

# The Prognostic Value of Fibrinogen/Albumin Ratio and Other Inflammatory Indices in Preterm Prelabor Rupture of Membranes

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## ABSTRACT

To investigate the ability of the fibrinogen-albumin ratio (FAR) and other combined inflammatory indices to predict adverse perinatal outcomes in cases of early preterm prelabor membrane rupture (PPROM).

Retrospective analysis of data from patients with PPRM between 24 and 34 weeks of gestation from January to August 2025 was performed. Delivery within 48 hours, chorioamnionitis, placental abruption, intrauterine fetal demise, neonatal death, neonatal pH below seven, and neonatal sepsis were considered composite adverse perinatal outcomes (CAPO). Clinical characteristics, hemogram parameters, fibrinogen, albumin, C-reactive protein (CRP), and inflammatory indices (FAR, neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory index (SII), systemic inflammatory response index (SIRI), and aggregate index of systemic inflammation (AISII)) were compared between patients with and without CAPO. The predictive accuracy of significant variables was evaluated using receiver operating characteristic (ROC) analyses.

Data from a total of 170 patients were included in the study. CAPO was present in 100 patients. Fibrinogen, CRP, and FAR values were higher in the CAPO group ( $p = 0.02$ ,  $p = 0.019$ , and  $p = 0.002$ , respectively). The albumin level was lower in the same group ( $p = 0.023$ ). No significant differences were observed between the groups regarding other laboratory parameters or inflammatory indices. CRP demonstrated higher sensitivity (71%) and lower specificity (59%) for predicting CAPO, while FAR exhibited higher specificity (73%) and lower sensitivity (58%).

FAR, a recently developed inflammatory marker, may be a useful tool for predicting adverse outcomes in PPRM cases. In the present study, FAR outperformed hemogram-derived combined inflammatory indices in this regard.

**Keywords:** Preterm prelabor rupture of the membranes, adverse perinatal outcomes, fibrinogen-albumin ratio

## Introduction

Preterm prelabor rupture of the membranes (PPROM) occurs in approximately 2–3% of all pregnancies and is responsible for nearly one-third of preterm deliveries (1). The consequences of this condition can be severe, with the potential to result in maternal and neonatal morbidity and mortality. Adverse maternal outcomes are a potential consequence of the condition, in addition to respiratory distress syndrome, neonatal sepsis and long-term neurodevelopmental problems associated with prematurity (2,3). The management of PPRM cases is predicated on a balance between the progression of fetal maturation and the risk of maternal-fetal infection. Nevertheless, predicting these risks at the time of presentation remains challenging in such cases (1-3). Even though the etiology of PPRM remains to be fully elucidated, it is recognised that infection, inflammation, and

mechanical stress can instigate a series of inflammatory cascades (4).

Several studies have been conducted to explore the relationship between indicators of inflammation and PPRM (5,6). Interest in this field is rapidly increasing, primarily due to the affordability and quick turnaround of hematological parameters that signify the inflammatory response. Markers such as the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic inflammation index (SII), derived from complete blood counts, have been studied for their potential as markers predicting obstetric complications (7-9). In recent years, the fibrinogen/albumin ratio (FAR), which combines a positive inflammatory protein (fibrinogen) with a negative one (albumin), has been explored as a prognostic marker across various clinical settings, including obstetric populations (10,11). This parameter, which

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reflects the inflammation and nutritional status present in cases of PPRM, may help predict perinatal outcomes and improve clinical management.

The objective of this retrospective study was to examine the relationship between FAR and other hematological indices measured at presentation in patients in whom PPRM occurred between 24<sup>th</sup> and 34<sup>th</sup> gestational weeks, as well as maternal and neonatal short-term outcomes. Furthermore, the objective was to compare the performance of these biomarkers in predicting adverse perinatal outcomes.

## Materials and Methods

The study was a retrospective cross-sectional analysis conducted at the Ankara Bilkent City Hospital Obstetrics and Gynecology Clinic, a tertiary referral center, including patients admitted between January 2025 and August 2025. All researchers adhered to the principles outlined in the Helsinki Declaration. The research protocol was approved by the Ankara Bilkent City Hospital Medical Research Scientific and Ethical Evaluation Board with reference number 1-25-1770. Data were collected from the hospital's electronic database and archived medical records.

During the study period, a total of 8,274 pregnant women were monitored at our clinic. Of these, 170 cases presented with PPRM occurring during the 24<sup>th</sup>–34<sup>th</sup> gestational weeks. The diagnosis of PPRM was made based on the patient's history and the observation of amniotic fluid passing through the cervical canal and accumulating in the vagina. Antibiotic treatment was initiated for all cases diagnosed with PPRM. The gestational age of patients was calculated based on the crown-rump length (CRL) measured in the first trimester. Pregnancies in which PPRM occurred beyond 34 weeks of gestation were excluded from the study due to the patients' clinical condition and follow-up status, as these individuals delivered at various times and underwent labor induction. The study excluded cases with multiple pregnancies, smoking or substance use, chronic inflammatory maternal diseases, known liver disease, malignancy, autoimmune disorders, fetal anomalies, and uterine anomalies, as these conditions may affect fibrinogen and albumin levels and increase the risk of PPRM. Patients presenting with clinical signs of chorioamnionitis or abruptio placentae at the time of admission, as well as those with a very low (<18.5 kg/m<sup>2</sup>) or high (>35 kg/m<sup>2</sup>) body mass index, were also excluded from the study. Cases of PPRM developing after invasive diagnostic procedures such

as amniocentesis and fetal blood sampling were not included in the study because their pathogenesis and clinical course are different. Cases presenting with complaints of membrane rupture but without confirmed active amniotic fluid leakage on examination, as well as those who did not deliver at our institution, were also excluded. All participants completed antenatal corticosteroid therapy before delivery, and neuroprotective magnesium sulfate was administered to those with gestational age below 32 weeks.

A composite adverse perinatal outcome (CAPO) was defined as the occurrence of at least one of the following perinatal complications: delivery within 48 hours after membrane rupture, placental abruption, chorioamnionitis, intrauterine fetal demise, neonatal death, neonatal blood gas pH <7.0, or neonatal sepsis.

Patients were divided into two groups according to the presence or absence of CAPO. The comparison between the groups encompassed clinical and demographic data (age, gravidity, parity, gestational age at PPRM diagnosis, gestational age at delivery); hematologic parameters (white blood cell count (WBC) ( $\times 10^9$  /L), neutrophil count ( $\times 10^9$  /L), lymphocyte count ( $\times 10^9$  /L), monocyte count ( $\times 10^9$  /L), platelet count ( $\times 10^9$  /L)); C-reactive protein (CRP) (mg/L), fibrinogen (g/L), and albumin levels (g/L); combined inflammatory markers (NLR, SII, systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), FAR); and neonatal outcomes including birth weight, 1st- and 5th-minute Apgar scores, and neonatal blood gas pH levels. Intrauterine fetal and neonatal deaths were documented.

### Calculation of Combined Inflammatory Indices

NLR: neutrophil count / lymphocyte count

SII: (neutrophil count  $\times$  platelet count) / lymphocyte count [12]

SIRI: (neutrophil count  $\times$  monocyte count) / lymphocyte count [13]

AISI: (neutrophil count  $\times$  platelet count  $\times$  monocyte count) / lymphocyte count [14]

FAR: fibrinogen level / albumin level

**Statistical Analysis:** Statistical analyses were conducted using SPSS version 30.0 (IBM Corp., Armonk, NY, USA). Given the study's retrospective design, the sample size was determined by all eligible cases of PPRM during the study period. To evaluate the adequacy of the sample size, a power analysis was conducted, drawing upon a study in the literature that examined the same biochemical marker [15]. The sample size was determined to be a minimum of 22

patients per group, with  $\alpha = 0.05$  and 95% power. In the present study, this minimum requirement was met, and the sample size was determined to be adequate. The Shapiro–Wilk test was applied to assess the normality of data distribution. As the variables did not follow a normal distribution, group comparisons for continuous variables were performed using the non-parametric Mann–Whitney U test, and data were presented as median (interquartile range, IQR). Variables showing significant differences between groups were further evaluated for their ability to predict CAPO using receiver operating characteristic (ROC) curve analysis. The optimal cut-off values, which provided the best sensitivity and specificity, were determined using Youden’s index. The positive and negative predictive values (PPV and NPV) were calculated using the determined cut-off points, and a p-value of less than 0.05 was considered statistically significant.

## Results

A total of 170 patients were included in the study. While 70 patients showed no evidence of CAPO (Group 1), 100 patients were classified into the CAPO group (Group 2). The groups were comparable with respect to maternal age, gravidity, parity, hematological variables, gestational age at delivery, neonatal birth weight, Apgar scores, and umbilical cord blood gas pH values. The most common adverse perinatal outcomes were delivery within 48 hours (46.5%) and NICU admission (40%).

The gestational age at the occurrence of PPRM was significantly lower in Group 2 compared to Group 1 ( $p = 0.047$ ). CRP and fibrinogen levels were significantly lower in Group 1, while albumin levels were significantly higher than in Group 2 ( $p = 0.019$ ,  $p = 0.020$ , and  $p = 0.023$ , respectively). Table 1 summarizes the comparison of clinical and demographic characteristics, laboratory results, and neonatal outcomes between the two groups.

No statistically significant intergroup differences were found in the values of combined inflammatory indices, including NLR, SII, SIRI, and AISI. However, the median FAR value was 0.137 in Group 2 and 0.124 in Group 1, and this difference was statistically significant ( $p = 0.002$ ). The comparison of combined inflammatory indices between groups is presented in Table 2.

According to the ROC curve analysis, both CRP (AUC: 0.606, Std. Err.: 0.044, 95% CI: 0.519–0.692) and FAR (AUC: 0.642, Std. Err.: 0.044, 95% CI: 0.555–0.729) demonstrated significant predictive performance for CAPO ( $p = 0.019$  and

$p = 0.002$ , respectively). Both CRP and FAR demonstrated moderate discriminative ability. However, FAR showed better overall performance, with a higher AUC and a confidence interval that remained further above the non-informative threshold, indicating superior discriminatory power. When the cut-off value for CRP was set at 1.03, the sensitivity and specificity were 71% and 59%, respectively. For FAR, with a cut-off value of 0.135, sensitivity was 58% and specificity was 73%. The PPV and NPV were 71% and 58% for CRP, and 76% and 55% for FAR, respectively. The ROC curve analyses and predictive performances of these parameters for CAPO are summarized in Table 3.

## Discussion

PPROM is a significant obstetric condition due to both the risk of both maternal and fetal infection and the adverse neonatal outcomes associated with prematurity. The ability to predict adverse outcomes associated with PPRM may be beneficial in preventing maternal and neonatal complications. In the present study, the performance of FAR in predicting adverse perinatal and maternal outcomes in cases of PPRM was examined. The results demonstrated the efficacy of FAR in this regard.

The pathophysiology of PPRM remains to be fully elucidated. However, premature rupture of the fetal membranes may occur due to conditions such as increased intrauterine pressure, intrauterine infection, inflammatory processes, and oxidative stress, or as a result of these conditions initiating the inflammatory cascade (1,16). Conditions such as inflammation, intraamniotic infection and oxidative stress are hypothesized to cause collagen-mediated weakening of fetal membranes (3,16). In cases of PPRM, biomarkers such as IL-6, IL-8, and TNF- $\alpha$ —recognized as direct indicators of intra-amniotic inflammation—as well as matrix metalloproteinases, which are closely associated with collagen degradation, have been investigated (17-19). However, the use of these parameters is generally expensive, requires invasive sampling procedures, and necessitates specialized laboratory facilities for analysis.

In pregnant women with PPRM, the prediction of adverse perinatal outcomes and timely preventive treatment can significantly improve neonatal outcomes. The morbidity and mortality in newborns born to pregnant women with PPRM are primarily associated with respiratory and cardiovascular complications related to

**Table 1:** Comparison of Clinical and Demographic Characteristics, Laboratory Findings, and Neonatal Outcomes Between Groups With and Without CAPO

Variable	Group 1 (n:70) Median (IQR)	Group 2 (n:100) Median (IQR)	p value
Age (years)	27 (8)	27 (8)	0.884
Gravidity	2 (2)	2 (2)	0.191
Parity	1 (2)	1 (2)	0.799
Gestational age at PPROM occur (weeks)	32 (3)	32 (4)	0.047
WBC ( $\times 10^9/L$ )	11.29 (3.58)	12.23 (4.09)	0.080
Platelet count ( $\times 10^9/L$ )	275 (101)	261 (99)	0.581
Neutrophil count ( $\times 10^9/L$ )	8.49 (3.68)	9.36 (3.75)	0.086
Monocyte count ( $\times 10^9/L$ )	0.49 (0.31)	0.55 (0.27)	0.710
Lymphocyte count ( $\times 10^9/L$ )	1.78 (0.83)	1.58 (0.92)	0.204
CRP (mg/L)	1 (3.05)	3.22 (6.08)	0.019
Fibrinogen (g/L)	4.78 (1.21)	5.11 (1.1)	0.020
Albumin (g/L)	38 (3)	37 (3)	0.023
Gestational age at birth (weeks)	33 (2)	32.5 (4)	0.093
Neonatal weight (grams)	2075 (515)	2025 (785)	0.352
1st minute APGAR score	7 (1)	7 (1)	0.662
5th minute APGAR score	8 (0)	8 (1)	0.288
Neonatal blood gas pH value	7.34 (0.09)	7.35 (0.11)	0.513

CAPO: composite adverse perinatal outcomes, IQR: interquartile range, PPROM: preterm prelabor rupture of membranes, CRP: C-reactive protein, WBC: white blood cell count, statistical analyses were performed using the Mann-Whitney U test and  $p < 0.05$  was accepted as statistically significant

**Table 2:** Comparison of Combined Inflammatory Indices Between the Study Groups

Variable	Group 1 (n:70) Median (IQR)	Group 2 (n:100) Median (IQR)	p value
NLR	5.08 (3.11)	5.39 (3.61)	0.122
SII	1255 (1041)	1520 (1572)	0.129
SIRI	2.49 (2.03)	2.62 (2.43)	0.231
AISI	604.38 (629.08)	707 (860.08)	0.256
FAR	0.124 (0.03)	0.137 (0.03)	0.002

IQR: interquartile range, NLR: neutrophil-lymphocyte ratio, SII: systemic inflammation index, SIRI: systemic inflammatory response index, AISI: aggregate index of systemic inflammation, FAR: fibrinogen-albumin ratio, statistical analyses were performed using the Mann-Whitney U test and  $p < 0.05$  was accepted as statistically significant

preterm birth (19,20). Furthermore, the presence of prolonged oligohydramnios and intra-amniotic infection also paves the way for many adverse outcomes, such as lung hypoplasia, fetal distress, and neonatal sepsis (1,2,19). Approximately 17% of pregnancies diagnosed with PPROM result in delivery within 48 hours, while about 29% of cases are complicated by chorioamnionitis and about 1.1% by placental abruption (21-23). As a result, adverse outcomes such as neonatal death, acidosis and sepsis are observed. Antenatal corticosteroid administration to enhance fetal lung maturity and

magnesium sulfate therapy for neuroprotection in preterm fetuses have both been shown to improve neonatal outcomes (24,25). In this context, the ability to predict the likelihood of imminent delivery and the occurrence of potential complications in pregnancies diagnosed with PPROM is crucial to ensure that deliveries take place in appropriate healthcare facilities and the initiation of timely, adequate treatment. Indeed, various inflammatory markers have been evaluated in the literature to predict prognosis in pregnancies complicated by PPROM. Among

**Table 3:** Predictive Performance of CRP and FAR for CAPO Based on ROC Curve Analysis

Variable	AUC	Std. Error	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p value
CRP	0.606	0.044	0.519-0.692	1.033	71	59	71	58	0.019
FAR	0.642	0.044	0.555-0.729	0.135	58	73	76	55	0.002

CRP: C-reactive protein, FAR: fibrinogen-albumin ratio, CAPO: composite adverse perinatal outcomes, ROC: receiver operating characteristics, AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, statistical analyses were performed using Receiver Operating Characteristics curve analysis and  $p < 0.05$  was accepted as statistically significant

these markers, CRP, SIRI, and AISI have been identified as potential predictors of adverse neonatal outcomes (7,8,26). Additionally, several markers have been evaluated to estimate the latency time in cases of PPRM. According to previous research, the composite indices MII-1 ( $NLR \times CRP$ ), MII-2 ( $PLR \times CRP$ ), and MII-3 ( $SII \times CRP$ ) demonstrate good predictive accuracy for the occurrence of labor within 72 hours (7).

Pathophysiological processes, such as oxidative stress and infection, lead to decreased albumin levels and increased fibrinogen levels (10). This makes fibrinogen a valuable tool as a positive marker of inflammation, while albumin serves as a helpful negative marker of inflammation. Albumin is also a nutritional marker and an indicator of metabolic status. Based on this information, the idea has emerged that FAR, obtained by comparing both markers, could be a useful inflammatory index (10,27). Studies on this subject have shown that FAR may be useful in diseases such as inflammation-related breast cancer, various malignant tumors, and COVID-19 [28–30]. The literature has reported that FAR is valuable as a prognostic marker for obstetric complications such as preeclampsia, severe preeclampsia and late-onset fetal growth restriction (15,27).

In the present study, commonly evaluated inflammatory indices, such as NLR, SII, SIRI, and AISI, did not demonstrate statistically significant prognostic performance in cases of PPRM. In contrast, the conventional marker CRP, along with FAR, showed a significant association with predicting composite adverse perinatal outcomes. In particular, FAR stands out for its higher specificity and PPV. Considering the effect of maternal nutritional and metabolic status on perinatal outcomes, FAR's ability to reflect not only the inflammatory process but also maternal metabolic status may explain its performance. Specifically, the FAR cutoff value (0.135)

identified in this study may facilitate the classification of patients with PPRM by risk level. Patients above this threshold may require closer maternal-fetal monitoring, intensive evaluation for infection, and timely referral to a tertiary center when necessary.

Inflammatory markers such as FAR are readily available even in low-setting centers. Should further studies support their clinical utility, they may be adopted in clinical practice. This approach may facilitate the identification of patients with PPRM who are at higher risk for delivery and adverse maternal-fetal outcomes. It has the potential to guide the follow-up and delivery of high-risk patients in comprehensive centers. The present study, along with analogous studies, provides evidence that recently developed combined inflammatory markers, which have demonstrated prognostic value in numerous inflammatory diseases, may be beneficial for clinicians in obstetric complications.

However, this study has some limitations. The fact that the research was conducted at a single center may limit the generalizability of the results to the broader population. The FAR measurement used in the study was taken at the time of PPRM diagnosis; therefore, the follow-up of changes in the inflammatory process could not be evaluated. Prospective studies conducted at multiple centers with a large number of patients could increase the validity of FAR and strengthen its clinical applicability. Nevertheless, the FAR has proven to be a cost-effective and reproducible biomarker, as well as a practical predictor of adverse perinatal outcomes in cases of PPRM.

The present study found that high FAR levels were associated with adverse perinatal outcomes in cases of PPRM. Therefore, identifying cases with high FAR values early on enables appropriate follow-up and treatment, thereby improving neonatal and maternal outcomes.

**Ethical Approval:** This study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the Local Ethics Committee (Decision No:1-25-1770).

**Conflict of Interest:** No conflict of interest was declared by the authors.

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