NEU PRESS

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2024.01751
Selcuk Med J 2024;40(4): 171-176

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

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

Kubra Memnune Gundogan[1], Mehmet Murat Isikalan[2], Kazim Gezginc[3]

[1]Konya City Hospital, Department of Obstetrics and Gynecology, Konya, Türkiye
[2]Başkent University Adana Hospital, Department of Obstetrics and Gynecology, Adana, Türkiye
[3]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Türkiye

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 Yöntemler: 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 PPROM 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 istatiksel 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 cutt 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 kullanılabilecek 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

Geliş Tarihi/Received: 24 Mayıs/May 2024 **Kabul Tarihi/Accepted:** 30 Ağustos/August 2024 **Yayın Tarihi/Published Online:** 27 Aralık/December 2024

Sorumlu Yazar/Corresponding Author: Kubra Memnune Gundogan, Konya Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Konya, Türkiye
e-mail: kubramerdogan@gmail.com

Atıf yapmak için/ Cite this article as: Gundogan KM, Isikalan MM, Gezginc K. Predictive Value of Crp-Albumin and Neutrophil-Lymphocyte Ratio in Preterm Premature Rupture of Membranes. Selcuk Med J 2024;40(4): 171-176

Disclosure: *Author has not a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

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. PPROM 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 PPROM 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 PPROM (4).

Although the pathophysiological mechanism is speculative, infection and inflammatory processes play a significant role in the etiology of PPROM (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 PPROM (6). The role of inflammation in PPROM has been evaluated in numerous studies, and a significant relationship has been reported between various inflammatory markers and PPROM (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 PPROM 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 PPROM has not yet been translated into clinical practice. This study aimed to investigate the relationship between PPROM 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 PPROM.

MATERIALS AND METHODS

This prospective observational study included 143 pregnant women diagnosed with PPROM 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.

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 PPROM 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 PPROM 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 PPROM 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 ± 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 ± 5.4 years in the PPROM group and 28.6 ± 5.4 years in the control group (p=0.881). The mean gestational age was also similar: 33.8 ± 3.1 weeks in the PPROM group and 34.8 ± 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 PPROM 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)/mm^3 in the PPROM group and 10.300 (8.790-11.500)/mm^3 in the control group. Neutrophil counts were 8.665 (7.800-10.757)/mm^3 and 7.550 (6.565-8.900)/mm^3 in the PPROM 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)/mm^3 and 1.750 (1.460-2.330)/mm^3, and monocyte counts were 650 (500-860)/mm^3 and 580 (485-755)/mm^3 in the PPROM 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 PPROM group and 4.1 (3.7, 5.2) in the control group, showing a statistically significant elevation in the PPROM group (p<0.001). The CAR was 0.18850 (0.09003, 0.34868) in the PPROM group and 0.08097 (0.05601, 0.14917) in the control group, also significantly higher in the PPROM group (p<0.001). The PLR was 133.2 (105.4, 163.9) in the PPROM 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 PPROM 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 ± 5.4	28.6 ± 5.4	0.881[a]
Gestational Age (weeks)	33.8 ± 3.1	34.8 ± 1.1	0.916[a]
Gravida (number)	2.0 (1.0, 4.0)	2.0 (1.0, 3.5)	0.888[b]
Parity (number)	1 (0, 2)	1 (0,1)	0.912[b]

Data are presented as mean ± standard deviation, median (25th Percentile – 75th Percentile), or number (%). p-values were determined using Student's t-test or Mann-Whitney U test PPROM: 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 (/mm^3)	11550 (10375-13965)	10300 (8790-11500)	**<0.001[b]**
Neutrophils (/mm^3)	8665 (7800-10757)	7550 (6565-8900)	**<0.001[b]**
Lymphocytes (/mm^3)	1795 (1375-2420)	1750 (1460-2330)	0.510[b]
Monocytes (/mm^3)	650 (500-860)	580 (485-755)	0.154[b]
Platelets (/mm^3)	245158 ± 63864	228931 ± 68622	0.655[a]
Albumin (g/L)	37.5 (33.4-40.5)	38.8 (36.4-40.4)	0.069[b]
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[b]
CRP/Albumin Ratio	0.18850 (0.09003-0.34868)	0.08097(0.05601-0.14917)	**<0.001[b]**

Data are presented as mean ± 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

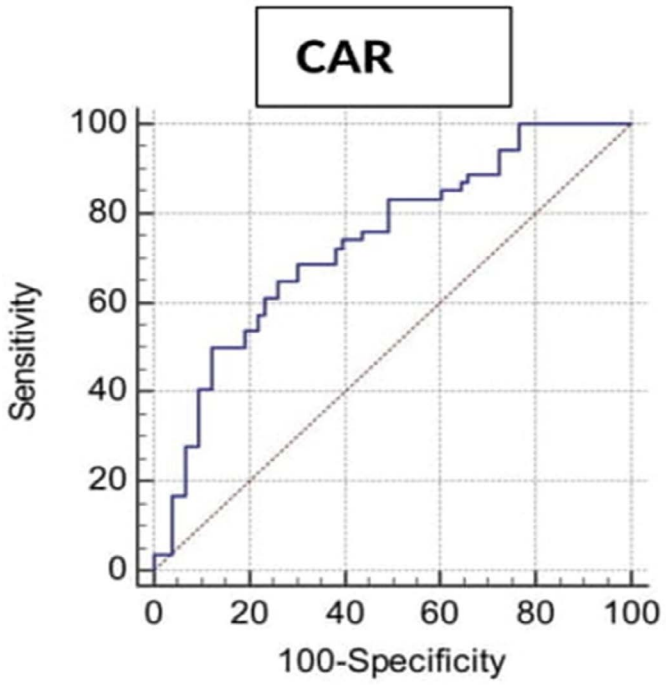

Figure 1. Receiver operating characteristics (ROC) curve analysis of C-reactive protein to albumin ratio (CAR) between the PPROM and Control groups (Optimal ROC cutoff value: 0.1433 with 64.81% sensitivity and 73.97% specificity, AUC: 0.734, p<0.001)

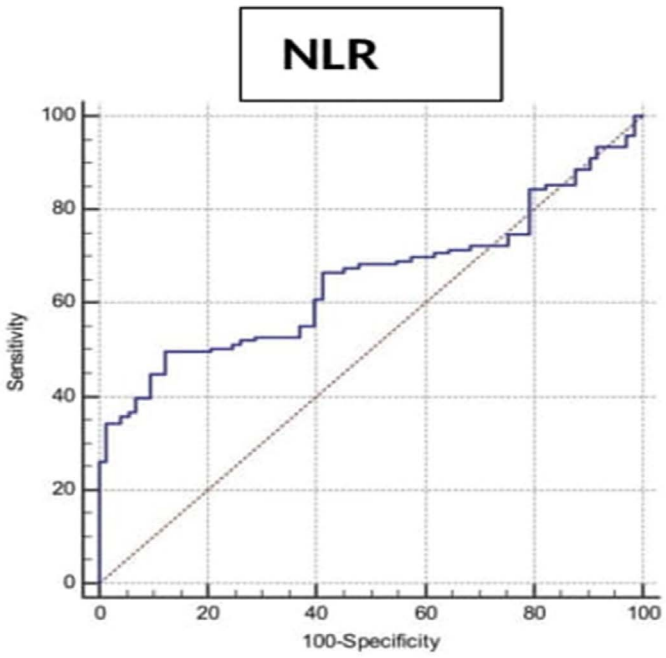

Figure 2. Receiver operating characteristics (ROC) curve analysis of neutrophil-lymphocyte ratio (NLR) between the PPROM and Control groups (Optimal ROC cutoff value: 5.3937 with 49.59% sensitivity and 87.67% specificity, AUC: 0.650, p<0.001)

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 PPROM 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 PPROM 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 PPROM.

PPROM remains a significant problem in obstetrics due to challenges and uncertainties in its etiology and associated serious maternal and fetal risks. PPROM occurs in approximately 1-3% of all pregnancies and in about one-third of preterm births (16). Although its exact pathophysiology is still debated, PPROM 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 PPROM is inflammation (17,18).

Cytokines involved in inflammatory reactions have been reported to be associated with PPROM. Satar et al. reported increased interleukin (IL)-8 levels in maternal serum and umbilical cord in PPROM. Similarly, IL-6 was found to be elevated only in the umbilical cord, especially in PPROM 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 PPROM 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 PPROM group compared to the control group, concluding that NLR is a useful marker for predicting PPROM. Consistent with the literature, our study found higher NLR levels in the PPROM 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 PPROM group compared to the control group, suggesting that PLR could be an independent marker in detecting PPROM. Although our study found higher PLR in the PPROM 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 PPROM compared to the control group. Furthermore, to our knowledge, our study is the first in the literature to demonstrate the relationship between CAR and PPROM.

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 PPROM and control groups.

In conclusion, CAR and NLR were significantly higher in the PPROM group compared to controls. CAR and NLR may be cost-effective, easy-to-use, and practical markers for the early diagnosis of PPROM, 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 PPROM.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Kubra Memnune Gundogan, Konya Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Konya, Türkiye*
e-mail: *kubramerdogan@gmail.com*

REFERENCES

1. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol. 2003;101(1):178-93. doi:10.1016/s0029-7844(02)02366-9.
2. Bouvier D, Giguère Y, Blanchon L, et al. Study of sRAGE, HMGB1, AGE, and S100A8/A9 Concentrations in Plasma and in Serum-Extracted Extracellular Vesicles of Pregnant Women With Preterm Premature Rupture of Membranes. Front Physiol. 2020;11:609. doi:10.3389/fphys.2020.00609.
3. Gabbe S, Niebyl J, Simpson J. Postpartum hemorrhage. Obstetrics: Normal and problems pregnancies. 5th ed. Churchill Livingston: Elsevier, 2007.
4. Owen J, Goldenberg RL, Davis RO, et al. Evaluation of a risk scoring system as a predictor of preterm birth in an indigent population. Am J Obstet Gynecol 1990;163(3):873-9. doi:10.1016/0002-9378(90)91086-r.
5. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2003;(2):CD001058. doi:10.1002/14651858.CD001058.
6. Ferguson SE, Smith GN, Salenieks ME, et al. Preterm premature rupture of membranes. Nutritional and socioeconomic factors. Obstet Gynecol. 2002;100(6):1250-6. doi:10.1016/s0029-7844(02)02380-3.
7. Isık H, Aynıoglu O, Sahbaz A, et al. Can plateletcrit, an underestimated platelet parameter, be related with preterm labour? J Obstet Gynaecol. 2015;35(7):676-80. doi:10.3109/01443615.2015.1004530.
8. Ekin A, Gezer C, Kulhan G, et al. Can platelet count and mean platelet volume during the first trimester of pregnancy predict preterm premature rupture of membranes? J Obstet Gynaecol Res. 2015;41(1):23-8. doi:10.1111/jog.12484.
9. Gioia S, Piazze J, Anceschi MM, et al. Mean platelet volume: association with adverse neonatal outcome. Platelets. 2007;18(4):284-8. doi:10.1080/09537100601078448.
10. Musilova I, Kacerovsky M, Stepan M, et al. Maternal serum C-reactive protein concentration and intra-amniotic inflammation in women with preterm prelabor rupture of membranes. PLoS One. 2017;12(8):e0182731. doi:10.1371/journal.pone.0182731.
11. Ryu HK, Moon JH, Heo HJ, et al. Maternal c-reactive protein and oxidative stress markers as predictors of delivery latency in patients experiencing preterm premature rupture of membranes. Int J Gynaecol Obstet. 2017;136(2):145-50. doi:10.1002/ijgo.12024.
12. Yazar FM, Bakacak M, Emre A, et al. Predictive role of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for diagnosis of acute appendicitis during pregnancy. Kaohsiung J Med Sci. 2015;31(11):591-6. doi:10.1016/j.kjms.2015.10.005.
13. Yavuzcan A, Cağlar M, Ustün Y, et al. Mean platelet volume, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in severe preeclampsia. Ginekol Pol. 2014;85(3):197-203.
14. Goh SL, De Silva RP, Dhital K, et al. Is low serum albumin associated with postoperative complications in patients undergoing oesophagectomy for oesophageal malignancies?. Interact Cardiovasc Thorac Surg. 2015;20(1):107-13. doi:10.1093/icvts/ivu324.
15. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9:69. doi:10.1186/1475-2891-9-69.
16. Porat S, Amsalem H, Shah PS, et al. Transabdominal amnioinfusion for preterm premature rupture of membranes: a systematic review and metaanalysis of randomized and observational studies. Am J Obstet Gynecol. 2012;207(5): 393.e1-11 doi:10.1016/j.ajog.2012.08.00.
17. Romero R, Miranda J, Chaemsaithong P, et al. Sterile and microbial-associated intra-amniotic inflammation in preterm prelabor rupture of membranes. J Matern Fetal Neonatal Med. 2015;28(12):1394-409. doi:10.3109/14767058.2014.958463.
18- Romero R, Espinoza J, Gonçalves LF, et al. The role of inflammation and infection in preterm birth. Semin Reprod Med. 2007;25(1):21-39. doi:10.1055/s-2006-956773.
19. Satar M, Turhan E, Yapicioglu H, et al. Cord blood cytokine levels in neonates born to mothers with prolonged premature rupture of membranes and its relationship with morbidity and mortality. Eur Cytokine Netw. 2008;19(1):37-41. doi:10.1684/ecn.2008.0118.

20. Popowski T, Goffinet F, Maillard F, et al. Maternal markers for detecting early-onset neonatal infection and chorioamnionitis in cases of premature rupture of membranes at or after 34 weeks of gestation: a two-center prospective study. BMC Pregnancy Childbirth. 2011;11:26. doi:10.1186/1471-2393-11-26
21. Yao Y, Yuan D, Liu H, et al. Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy. Cancer Immunol Immunother. 2013;62(3):471-9. doi:10.1007/s00262-012-1347-9.
22. Sen BB, Rifaioglu EN, Ekiz O, et al. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutan Ocul Toxicol. 2014;33(3):223-7. doi:10.3109/15569527.2013.834498.
23. Fu H, Qin B, Hu Z, et al. Neutrophil- and platelet-to-lymphocyte ratios are correlated with disease activity in rheumatoid arthritis. Clin Lab. 2015;61(3-4):269-73. doi:10.7754/clin.lab.2014.140927.
24. Oltulu R, Katipoğlu Z, Gündoğan AO, et al. Evaluation of inflammatory biomarkers in patients with keratoconus. Eur J Ophthalmol. 2022;32(1):154-9. doi:10.1177/11206721211000644.
25. Köseoğlu SB, Guzel AI, Deveer R, et al. Maternal serum amyloid A levels in pregnancies complicated with preterm prelabour rupture of membranes. Ginekol Pol. 2014;85(7):516-20. doi:10.17772/gp/1763.
26. İlhan M, İlhan G, Gök AF, et al. Evaluation of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and red blood cell distribution width-platelet ratio as early predictor of acute pancreatitis in pregnancy. J Matern Fetal Neonatal Med. 2016;29(9):1476-80. doi:10.3109/14767058.2015.1051026.
27. Sahbaz A, Cicekler H, Aynioglu O, et al. Comparison of the predictive value of plateletcrit with various other blood parameters in gestational diabetes development. J Obstet Gynaecol. 2016;36(5):589-93. doi:10.3109/01443615.2015.1110127.
28. Toprak E, Bozkurt M, Dinçgez Çakmak B, et al. Platelet-to-lymphocyte ratio: A new inflammatory marker for the diagnosis of preterm premature rupture of membranes. J Turk Ger Gynecol Assoc. 2017;18(3):122-6. doi:10.4274/jtgga.2017.0028.
29. Kaplan M, Ates I, Akpinar MY, et al. Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2017;16(4):424-30. doi:10.1016/S1499-3872(17)60007-9.
30. Liu Y, Chen S, Zheng C, et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. BMC Cancer. 2017;17(1):285. doi:10.1186/s12885-017-3220-x.
31. Yevgi R, Bilge N, Simsek F, et al. Vitamin D levels and C-reactive protein/albumin ratio in pregnant women with cerebral venous sinus thrombosis. J Thromb Thrombolysis. 2022;53(2):532-9. doi:10.1007/s11239-021-02541-0.