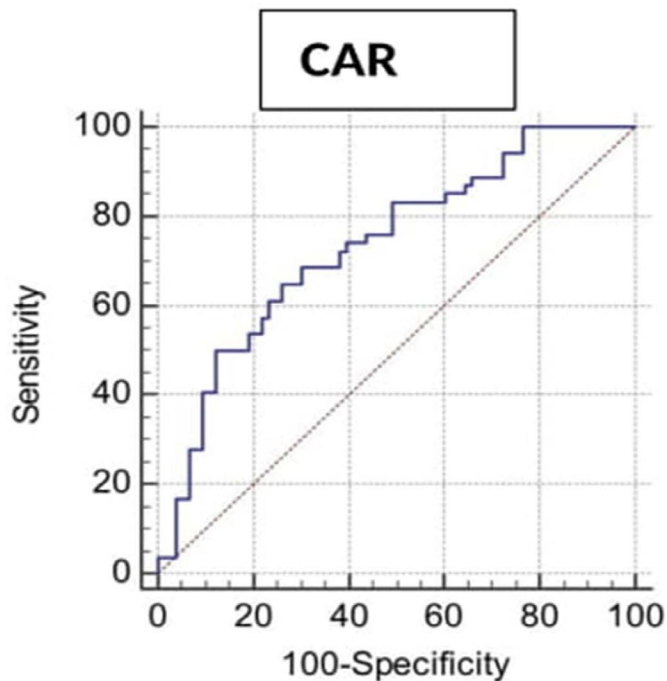
	PPROM grup (n=143)	Control Group (n=108)	p-value
Age (years)	$28.3 \pm 5.4$	$28.6 \pm 5.4$	0.881 <sup>a</sup>
Gestational Age (weeks)	$33.8 \pm 3.1$	$34.8 \pm 1.1$	0.916 <sup>a</sup>
Gravida (number)	2.0 (1.0, 4.0)	2.0 (1.0, 3.5)	0.888 <sup>b</sup>
Parity (number)	1 (0, 2)	1 (0,1)	0.912 <sup>b</sup>

Data are presented as mean  $\pm$  standard deviation, median (25th Percentile - 75th Percentile), or number (%). p-values were determined using Student's t-test or Mann-Whitney U test PPRM: Preterm Premature Rupture of Membranes; n: number

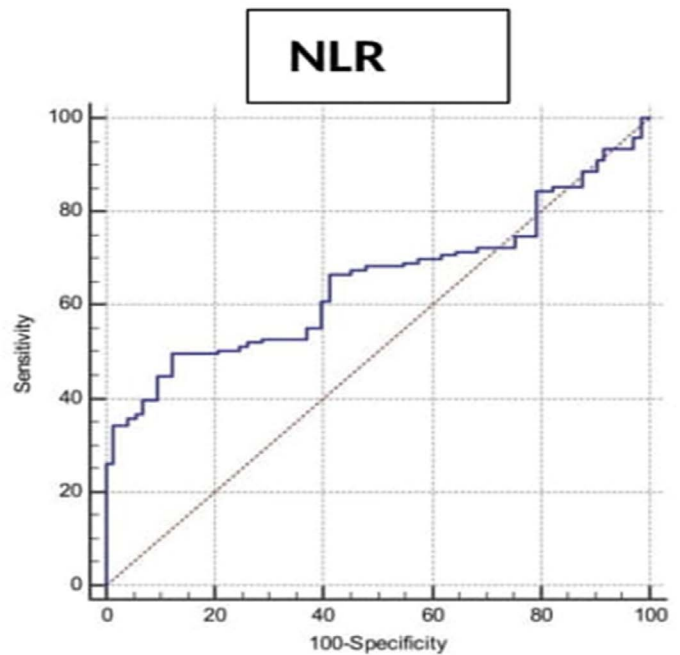
**Table 2.** Comparison of Laboratory Parameters of the Groups

	PPROM Group (n=143)	Control Group (n=108)	p-value
Leukocytes (/ $\text{mm}^3$ )	11550 (10375-13965)	10300 (8790-11500)	$<0.001^b$
Neutrophils (/ $\text{mm}^3$ )	8665 (7800-10757)	7550 (6565-8900)	$<0.001^b$
Lymphocytes (/ $\text{mm}^3$ )	1795 (1375-2420)	1750 (1460-2330)	0.510 <sup>b</sup>
Monocytes (/ $\text{mm}^3$ )	650 (500-860)	580 (485-755)	0.154 <sup>b</sup>
Platelets (/ $\text{mm}^3$ )	$245158 \pm 63864$	$228931 \pm 68622$	0.655 <sup>a</sup>
Albumin (g/L)	37.5 (33.4-40.5)	38.8 (36.4-40.4)	0.069 <sup>b</sup>
CRP (mg/dL)	7.9 (3.6-12.6)	3.3 (2.0-5.4)	$<0.001^b$
Neutrophil/Lymphocyte Ratio	4.6 (3.5-7.2)	4.1 (3.7-5.2)	$<0.001^b$
Platelet/Lymphocyte Ratio	133.2 (105.4-163.9)	117.7 (100.2-143.0)	0.121 <sup>b</sup>
CRP/Albumin Ratio	0.18850 (0.09003-0.34868)	0.08097(0.05601-0.14917)	$<0.001^b$

Data are presented as mean  $\pm$  standard deviation, median (25th Percentile - 75th Percentile), or number (%). P-values were determined using Student's t-test a, Mann-Whitney U test b. Significant p-values are shown in bold. WBC: White Blood Cell; CRP: C-Reactive Protein



**Figure 1.** Receiver operating characteristics (ROC) curve analysis of C-reactive protein to albumin ratio (CAR) between the PPRM and Control groups (Optimal ROC cutoff value: 0.1433 with 64.81% sensitivity and 73.97% specificity, AUC: 0.734,  $p < 0.001$ )



**Figure 2.** Receiver operating characteristics (ROC) curve analysis of neutrophil-lymphocyte ratio (NLR) between the PPRM and Control groups (Optimal ROC cutoff value: 5.3937 with 49.59% sensitivity and 87.67% specificity, AUC: 0.650,  $p < 0.001$ )

using ROC curve analysis, yielding an AUC of 0.734 ( $p < 0.001$ ). The cut-off value for CAR was determined to be 0.1433 with 64.81% sensitivity and 73.97% specificity (Figure 1). The ability of NLR to diagnose PPRM was also evaluated using ROC curve analysis, yielding an AUC of 0.650 ( $p < 0.001$ ). The cut-off value for NLR was 5.3937 with 49.59% sensitivity and 87.67% specificity (Figure 2).

## DISCUSSION

The main findings of our study are: Both NLR and CAR were significantly higher in the PPRM group compared to the control group. However, there was no significant difference in PLR between the groups. Furthermore, an NLR value  $> 5.3937$  and a CAR value  $> 0.1433$  were associated with an increased risk of PPRM.

PPROM remains a significant problem in obstetrics due to challenges and uncertainties in its etiology and associated serious maternal and fetal risks. PPRM occurs in approximately 1-3% of all pregnancies and in about one-third of preterm births (16). Although its exact pathophysiology is still debated, PPRM leads to common and severe pregnancy complications such as RDS, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and sudden intrauterine death due to

umbilical cord compression. Recent studies have shown that the primary etiological mechanism of PPRM is inflammation (17,18).

Cytokines involved in inflammatory reactions have been reported to be associated with PPRM. Satar et al. reported increased interleukin (IL)-8 levels in maternal serum and umbilical cord in PPRM. Similarly, IL-6 was found to be elevated only in the umbilical cord, especially in PPRM with microbial invasion and histological chorioamnionitis (19). CRP is another frequently used marker indicating the early stages of inflammation. Another study by Popowski et al. (20) showed that CRP is elevated in PPRM patients with clinical and histopathological chorioamnionitis.

NLR has recently been used as a marker of subclinical inflammation and has been found useful in detecting inflammation along with other inflammatory markers in various diseases such as different types of cancer, psoriasis, rheumatoid arthritis, and keratoconus (21-24). In a study by Köseoğlu et al. (25), NLR was found to be higher in the PPRM group compared to the control group, concluding that NLR is a useful marker for predicting PPRM. Consistent with the literature, our study found higher NLR levels in the PPRM group.

PLR is a widely used marker proven to predict thrombotic events, inflammatory diseases, and malignancies. In pregnant women, PLR has been investigated in conditions like gestational diabetes and acute pancreatitis (26,27). Toprak E. et al. (28) also showed that PLR was statistically significantly higher in the PPRM group compared to the control group, suggesting that PLR could be an independent marker in detecting PPRM. Although our study found higher PLR in the PPRM group, the difference was not statistically significant.

CAR has been found to correlate with inflammation severity and mortality in various inflammatory diseases and malignancies such as osteosarcoma, ovarian cancer, and colon cancer (29,30). CAR has been proposed as a better indicator of the inflammatory response in septic patients compared to CRP or albumin alone (31). Our study found that this ratio was statistically significantly higher in patients with PPRM compared to the control group. Furthermore, to our knowledge, our study is the first in the literature to demonstrate the relationship between CAR and PPRM.

The first limitation of this study is its single-center design and the relatively small sample size. Secondly, it does not provide insight into predicting the latent period. Serological parameters examined in this study are nonspecific, and undiagnosed diseases (subclinical hypothyroidism, etc.) or pathologies without clinical manifestations could be misdiagnosed in both the PPRM and control groups.

In conclusion, CAR and NLR were significantly higher in the PPRM group compared to controls. CAR and NLR may be cost-effective, easy-to-use, and practical markers for the early diagnosis of PPRM, potentially contributing to improved maternal and neonatal outcomes. Further research is needed to determine the applicability of CAR and NLR as early diagnostic markers for PPRM.

**Conflict of interest:** Author declares that there is no conflict of interest between the authors of the article.

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